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ABSTRACT SUPPLEMENT

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President's Address

New development of total joint arthroplasty for Rheumatoid Arthritis

Toru Suguro

Department of Orthopaedic Surgery, Toho University School of Medicine

For rheumatoid arthritis is necessary to have reconstructive surgery, because inflammatory changes will make the joint cartilage damages. The incidence of joints involvements should be so high on the hand, finger, elbow, hip, knee, ankle and foot. The joint destruction and deformity would be occurred with the duration of inflammatory process. The best reconstruction methods for RA destroyed joints are joints replacement, in Asia most total joint prosthesis are imported from United States and European countries. The imported implant does not suitable for Asian patients, for this reason we started to develop new total prostheses for Asia since 1980. First total knee prostheses was developed 1985, and then we have been getting good clinical results. Next generation FINE total knee prosthesis was developed 2000, and this implant has been showing so good ROM and clinical results for RA patients. On RA patients, it is necessary to make other joint prosthesis. We developed the elbow joint, ankle joint, finger joint for RA patient. However the implant has a lot of complications while longtime using, the one of the reason is wear and oxidization of poliechyren. Now in Japan, it is abatable to use the Blend-E polyethylene for keeping the longevity. Still we have to make a big revolutions and development for RA patients to keep a good quality functions in daily living.

Symposium

S1-1

Novel therapies for vasculitis syndrome

Shoichi Ozaki

Division of Rheumatology and Allergology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan

A therapeutic strategy for vasculitis syndrome has been established, and global evidence has been accumulated by several randomized controlled trials (RCTs), especially in Takayasu's arteritis, giant cell arteritis and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).

The standard regimen for Takayasu's arteritis is glucocorticoid (GC) therapy. In GC-resistant patients, an immunosuppressive agent is added, such as cyclophosphamide (CY), methotrexate (MTX), azathioprine (AZ), and mycophenolate mofetil (MMF). Recently, anti-TNF-alpha therapy or peripheral blood stem-cell transplantation has been employed.

In giant cell arteritis, GC is also the first-line drug. Prednisolone of 1mg/kg/day is administered to patients with ocular involvement, central nervous-system involvement or cranial nerve sign. For those lacking these signs, prednisolone of 30 - 40 mg/day is used. The usefulness of intravenous methylprednisolone is controversial. Several immunosuppressive agents have been used as adjunctive therapy. Among them, MTX was proved to be good for relapse-preventing and GC-sparing effects by a meta-analysis of three RCTs. In contrast, infliximab seemed to have little adjunctive effect to GC monotherapy.

Standard therapies for AAV are high-dose GC + CY in remission induction and low-dose GC + AZ in remission maintenance. In EULAR recommendations 2009, novel therapies for refractory AAV included intravenous immunoglobulin (IVIG), infliximab, rituximab, 15-deoxyspergualin, anti-thymocyte antibody, and MMF. Recently, two RCTs were reported, where rituximab was as effective and safe as CY in remission induction of AAV. A pilot study for Japanese patients with refractory AAV indicated the effectiveness of rituximab in induction of re-remission. Although most of the agents mentioned above are not approved in Japan, IVIG was approved for neurological impairment in Churg-Strauss syndrome in January, 2010.

S1-2

New therapy for ankylosing spondylitis

Kurusu Tada

Rheumatology and Internal Medicine, Juntendo University School of Medicine

TNF inhibitor is used in various inflammatory diseases including rheumatoid arthritis, Bechet disease, Psoriasis, and inflammatory bowel disease, and has been shown to be effective. In particular, rheumatoid arthritis, TNF inhibitor resulting in a paradigm shift in treating rheumatoid arthritis, "tight control", "treat to target" has been proposed that a new treatment strategy. Finally, in 2010 TNF inhibitor was indicated for ankylosing spondylitis. In conventional treatment, NSAIDs are recommended as first line drug, Sulfasalazine may be considered in patients with peripheral arthritis. Corticosteroid injections directed to the local site of musculoskeletal inflammation may be considered. However, NSAIDs were the only effective treatment in axial disease. In Europe and U.S, TNF inhibitor has been proved an immediate effect for ankylosing spondylitis, and has been shown highly effective in clinical trials in Japan. The predictors of a good response to TNF inhibitor were short disease duration,

elevated C-reactive protein and younger age. While the high clinical efficacy, however, inhibition of radiographic progression in ankylosing spondylitis is currently negative. The ankylosis of the spine has two steps, in the first step inflammation causes erosive structural damage with bony defect, which are filled with fibrous repair tissue, in the second step the repair tissue becomes ossified, which is made easier when inflammation disappears. Therefore early diagnosis and early use of TNF inhibitor may lead to better clinical course. This time, I will introduce the new treatment for ankylosing spondylitis, including the latest findings.

S1-3

Systemic lupus erythematosus

Yoshiya Tanaka

The First Department of Internal Medicine, School of Medicine, University of Occupational & Environmental Health, Japan

Systemic lupus erythematosus (SLE) is a representative autoimmune disease and immune complexes consisting of antigens and autoantibodies secreted from activated B cells cause severe inflammation in various organs. Since often patients with SLE are refractory to conventional treatments such as immunosuppressants and corticosteroids, innovative approaches need to be developed. Recently, the potential efficacy of biologics targeting B cells and cytokines has been emerging in the treatment of SLE. B cell depletion therapy with anti-CD20 antibody rituximab has shown a rapid onset of effect and prolonged efficacy in refractory SLE. We also reported that rituximab is safe for the treatment of active SLE by a multi-center phase I/II clinical trial. However, the placebo-controlled trials such as EXPLORER with rituximab in SLE did not achieve satisfied results and serious opportunistic infections have been reported in patients with SLE treated with rituximab. In addition, other B-cell targeted therapies such as CD20-directed small modular immunopharmaceutical (SMIP) product (SBI-087) and anti-CD22 antibody epratuzumab, agents that interrupt cellular interaction among B cells, T cells, monocyte and dendritic cells, including anti-BAFF antibody belimumab, CTLA4-Ig fusion protein abatacept, TACI-Ig fusion protein atacicept, and anti-IFN- α antibody sifalimumab also have potential of the therapeutic application.

S1-4

Novel approach to osteoporosis treatment

Sakae Tanaka

Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan

Japan is one of the most rapidly aging countries in the world. People aged 65 and over numbered 27,440,000 in 2007, which is 22% of the population, and thus Japan is already in a "super-aged" society. 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. Osteoporosis is a burden not only for the patients but also for the society although the exact pathology has not been clarified yet. 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 symposium, I would like to introduce novel anti-osteoporotic drugs: a novel bisphosphonate minodronate, an anabolic agent teriparatide, and a novel SERM

basedoxifene. In addition, I will also introduce some drugs which are under development.

S1-5

Sjogren's syndrome

Takayuki Sumida, Hiroto Tsuboi, Mana Iizuka, Naomi Matsuo, Isao Matsumoto

Department of Internal Medicine, University of Tsukuba

Sjogren's syndrome (SS) is an autoimmune disease characterized pathologically by lymphocytic infiltration into the lacrimal and salivary glands, and clinically by dry eyes and mouth. Lymphocytic infiltration is also found in the kidneys, lungs, thyroid, and liver. Immunohistochemical studies have shown that most infiltrating lymphocytes around the labial salivary and lacrimal glands and the kidneys are CD4-positive $\alpha\beta$ T cells. Candidate autoantigens recognized by T cells that infiltrate the labial salivary glands of SS have been analyzed and Ro/SS-A 52 kD, α -amylase, heat shock protein, TCR BV6 have been identified. Recently, we observed evidence that muscarinic-3 acetylcholine receptor (M3R) works as an autoantigen recognized by T cells in patients with SS. Additionally, various autoantibodies (autoAbs) have been identified in sera of patients with SS, and some of these autoAbs, such as anti-SS-A antibody (Ab) and anti-SS-B Ab are used as diagnostic markers. Muscarinic-3 acetylcholine receptor (M3R) is involved in activation of salivary and lacrimal glands. We reported that antibodies against M3R has been detected in serum from subgroup of patients with Sjogren's syndrome (SS). Recently, we succeeded to establish autoimmune sialoadenitis such as SS by cell transfer experiments using M3R-/- mice immunized with M3R peptides and Rag1-/- mice. These findings support the notion that the immune reaction against M3R molecule might play a crucial role in the generation of SS. In the present symposium, I will summarize the molecular mechanism of SS, present our new data on the role of M3R reactive T cells and anti-M3R Abs in the generation of SS, and discuss an antigen-specific therapeutic strategies on SS in near future. Moreover, I will show you the progress on the new therapies on SS using biologics such as antibodies against CD20, CD22, and BAFF.

S1-6

Behcet's disease

Shunsei Hirohata¹, Hiroto Kikuchi²

¹Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, ²Department of Microbiology, Teikyo University School of Medicine

One of the most serious manifestations in Behcet's disease is sight-threatening uveitis. Although cyclosporin has been used to prevent an attack of uveitis, approximately 50% of the patients still present recurrent uveitis attacks. Recently, infliximab has been shown to be effective in suppressing the occurrence of uveitis attacks, and to have favorable implications for the visual prognosis of patients with recalcitrant Behcet's uveitis. Another intractable complications of Behcet's disease include vascular involvement (vasculo-Behcet), neurological involvement (neuro-Behcet [NB]), and intestinal involvement (intestinal-Behcet). The use of infliximab for vasculo-Behcet is still controversial, since some reports suggest the thrombogenicity of infliximab. NB can be classified into acute type and chronic progressive type. Acute type NB responds to corticosteroid therapy, and is usually self-limiting, although recurrence of the attacks sometimes takes place. Some case reports suggest the efficacy of infliximab in preventing the recurrence of attacks, although controlled trials are required for confirmation. Chronic progressive

type NB is characterized by intractable, slowly progressive neurobehavioral changes, ataxia and dysarthria, with persistent marked elevation of cerebrospinal fluid (CSF) IL-6. Although chronic progressive NB is resistant to conventional treatment with corticosteroid, cyclophosphamide, or azathioprine, low-dose weekly methotrexate (MTX) has been shown to be effective. Recent studies with an open trial have disclosed that infliximab inhibits the progression of neurological manifestations by decreasing CSF IL-6 in patients with recalcitrant chronic progressive NB. As to intestinal Behcet's disease, there are several case reports, suggesting the efficacy of infliximab. However, further studies are necessary to confirm its efficacy with a larger numbers of patients.

S2-1

Inhibition of cyclin-dependent kinase 4/6 for treatment of rheumatoid arthritis

Hitoshi Kohsaka, Tadashi Hosoya, Hideyuki Iwai, Nobuyuki Miyasaka

Department of Medicine and Rheumatology, Tokyo, Japan

Recent research studies on rheumatoid arthritis (RA) have led to development of biological agents that target specific molecules. However, we still have patients refractory to these expensive agents and/or suffering from severe adverse events, especially infections. During our search for non-immunosuppressive approaches, we found 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. When small-molecule (sm) CDK4/6 inhibitors were tested, they suppressed proliferation of synovial fibroblasts (SF) in vitro and also the animal models without affecting lymphocyte functions. In vitro, smCDK also inhibited expression of stromelysin-1 (MMP-3) from SF. We assume that CDK4/6 inhibition has dual anti-rheumatic effects: inhibition of proliferation and MMP-3 expression of SF. Chemical CDK4/6 inhibiting compounds that are superior in the dual effects are now being screened.

S2-2

Inflammation, joint destruction and c-Fos/AP-1 in rheumatoid arthritis.

Shunichi Shiozawa¹, Akira Hashiramoto¹, Yukihiro Aikawa²

¹Division of Rheumatology, Kobe University Graduate School of Health Sciences and Medicine/ The Center for Rheumatic Diseases, Kobe University Hospital, ²Research Laboratories, Toyama Chemical Co., Ltd.

Synovial mesenchymal cells, matrix metalloproteinases (MMPs), and osteoclasts are the 3 major players responsible for the pathogenesis of rheumatoid joint destruction.

First, synovial mesenchymal cells, internally driven by a transcription factor c-Fos/AP-1, not only directly invade cartilage and bone as a granulation tissue called 'pannus' but also release inflammatory cytokine interleukin-1b (IL-1b). IL-1b induces MMPs and activates osteoclasts. Synovial cells can also present antigen to T cells to drive antigen-specific immune responses.

Second, cartilaginous joint matrix can only be degraded after the first attack of collagen fibrils by MMPs, and importantly, most of the MMPs are under the control of c-Fos/AP-1 and IL-1b as well.

Therefore, IL-1b and c-Fos/AP-1 influence each other's gene expression and activity, resulting in an orchestrated cross-talk that is crucial to arthritic joint destruction, and thus, blockade of IL-1b and/or c-Fos/AP-1 can be most promising as a therapeutic target, and in

fact, a selective inhibition of c-Fos/AP-1 does resolve arthritic joint destruction.

S2-3

S1P receptor as a new target for the therapy of autoimmune diseases

Kenji Chiba

Pharmacology Research Laboratories I, Research Division, Mitsubishi Tanabe Pharma Corporation

Sphingosine 1-phosphate (S1P), a lysophospholipid mediator, is generated from sphingosine by sphingosine kinases and binds 5 types of G protein-coupled S1P receptors. It has been well documented that S1P receptor type 1 (S1P1) plays an essential role in lymphocyte egress from secondary lymphoid organs (SLO), because lymphocytes are unable to exit from SLO to periphery in mice lacking lymphocytic S1P1 conditionally. FTY720 (fingolimod) is an orally active first-in-class S1P receptor modulator and is highly effective in various experimental autoimmune disease models including encephalomyelitis, adjuvant- or collagen-induced arthritis, and lupus nephritis. FTY720 is a structural analogue of sphingosine and is effectively converted to an active metabolite, FTY720 phosphate (FTY720-P) by sphingosine kinases. FTY720-P binds to four types of S1P receptors (S1P1, S1P3, S1P4, and S1P5) except for S1P2 and acts as an agonist at these receptors. Particularly, FTY720-P strongly internalizes S1P1 from the cell surface, almost completely inhibits S1P responsiveness of lymphocytes in SLO, and acts as a functional antagonist at lymphocytic S1P1. Consequently, FTY720 inhibits S1P1-dependent lymphocyte egress from SLO to decrease circulation of lymphocytes including autoreactive Th 17 cells and Th1 cells, and shows immunomodulating effects on autoimmune disease models. Recently, it has been reported that FTY720 has a superior efficacy in relapsing remitting multiple sclerosis patients compared to interferon- β (Phase 3, TRANSFORMS study). From these results, it is presumed that S1P1 is a novel target for the therapy of autoimmune diseases including multiple sclerosis.

S2-4

Innovation of therapy for autoimmune diseases by targeting CD26

Kei Ohnuma

Division of Rheumatology and Allergy, Research Hospital, Institute of Medical Science, University of Tokyo, Tokyo, Japan

CD26 is a 110-kDa cell surface glycoprotein with known dipeptidyl peptidase IV activity in its extracellular domain. CD26 plays an important role in infection, autoimmunity, diabetes and cancer. CD26 role in immune regulation has been extensively characterized, with our recent findings elucidating its linkage with signaling pathways and structures involved in T cells activation as well as antigen presenting cell -T-cell interaction. CD26 is preferentially expressed on human CD4+ memory T cells and CD4+CD45RO+CD26+ T cells exhibit a response maximally to the recall antigen, such as tetanus toxoid. Human Th1 cells display a higher expression of CD26 and are much more sensitive to CD26-mediated costimulation than human Th2 cells. While CD8+ T cells express CD26 as well as CD4+ T cells, precise role of CD26 in CD8+ T cells has not yet been studied. We recently investigated the effector function of CD26-mediated costimulation of CD8+ T cells. In comparison with CD28-mediated costimulation, which is one of extensively characterized T cell costimulatory pathway, CD26-mediated costimulation in CD8+ T cells showed delayed proliferation than that of CD28 stimulation. Moreover, the expression of Granzyme B, one of the

major effector molecules in the cytotoxic activity of CD8⁺ T cells, was markedly enhanced by CD26-mediated costimulation. Furthermore, with CD26-mediated costimulation, CD8⁺ T cells were observed to kill target cells in a Granzyme B-dependent manner. Next, we examined CD26-dependent organ injury by human T cells using xenogeneic chronic GVHD (x-cGVHD) mice model. Administration of anti-human CD26 mAb decreased onset of x-cGVHD, while human lymphocytes were grafted successfully. Taken together, our data strongly suggest that CD26 plays an important role in CD8⁺ T cell dependent defense against immune reaction. The present study offers a novel notion that CD26 may become one of therapeutic targets of intractable immune diseases.

S2-5

Cathepsin K inhibitor for the treatment of osteoporosis and rheumatoid arthritis

Hiroshi Takayanagi

Department of Cell Signaling Tokyo Medical and Dental University / JST, ERATO

Osteoclasts attracted much attention as the crucial target in the treatment of osteoporosis and rheumatoid arthritis. Since cathepsin K was identified and specifically detected in osteoclasts, cathepsin K inhibitor has been thought to be a specific inhibitor of osteoclastic bone resorption. We have developed a new oral inhibitor of cathepsin K NC-2300, which efficiently suppressed in vitro osteoclast activity and in vivo bone loss in osteoporosis models. Unexpectedly, in the treatment of rat adjuvant arthritis, NC-2300 inhibited inflammatory responses in addition to osteoclastic bone resorption. We revealed dendritic cells express cathepsin K, which plays an essential role in the TLR9 signaling required for the induction of cytokines such as IL-6, -12 and -23. Cathepsin K inhibitor also suppressed the disease activity and induction of Th17 cells in experimental encephalitis. Thus, cathepsin K will serve as an auspicious therapeutic agent in the autoimmune arthritis by suppressing both immune responses and bone resorption.

S3-1

Inflammation condition clarified from effect of biologics to joint type JIA

Yasuhiro Nerome

Pediatric Medical Center, Kagoshima University Hospital

The rate of drug free remission was reported 5% in RF-positive polyarticular-course JIA, 25% in RF-negative polyarticular-course JIA and 36% in oligoarthritis JIA with the traditional treatment. Not only clinical remission but also radiological remission is proven by biological treatments, and the possibility of the drug free remission is being suggested. On the other hand, clinical remission is proven in JIA, but there are little evidence of radiological remission and drug free remission. There are controversial that the evidence of biologics in RA is applied to JIA.

The clinical trial of etanercept in refractory JIA starts in 2003 in Kagoshima University, and the clinical trial of tocilizumab starts in 2004. Then, it was examined whether the rate of drug free remission is changed after 2004. In Kagoshima University, there were 66 joint type JIA patients had developed before 2003 (23 RF-positive, 15 RF-negative, and 23 oligoarthritis) and there were 70 joint type JIA patients had developed after 2004 (37, 16, and 17). 21 of these patients treated with biologics (14, 6, and 1). The drug free remission rate within five years was observed about 32% of RF-positive, 66% of RF-negative, and 58% of oligoarthritis JIA patients had developed before 2003. The drug free remission rate within five years is

observed about 0% of RF-positive, 10% of RF-negative, and 32% of oligoarthritis JIA patients had developed after 2004. The biologic treatment can not improved the rate of drug free remission in JIA.

Biologics do not necessarily at least has the ability to improve the rate of drug free remission in Kagoshima University. But it is necessary to consider the following points: this data is result of one facility, a possibility to insufficient try to stop the biologics. If guidelines to discontinued biologics provide, or the number of early-onset JIA treated with biologics, this conclusion may be changed.

S3-2

Pathological status of adult patients with RA learned from the biologics therapy

Norihiro Nishimoto

Laboratory of Immune Regulation, Wakayama Medical University, Wakayama, Japan

Rheumatoid arthritis (RA) is a common autoimmune disease in adulthood, which is characterized by joint destruction. Considerable similarities between adult RA and juvenile idiopathic arthritis have suggested that study for pathological mechanism of RA is also useful for understanding that of JIA. Biologics targeting various molecules, including inflammatory cytokines such as TNF, IL-6, IL-1, IL-12, IL-15, IL-17 as well as molecules expressed on T and B cell, have been developed for RA, and they have mostly shown excellent therapeutic efficacy with higher clinical remission rate than conventional DMARDs. The fact also confirmed that the target molecules indeed play pathological roles in RA. On the other hand, they are not always effective for every patient, or even amongst responders, the majority experience only partial improvement in disease activity. Such cases often respond to another biologic agent. Interestingly, TNF inhibition sometimes decreases IL-6 levels while IL-6 inhibition also decreases TNF levels. This clearly indicates that there is not a simple cascade but a complex network with molecular interactions. Indeed, we found synergistic effect between IL-6 and TNF or IL-1 in inducing VEGF and MMPs from RA synoviocytes. Thus it is required to know network regulations for better understanding of RA pathology. DNA microarrays can be amenable to exhaustively analyze the gene expressions of such multiple molecules and depict such network regulations of the molecules. At the symposium, in addition to abnormalities in immunological networks of RA and comparison between RA and JIA, therapeutic effect of biologics on the networks will be discussed.

S3-3

Differences in radiographic features between two subtypes of juvenile idiopathic arthritis: Systemic arthritis and polyarthritis

Yutaka Inaba¹, Remi Ozawa², Chie Aoki¹, Tomoyuki Imagawa², Takako Miyamae², Masaaki Mori², Tomoyuki Saito¹, Shumpei Yokota²

¹Department of Orthopaedic Surgery, Yokohama City University,

²Department of Pediatrics, Yokohama City University

Objective: To investigate the differences in radiographic findings between systemic-onset juvenile idiopathic arthritis (sJIA) and polyarticular juvenile idiopathic arthritis (pJIA).

Methods: Twenty patients with sJIA and 16 with pJIA were enrolled. Plain radiographs were obtained before the induction of biologics. All radiographs were examined for the presence of soft tissue swelling, juxta-articular osteopenia, joint space narrowing, subchondral bone cyst, erosion, epiphyseal irregularity, growth abnormali-

ties. Carpal length and bone mineral density of lumbar spine were investigated in all the patients enrolled. We also checked for the presence of compression fractures of any vertebral bodies. Laboratory examinations were involved white blood cell counts, CRP, rheumatoid factor, and anti-CCP antibody.

Results: The most frequent radiographic abnormality in sJIA was juxta-articular osteopenia (70.2%) in comparison to 53.5% in pJIA. Joint space narrowing was detected in 19.7% of sJIA comparable to 47.7% in pJIA. Subchondral bone cyst and erosion were more frequent in pJIA than sJIA. Carpal length was statistically shorter in pJIA patients ($p<0.05$). Bone density in s-JIA patients was lower than in p-JIA patients, but this difference was not statistically significant ($p=0.13$). In contrast to the 25% frequency of vertebral compression fractures in the s-JIA patients, not a single case was seen among the p-JIA patients. The comparison of laboratory findings between sJIA and pJIA indicated that the titers of rheumatoid factor and anti-CCP antibody were significantly increased in pJIA sera ($p<0.05$).

Conclusions: There were differences of radiographic characteristics and laboratory data between sJIA and pJIA in this study. In radiographic evaluation, bone-related abnormality was prominent in sJIA and joint-related abnormality was striking in pJIA, and these results indicated that the pathogenic bases of arthritis would differ between these two subtypes of JIA.

S3-4

The pathophysiology of macrophage activation syndrome during the treatment with IL-6/IL-1 beta blocking agents for systemic juvenile idiopathic arthritis.

Tomoyuki Imagawa, Shumpei Yokota

Department of Pediatrics, Yokohama City University School of Medicine

The systemic juvenile idiopathic arthritis is one of the Pediatric rheumatic diseases. The patients with SJIA sometime develop to the macrophage activation syndrome as the poor prognostic factor in SJIA. Interleukin 6 (IL-6) and IL-1 β is related with the pathologic condition of SJIA. The therapeutic drugs for refractory SJIA to inhibit the signals of these inflammatory cytokines have been developed.

Tocilizumab that is humanized anti-human IL-6 receptor monoclonal antibody has been approved for refractory SJIA since 2008. Tocilizumab improved the joint function and ADL of the patient with refractory SJIA. Moreover, Canakinumab, humanized anti-IL-1 beta antibody, and anakinra, IL-1 receptor antagonist, have been applied to the refractory SJIA in Europe and United States. The post-marketing surveillance study has been done in Japan for Toshirizumab since 2008. The MAS case of 19 examples is reported in the result of the survey until December, 2010.

This event shows that MAS causes the cytokine storm by multi-inflammatory cytokines, and the organ damage is caused.

S3-5

What part does dysregulation of IL-1 β play in CAPS?

Ryuta Nishikomori

Kyoto University Graduate School of Medicine, Department of Pediatrics, Kyoto, Japan

Cryopyrin-associated periodic syndrome (CAPS) is an autoinflammatory syndrome with early-onset urticarial rash and inflammation. NLRP3 has been identified as a responsible gene for CAPS. The main pathophysiology underlying CAPS is uncovered by the discovery of NLRP3 inflammasome, which causes dysregulated pro-

duction of IL-1 β through the mutated NLRP3 gene. On the other hand, we report that the overexpression of mutated NLRP3 causes necrotic cell death on monocytic cell line THP-1 and the CAPS patient monocytes (Fujisawa, Blood, 2007). But the contribution of the necrotic cell death by the mutated NLRP3 to CAPS pathophysiology has not been elucidated yet. Recently, long-term effect of anakinra on CAPS patients has been reported. In this review talk, I will discuss what role IL-1 β plays in the pathophysiology of CAPS through the clinical effect of anakinra on CAPS. In addition, I am going to present our data on the international collaboration study of NLRP3 mosaicism among NLRP3 mutation-negative CINCA/NOMID patients and try to discuss the pathophysiology of CAPS based upon the fact that the somatic mosaicism can cause the CINCA/NOMID.

S3-6

Mechanisms of inflammation in adult autoinflammatory diseases

Hiroaki Ida

Division of Respiriology, Neurology, and Rheumatology, Department of Medicine, Kurume University School of Medicine, Fukuoka, Japan

Autoinflammatory disease is characterized by 1) the episodes of seemingly unprovoked inflammations, 2) the absence of high titer of autoantibody or auto-reactive T cell, and 3) the inborn error of innate immunity.

Main adult autoinflammatory diseases are Familial Mediterranean fever (FMF) and TNF receptor associated periodic syndrome (TRAPS) in Japan.

FMF is an inflammatory disorder caused by activation of inflammasome via *MEFV* mutation. Recently, the incomplete type of FMF, such as *MEFV* exon3 variants is reported and came to the front.

The pathogenesis of TRAPS has not been determined yet. Recent study demonstrated that the activation of MAP kinase cooperates with NF- κ B signaling leading to persistent inflammation.

Nakajo-Nishimura syndrome, which was characterized by recurrent fever, partial lipodystrophy, joint contracture, steroid responded skin eruption, calcification of basal ganglia, persistent inflammation, and hyper gamma globulinemia. This syndrome is an autosomal recessive inheritance disorder and was first reported in 1939. Recent advances in genetics and molecular biology have proceeded our understanding of the pathogenesis of this disease.

In this meeting, I focus the three adult autoinflammatory diseases, and I discuss with the mechanisms of inflammation about these diseases.

S4-1

The variety of Biologic DMARDs and their risk of surgical infection

Naoki Ishiguro, Toshihisa Kojima

Department of Orthopedic Surgery Nagoya University, School of Medicine

TNF inhibitors have been approved for clinical use for more than 7 years in Japan and have entirely changed the goal of RA therapy. Currently, three TNF inhibitors are available in Japan. Two are monoclonal antibodies (infliximab, adalimumab) while one (etanercept) is a soluble receptor fusion protein. Their efficacy in RA is considerably similar among these products across many trials. Consequently, it has been shown that these TNF inhibitors substantially retard or abrogate radiographic progression. Tocilizumab, a monoclonal antibody directed against IL-6 receptor, is approved and widely used in clinical practice in Japan. It is remarkably effective in RA

patients with an inadequate response to MTX and/or TNF inhibitors. Efficacy of Tocilizumab is almost similar to that of TNF inhibitors. Abatacept (CTLA4-Ig) is recently approved in Japan and increasingly employed in the treatment of RA, particularly after TNF blockade. The mechanism of action of abatacept may induce the T cell anergy by prevention of the two signal stimulations (TCR and CD86/86-CD28) that are required for activation of T cells. A variety of adverse events are now recognized with reactivation of latent tuberculosis, other pulmonary infections, interstitial pneumonia, soft tissue and joint infections, concerns for lymphoma, solid malignancy. AE can exist in an individual patient at surgical intervention depend on the patients back ground and drugs including biologics and steroid. Risk/benefit trade-offs need to take into account to make decisions of surgical intervention such as joint replacement. The post-operative infectious rate in joints replacements with biologic were under discussion. The several reports showed different results. The surgeon who will undertake the joint replacement should consider the methods to facilitate intimate informed discussion with patients.

S4-2

Timing of the orthopaedic surgery for RA patients using biologic agents

Keiichiro Nishida¹, Tomoko Kanazawa², Ryuichi Nakahara², Kenzo Hashizume², Yoshihisa Nasu³, Taichi Saito², Toshifumi Ozaki²

¹Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, ²Department of Orthopaedic Surgery, Okayama University Hospital, ³Department of Orthopaedic Surgery, Kurashiki Kosai Hospital

Biologic agents exhibit strong anti-inflammatory property and inhibitory effect against joint destruction of rheumatoid arthritis (RA). Early intensive management using these drugs made clinical remission or bio-free remission a realistic goal, with recent revision in dose limitation of methotrexate to match the level of foreign countries. However, biologic agent is not always effective for RA with high disease activity, and cannot be used for some population of patients who experienced adverse events, or have risk factors of these events. Some patients cannot use biologic agents for economic reason, and other patients already show severe joint destruction or irreversible disability in physical function at the introduction of biologic agent. For these patients, surgical intervention is still necessary as an adjuvant therapy.

We retrospectively investigated a total of 887 elective orthopaedic procedures for RA performed between April 2004 and December 2010 at two centers (Okayama University Hospital and Kurashiki Kosai Hospital). 128 procedures have been done in patients using biologic agents. The yearly number of these cases has been increasing, including total joint arthroplasty (44 procedures) and foot plasty (23 procedures). Basically, the operation is withheld for three months after introduction of biologic agents, and treatment by biologics is interrupted before surgery and restarted 1-2 weeks after the procedure, on the balance of the safety of the surgery and control of disease activity. Introduction of biologic agent takes precedence over surgery when healing of the joint can be expected, but surgery may be indicated before biologics for the joint with irreversible functional damage. Surgical intervention might be required for the joints with progressive destruction and/or with insufficient effects of biologics. In this symposium, based on the review of our cases, we discuss the indication and timing of the surgery for RA patients using biologics.

S4-3

Early Assessing of Postoperative Infection in Patients with Rheumatoid Arthritis Treated with Biological Agents

Jun Hashimoto

NHO Osaka Minami Medical Center

For early detection of surgical site infection (SSI), the surgeons assess the laboratory test such as CRP, ESR and WBC count, fever and local symptoms and signs such as swelling, warmth, redness and pain. These could be, however, influenced by the disease activity of rheumatoid arthritis (RA) and so the diagnosis of postoperative infection in patients with RA is often difficult. To the matter more difficult, oral medication used quite frequently for treatment of RA such as glucocorticoid and methotrexate could also modify both laboratory and clinical findings. Moreover, recently frequently used biological DMARDs could also strongly influence these findings used for the early detection of SSI. Therefore, it is growing more important issue how we should do for the early detection of SSI in patients with RA. But, we have to recognize that the successful tight control of RA with biologic/nonbiologic DMARDs eliminate the influence of disease activity of RA on the local findings and laboratory data used for the early detection of SSI. So, we have to become skilled in early diagnosis of SSI in case of tightly controlled RA. On the contrary, it could remain to be very difficult to detect the SSI in case of RA insufficiently controlled with biologic DMARDs. It might be also very difficult to assess SSI adequately in patients with disease flare-up of RA due to postponing administration of biologics for the sake of elective surgery. It is the one of reasons why we, orthopaedic surgeons, must verify the benefit and risk of postponing administration of biologics for the sake of elective surgery.

On the other hand, it is ideal that we have the tool for the early detection of SSI never influenced by either of the disease activity of RA, glucocorticoid and biologic/nonbiologic DMARDs. Nishino J (2010) has already reported the usefulness of neutrophil CD64 expression in the diagnosis of local infection in patients with RA, and its coming into wide use is awaited.

S4-4

Histological analyses of synovium in RA treated with/without biological drugs.

Yuichi Mochida¹, Katsushi Ishii¹, Kengo Harigane¹, Yasushi Akamatsu², Naoto Mitsugi², Yuichiro Yamaguchi³, Tomoyuki Saito³

¹Center for Rheumatic Diseases, Yokohama City University Medical Center, ²Department of Orthopaedic Surgery, Yokohama City University Medical Center, ³Department of Orthopaedic Surgery, Yokohama City University School of Medicine

Objective: We evaluated histological findings of synovial tissues in rheumatoid arthritis (RA) patients treated with/without biological drugs.

Materials and methods: Fifty-four RA patients who underwent orthopaedic surgery were divided into two groups. Twenty-six patients treated with biological drugs (Group B) were compared with 27 patients treated with non-biological drugs (Group C). In group B, etanercept, infliximab, tocilizumab, and adalimumab were administered to 9, 8, 2 and 2 patients respectively. The synovial tissues obtained during surgeries were assessed using scoring system by Rooney et al., which are composed of 6 histological features: synovocyte hyperplasia, fibrosis, proliferating blood vessels, perivascular infiltrates of lymphocytes, focal aggregates of lymphocytes, and diffuse infiltrates of lymphocytes.

Results: The scores of focal aggregates of lymphocytes and total score in group B were lower than in group C. The other features,

proliferating blood vessels and perivascular infiltrates of lymphocytes, also showed relatively lower scores in group B.

Conclusion: Our findings suggested that biological drugs have suppressive effects on focal aggregates of lymphocytes and total Rooney's score.

S4-5

Surgical site Infections in rheumatoid patients receiving biological agents

Toshihito Mori, Takuo Juji, Kimio Masuda, Mitsuyasu Iwasawa, Hiroshi Takamura

Department of Orthopedic Surgery, NOH Sagamihara Hospital, Sagamihara, Japan

Objective. To identify risk and surgical site infection (SSI) rate in patients with rheumatoid arthritis (RA) who had undergone elective orthopedic surgery with special attention for biological agents.

Methods. Preoperative and late surgical site infection (SSI) in patients with RA who had undergone elective orthopedic surgery was studied.

Results. A total of 1153 procedures were performed for the rheumatoid patients in our hospital between January 2005 and December 2010. Ninety-nine procedures (8.6%) were performed on patients who used Biological agents. Biological agents were stopped perioperatively. Early deep SSI occurred in 1 patient who had undergone total hip arthroplasty (THA), and 1 patient who had undergone total elbow arthroplasty (TEA). Patients that had early SSI did not use Biological agents. Early deep SSI rate were 0 % (0/375), 0.7 % (1/140), and 0.8% (1/126) after TKA, THA and TEA, respectively. Early SSI did not occur in patients who used Biological DMARDs. Use of Biological agents was not associated with an increase in early SSI rates. Late deep SSI (prosthetic joint infection) occurred in 4 TKAs, 1 THA and 1 MP Arthroplasty during the same period. Late deep SSI occurred in 2 TKAs secondary to sepsis after the introduction of Biological agents.

Conclusion. Our study shows that early SSI rates in RA patients after elective orthopedic surgery are very low. Perioperative management is an important issue in the general care of patients with RA. Patients who used Biological agents do not seem to be a strong risk factor for SSI. Discontinued perioperative use of Biological agents seems to be a standard management for patients with RA who had undergone elective orthopedic surgery. Late SSI is a big concern for patients with RA who had underground multiple surgeries and used Biological agents.

S4-6

Influence of the biologics to the postoperative rehabilitation for RA patients

Ryuichi Saura¹, Kazunari Tanaka¹, Haruki Nakano^{2,3}, Michiaki Takagi^{2,3}, Isao Matsushita⁴

¹Department of Rehabilitation Medicine, Division of Comprehensive Medicine, Osaka Medical College, Osaka, Japan, ²Department of Orthopaedic Surgery, Yamagata University, Yamagata, Japan, ³Rehabilitation Unit, Yamagata University Hospital, Yamagata, Japan, ⁴Department of Orthopaedic Surgery, Faculty of Medicine, Toyama University, Toyama, Japan

Protraction of RA induces the disorders of joint function such as contractures and deformities. 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. In present, surgical treatments for RA patients succeed in the functional recovery of the deteriorated joints

and restoring the ability of ADL. However, there are some difficulties in terms of the postoperative rehabilitation for RA patients. The dysfunction of joint on contra- or ipsi-lateral side of treated joint in lower extremities might affect the progression of program due to the contracture and the pain on motion. Also, problems in upper extremities might disturb the transference in ADL and the ambulation with partial weight bearing by crutches. 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 biologics, the problems confronting the execution of rehabilitation might be reduced. It is also 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. These results might suggest that the preoperative exercise in combination with biologics let the RA patients execute the postoperative one more easily. However, even if RA patients have achieved their clinical remissions by biologics, joint destruction might progress rapidly by overuse of that joint when it had been damaged beyond the moderate stage. It seems that similar troubles such as tendon rupture during exercise may be observed in upper extremities. In conclusion, it must be emphasized that both the execution of more prudent postoperative and preoperative exercise are very important even in the time of biologics mainly used for the treatment of RA.

Current Symposium

CS1-1

The assessment of RA patients using FDG-PET

Koichi Okamura¹, Yukio Yonemoto¹, Kimihiko Takeuchi^{1,2}, Masatoshi Matsushita², Tsuyoshi Ichinose¹, Tetsuya Kaneko¹, Tsutomu Kobayashi¹, Kenji Takagishi¹

¹Department of Orthopaedic Surgery, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan, ²Department of Orthopaedic Surgery, Iseaki Fukushima Hospital

Background Positron emission tomography (PET) with 2-[18F]-fluoro-2-deoxy-D-glucose (18F-FDG) could possibly evaluate metabolic activity of synovitis and measure disease activity in rheumatoid arthritis (RA) by whole-body imaging. 18F-FDG-PET studies are proposed to assess the metabolic activity measured quantitatively by standardized uptake value (SUV). In this study, we evaluated if the FDG uptake of the affected joints correlated with the clinical assessment of RA patients and if there were correlations between the difference of SUVs and improvement of clinical findings in the patients undergoing anti-TNF therapies. In addition, we assessed RA synovitis of shoulder joints with FDG-PET in comparison with MRI. Furthermore, we examined the relationship between FDG-PET findings and the progress of the later joint destructions.

Methods Whole-body 18F-FDG-PET were performed. Patients were scanned from the head to the toe in the arms-down position. The increased 18F-FDG uptakes in bilateral shoulder, elbow, wrist, hip, knee and ankle joints were recorded. For the semiquantitative analysis, functional images of the SUV were produced and the maximal SUV (SUVmax) was used as a representative value for the assessment. For the assessment of joint destruction, we reviewed SUV and changes of Larsen grade in RA patients.

Results The total SUVmax significantly correlated with DAS28, DAS28-CRP, ESR, CRP and RF. Δ SUV, the difference of SUVmax-sum between before and after treatment, significantly correlated with Δ DAS28, Δ DAS28-CRP, Δ ESR, Δ CRP and Δ RF, respectively. The total number of the synovitis in the shoulder joints were significantly correlated with SUV of the joints. The progress of the joint destructions significantly related to SUV.

Conclusions FDG-uptake represented by SUVs in the inflamed RA joints may reflect disease activity. FDG-PET might play an important role in the evaluation of biological treatment and the prediction of the joint destruction progress for RA.

CS1-2

MR imaging of cartilage in RA

Atsuya Watanabe

Department of orthopedic surgery, Teikyo University Chiba Medical Center, Chiba, Japan.

In recent years, treatment strategy in rheumatoid arthritis (RA) has been dramatically improved. Early initiation of disease modifying ant-rheumatic drugs (DMARDs) and biological drugs require methods for early diagnosis and sensitive monitoring of the disease process. Blood tests can help diagnose arthritis, monitor treatments, and track disease activity, however, it could not evaluate the specific joint status in RA. magnetic resonance (MR) imaging may be important in detecting early disease manifestations in joints such as inflammatory changes in the soft tissues and bone. However, conventional MRI could not quantify the change in joints associated with RA. Several qualitative MR imaging techniques have been developed to monitor the cartilage matrix status. Transverse relaxation time (T2) mapping is sensitive to the integrity of the collagen network structure, collagen concentration, and water concentration in

cartilage. As collagen is one of the major solid constituents of articular cartilage, monitoring collagen status with T2 mapping is useful for determining the quality and function of cartilage. T2 mapping was used in numerous studies that involved mainly degenerative cartilage associated with osteoarthritis (OA), and they may also have the potential to assess the cartilage matrix status in RA patients. As deterioration of cartilage is observed from the early stage of RA, and it affects prognosis of joints, T2 mapping can be an ideal marker for monitoring disease activity and joint damage in RA. In this presentation, the ability of T2 mapping to evaluate the cartilage damage and the characteristics of cartilage degeneration in RA are discussed.

CS1-3

Evaluation of rheumatoid arthritis using musculoskeletal ultrasound

Yoshiaki Ishigatsubo

Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine.

Musculoskeletal ultrasound (MSUS) has been demonstrated to be more sensitive than clinical assessment in the detection of joint swelling, and more sensitive than conventional radiography in the detection of bone erosions.

According to our survey by questionnaire, rheumatologists have increasingly incorporated MSUS technology into their practices and research during the last few years in Japan.

Grey scale ultrasound is more accurately and objectively in assessing synovial thickness, effusion and bone erosion than clinical assessment. Power Doppler ultrasound has proved to be a feasible tool for evaluating the degree of inflammation of synovial tissues (active synovitis). It is therefore useful to evaluate the disease state of RA by MSUS for making early diagnosis and understanding the course of the disease correctly. It's also useful for detection of ruptured tendon, edematous nerve, and crystal deposits in the joint with gout and CPPD disease.

Recently, the utility of a power Doppler has been focused for its ability to predict joint destruction. The above including our cases will be discussed.

CS1-4

Radiographic examination for diagnosis and evaluation of rheumatoid arthritis

Isao Matsushita, Hiraku Motomura, Eiko Seki, Tomoatsu Kimura

Department of Orthopaedic Surgery, Faculty of Medicine, University of Toyama

Radiographic examination is an important tool to perform diagnosis and to assess therapeutic efficacy in rheumatoid arthritis (RA), and is a gold standard among various imaging modalities. Plain X-ray examination at early stage may show soft tissue swelling and bone atrophy around joints. Pocket erosion in bear areas, joint space narrowing and roughness of subchondral bone are detected at progressive stage in RA. At the end stage, joint deformity and ankylosis may be observed. It is now also known that radiographic repair could be recognized under good therapeutic control. Critrias of Steinbrocker and Larsen has been useful to evaluate radiographic progression of joint damage in RA. Larsen method judges joint damage by 6 grades (0-V) employing standard films and is appropriate to assess the damage of large joints. Modified total Shrap score is useful method for detecting a small structural change in joint. However, only small joints in hand and feet, not large joints, are assessed by this scoring system. We developed ARASHI scoring system for evaluation of large joint damage in RA. This scoring system

has status and change score s. Status score shows condition of joint damage, and is well-related to Larsen grade. Change score indicates progression or repair of joint damage. The detail of large joint destruction can be evaluated using this scoring system. We hope that this scoring system will become a useful evaluation to prevent the progression of joint damage in RA.

CS1-5

Current and future role of computed tomography in rheumatoid arthritis

Hideharu Sugimoto, Waka Nakata

Department of Radiology, Jichi Medical University School of Medicine

Inflammation of articular and periarticular tissues is the hallmark of RA. In the 2010 RA classification criteria, to classify as 'definite RA' is based on the confirmed presence of synovitis in at least one joint, rather than the detection of bone erosion or cortical decalcification in the former criteria. However, skeletal destructions are the key to the diagnosis and assessment of long-term prognosis in RA. This presentation is aim to re-acknowledge the potential role of CT scan in RA.

In RA, not only may skeletal tissues be involved at juxtaarticular and subchondral sited as marginal erosion, but also there is an evidence that RA effects on bone remodeling that affect the entire skeleton as generalized osteoporosis. Further, CT has been used to validate marginal erosion detected by MR imaging and US. It has also been used to investigate generalized axial osteoporosis by means of QCT.

Although, marginal erosion is not a specific finding of RA, small erosions could be observed in healthy individuals and RA patients, whereas lesions >1.9 mm in diameter were highly specific for RA. Marginal bone erosion is still recognized as an important finding in the 2010 RA criteria, and is described as follows; those with erosions typical of RA are deemed to have prima facie evidence of RA and can be classified as such.

MR imaging and US can detect erosion. However, sensitivity of these modalities is limited compared to CT. Actually, erosions detected by CT are considered to be reference standard to evaluate diagnostic accuracy of erosion in these modalities. There are, however, few study on coherence in between MR/US bone erosion and CT erosion.

A variety of therapeutic agents are involved in the control of bone remodeling. They include osteoprotegerin, anti-LANKL ligand antibody, and cathepsin K. To assess therapeutic effect of these agents, CT may be used to evaluate bone formation and improvement of osteoporosis.

CS2-1

The window of opportunity for drug therapy and surgical intervention for RA

Daisaku Tokunaga, Ryo Oda, Toshikazu Kubo

Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine

Recent developments in drug therapy with methotrexate and biological agents have provided great benefit to patients with rheumatoid arthritis (RA) by reducing joint inflammation and pain. In the recommendations for achieving optimal therapeutic outcomes in RA published in 2010, it is stated that the primary target for treatment of rheumatoid arthritis should be a state of clinical remission, in the strategy of ten treat to target (T2T) activities. In order to alter the natural history and accomplish remission of the disease, early diagnosis and aggressive therapy during the 'window of opportunity' is

necessary. The surgical therapy for rheumatoid arthritis has therefore been changed both quantitatively and qualitatively. The numbers of the patients who require surgical therapy decreases with age. However, for the patients with established joint destruction and for those who are not able to undergo radical drug therapy, surgical therapies should be recommended. In addition, biological agents do not necessarily induce remission of the disease. Despite the fact that adequate disease control is often established by biological agents, some cases show rapid joint destruction of limited area of joints, especially in the hands and weight bearing joints. In fact, the rapid improvements in the quality of life and ability of daily living due to the pharmacotherapy may further increase the load on the already fragile joint, resulting in the aggressive joint destruction. Therefore, careful evaluation of not only parameters such as DAS28, CDAI and SDAI, but also close evaluation of each joint, should be performed. Currently, total hip arthroplasty is often performed for patients with RA. It is desirable to plan surgery before shortening of the lower limb by joint destruction and bone loss of the acetabular joint. It is therefore of high importance to determine individual articular prognoses, and to implement an appropriate surgical plan for individual patients.

CS2-2

Significance of Hip Surgery for RA Patients in the Era of Biologics Therapy

Naoto Mitsugi¹, Kengo Harigane¹, Katsushi Ishii¹, Yuichi Mochida¹, Naoya Taki¹, Yuichiro Yamaguchi², Tomoyuki Saito², Izumi Saito³, Shigeki Momohara⁴, Kosei Kawakami⁴, Katsunori Ikari⁴

¹Yokohama City University Medical Center, Yokohama, Japan,

²Dept. of Orthopaedic Surg., Yokohama City University School of Medicine, ³Yokohama Municipal Hospital, Yokohama, Japan, ⁴Institute of Rheumatology, Tokyo Woman's Medical University, Tokyo, Japan

(Backgrounds) Biological agents therapy provides great benefit to rheumatoid patients. In Europe and United States, there are several reports of decreasing in rates of orthopedic joint surgery for rheumatoid arthritis. Although, in Japan, decrease of some kind of surgery for example knee synovectomy was reported, it is uncertain whether total numbers of orthopedic surgery for rheumatoid arthritis decrease or not. In this study, it will be investigated for hip surgery for rheumatoid arthritis in the age of biologics therapy.

(Material and Methods) Rheumatoid Patients who underwent THA in Yokohama City Universal Medical Center and Institute of Rheumatology, Tokyo Woman's Medical University were analyzed. The patients were classified into a biologics therapy group and non biologics group. Complication of surgery, periods of hospitalization, course after surgery were examined.

(Results) The total numbers of yearly THA were stable from 2000 to 2010. The numbers of the patients who underwent THA with biologics therapy was 17. In this group, there was no findings of surgical site infection and delayed wound healing.

(Discussion) There was no decrease in total numbers of rheumatoid hip surgery. In this study, There is no surgical complication in THA with biologics therapy. Since the sample size was small, it is necessary that bigger sample study should be performed.

CS2-3

Mid term results of total hip arthroplasty in patients with rheumatoid arthritis

Shu Saito

We reviewed 58 cementless total hip arthroplasties (THAs) in 39 patients with rheumatoid arthritis (RA) at an average follow-up of 9.6(5-18) years. Preoperatively, 19 joints had a protrusio acetabuli of grade I or higher (Sotelo-Garza-Charnley classification). We reconstructed THA in cases with protrusio acetabuli with morsellized and sliced autologous bone grafts from the femoral head. Postoperatively, 29 joints were rated excellent; 23, good; 6, fair (Harris hip score). There was no thigh pain and deep infection. There was an intraoperative fracture of the femur in one joint. Radiography showed that the acetabular component was stable in 56 joints, and possibly unstable in 2 joints. The femoral component was bone-ingrown in 54 joints, and stable fibrous in 4 joints. Postoperatively, we observed dislocation in 4 joints, and disuse atrophy of the femur in 4 joints. There were no clear signs of loosening, migration or osteolysis at an average follow-up of 9.6 years and no patients required revision surgery. These results indicate that the cementless THA had excellent mid-term outcome and the current method with morsellized and sliced autologous bone grafts is extremely useful in cases with protrusio acetabuli in hip joints for the treatment of RA.

CS2-4

Selection of Components in Total Hip Arthroplasty for Rheumatic Patients

Hideo Okumura, Norikazu Takeda, Kenzou Fuse, Kenji Matsumoto
Orthopaedic Surgery, Rakuyo Hospital, Kyoto, Japan

The treatments of rheumatic patients have been much improved by development of biological drugs, and the destruction of the joints has been prevented. However, total hip arthroplasties (THA) are necessary in the patients with severely destructed hip joints. The clinically affected factors of THA for rheumatic patients are infection under immune abnormality, steroid administration, osteoporosis, muscle weakness and dislocation. Many components have been developed and useful. Each component has each characteristic. Two points of view are there, quality of bone tissue and complications in the selection of components.

Selection of components according to quality of bone tissue : Common THAs have been done in the almost normal and not destructed hips. The most important thing is initial fixation of the component in both cement fixation and cementless fixation. In the case of cement fixation, the cement technique must be sufficiently practiced. Pressurizing of cement is especially important. Flange socket in acetabulum and the stem with smooth surface in femur must be selected. In the case of severely destructed hip joints, some support rings or KT-plate must be used. In the case of very thin cortical femur, impaction bone grafting and the stem fixed with screws are useful.

Selection of components according to complications : Antibiotic-contained cement is useful for the prevention of infection. To prevent the dislocation, the components with thin neck and the stem with large offset must be used. Cross-linked polyethylene and large head are useful in the prevention of dislocation.

Summary : Detailed preoperative planning and careful selection of component are very important in total hip arthroplasty for rheumatic patients. The components must be selected according to quality of bone tissue and complications.

CS2-5

Methods for reconstruction in THA revision using allograft bones on rheumatic joints

Naonobu Takahira¹, Katsufumi Uchiyama², Kensuke Fukushima², Tadashi Kawamura², Mitsutoshi Moriya², Masashi Takaso², Moritoshi Itoman³

¹Department of Rehabilitation, Kitasato University School of Allied Health Sciences, Kanagawa, Japan, ²Department of Orthopaedic Surgery, Kitasato University School of Medicine, Kanagawa, Japan, ³Kyushu Rosai Hospital, Fukuoka, Japan

【Acetabular side】 In THA revisions, restoring bone defects on the damaged acetabulum is required to ensure strong primary fixation to host bone. Itoman classification characterizes bone loss on the acetabular side: Type A (lateral defect) includes osteoarthritis of the hip secondary to dysplasia, rapidly destructive coxarthrosis (RDC) and loosening of the artificial joint. Type B (central defect) includes protrusio acetabuli in rheumatoid arthritis (RA) and central migration of hemiarthroplasty. Type C (cranial defect) includes RDC. Type D (cranio-central defect) includes loosening of the cemented cup or high hip center cup, or progression of RA bone destruction. It is important to determine the exact location and extent of bone loss prior to surgery and reconstruct the hip joint center position at the original site. Type B and C allow reconstruction with allograft bone using a support ring. Type D utilizes the addition of strut screws.

【Femoral side】 Reconstruction of the femur requires different allogenic bone depending of the degree of bone loss. Gustilo classification is used to categorize bone loss into Types I-IV. Defects are classified by degree of bone loss and loosening. Gustilo Types I, II or unclassified cases allow the use of morsellized allogenic grafts or chipped bone to fill defects. Type III allows cortical struts to be employed at the site of calcar defect. Type IV also allows reconstruction with a segmental cortical allograft.

Drawbacks of allogenic grafting include a longer time compared with autologous bone for incorporation and firm initial fixation, the need for bone banking, and transmissible disease risk. Benefits include securing of bone stock and a priori preparation of necessary amounts of bone.

CS2-6

Hybrid THA after the operation to rheumatoid arthritis

Tamotsu Okuaki, Kazuaki Tsuchiya, Toshinao Fukuda, Masato Sonobe, Tatsuro Sakurai, Toru Suguro

Department of Orthopaedic Surgery, Toho University School of Medicine

Occasions to perform THA for hip disorder in RA are not infrequent. We used hybrid THA to RA. In this study, we report our consideration of cases which were more than ten years post-operation. The subjects were 54 cases/79 joints who had hybrid THA for hip disorder of RA since 1992, and the average age at operation was 63.2 years. The average follow-up term was 17 years and 4 months. Clinical evaluation of these cases was made by JOA Score, and radiological evaluations were made, on the socket side by the change of the abduction angle with time with and without bone transplant and by the frequency of occurrence of clear zones by Delee's method, and on the stem side by the relationship between the cementing technique and the grade and by the frequency of occurrence of clear zones by Gruen's method. The JOA Score improved significantly compared to the pre-operative score. On the socket side, no significant change with time of the abduction angle was seen with or without bone transplant. The greatest occurrences of clear zones were in

zone II. On the stem side, there were more cases of cementing grade A for the second compared to the first generation cementing technique. The greatest occurrences of clear zones were in zones I and VII, and on the central side, regardless of the grade. Also, occurrences in zones III and V for grade B or lower were greater compared to grade A. Re-implantations were required in 8 joints. Causes for this included loosening, and wear of polyethylene. The survival curve by the Kaplan-Meier method with the time of re-implantation as the end point indicated 89.9% at 18 years. The long-term post-operative outcome of hybrid THA for RA was considered. Stable outcomes were obtained and it was considered that hybrid THA for RA is a useful operative procedure.

CS3-1

Prevention and control of infection under the treatment with biologics

Toshihiro Matsui

Department of Rheumatology, Sagami Hospital, National Hospital Organization, Kanagawa, Japan

Infection is one of the frequent and important complications in patients with rheumatoid arthritis (RA). Their risk of infection is increased twofold compared with non-RA subjects (Arthritis Rheum 2002;46:2287-93), and increasing age, comorbidities and use of corticosteroids are strong predictors of infection in RA (Arthritis Rheum 2002;46:2294-300). Biologic therapy has led to remarkable patient benefit in recent years; however, it also increased the risk of infection in patients with RA (JAMA 2006;295:2275-85, et al.). For the maintenance of efficient treatment with biologics, prevention and control of infection is essential.

Prevention and control of infection under the treatment with biologics in patients with RA are very important and sometimes difficult in the conditions, such as 1) screening and prevention of infection before starting treatment with biologics, 2) monitoring and prevention of infection during the treatment with biologics, 3) quick and adequate response against infection, 4) decision to resume biologics after recovery from infection, and 5) decision to resume biologics or monitoring of infection after surgical procedure. In this presentation, we summarize the data published so far and our efforts about prevention and control of infection.

We have reported the utility of neutrophil CD64 in RA as an infection marker which is less affected with the disease activity of RA itself (J Rheumatol 2006;33:2416-24, J Orthop Sci 2010;15:547-552). Neutrophil CD64 is useful for screening, monitoring, and early detection of infection and can be effective even under the treatment with tocilizumab (Mod Rheumatol 2009;19:696-7). Of course, history taking, physical examination, and education of patients and their family are more important for detection of infection; however, infection markers, such as neutrophil CD64, should be more utilized as a supportive tool for monitoring and early detection of infection.

CS3-2

Pneumocystis pneumonia

Hideto Kameda

School of Medicine, Keio University

Acute-onset diffuse interstitial lung diseases (AoDILD) in patients with rheumatoid arthritis (RA) has been a serious concern, especially for those under treatment with biological agents which may affect the presentation and outcome of AoDILD. A retrospective, multi-center study of AoDILD in RA patients receiving biological agents (infliximab, etanercept, adalimumab and tocilizumab) has demonstrated the importance of *Pneumocystis pneumonia* (PCP)

among AoDILD in those patients. In that study, definite PCP was defined as patients who showed either *P. jirovecii* organisms in their respiratory samples by microscopic examination, or positive tests for both *P. jirovecii* DNA-PCR with respiratory samples and an elevated serum 1,3- β -D-glucan level above the cut-off value. And probable PCP was defined as either a positive test for *P. jirovecii* PCR or an elevated serum β -D-glucan level. Chest HRCT findings were evaluated and scored by two board-certified radiologists. The final diagnoses for 26 patients examined were definite PCP for 13 patients, probable PCP for 11, and methotrexate-associated pneumonitis in 2 patients. Definite and probable PCP cases were clinically indistinguishable. Generalized, diffuse ground-glass opacity (GGO) is the characteristic HRCT finding in patients with definite or probable PCP, which was different from our previous findings in RA patients, mostly without biologics, showing GGO distributed in a panlobular or multilobular manner. The clinical outcome was favorable by treatment with trimethoprim-sulfamethoxazole (TMP/SMX) and glucocorticoids. However, adverse events with TMP/SMX such as gastrointestinal and hematological disorders were commonly observed at an approximate rate of two-thirds in the patients. Consequently, more than one-third of the patients could not complete TMP/SMX treatment. Taking this fact and less organism burden than AIDS-PCP into consideration, a reduced dose of TMP/SMX may be sufficient for RA-PCP patients with biologics.

CS3-3

Treatment of nontuberculous mycobacteriosis

Atsuyuki Kurashima

Japan Anti Tuberculosis Association Fukujuji Hospital

TNF is an essential cytokine that confine tuberculous lesion with granuloma formation. Thus administration of TNF-blocker may lead a danger of spreading mycobacteria through the disintegration of granuloma. In Japan, 15 TB cases out of 5000 Infliximab treated cases were reported (about 15 times higher compared with general population). But attention related nontuberculous mycobacteriosis (NTM) has been focused in recent years. Okubo reported the world's first case of pulmonary *mycobacterium avium* disease with Infliximab treatment at Modern Rheumatology in 2005. Winthrop collected 105 NTM cases with TNF-blocker treatment including Japanese 12 cases from all over the world. These data reveal 9 death cases and 54% cases of extra pulmonary lesions. Today, NTM lung disease in non-compromised host has been increased in many developed countries. 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, but the distribution of them shows very differently by country. 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. The appropriate chemotherapy may become a status of certain improvement, but it needs a long period often exceed one or two years. 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 tuberculosis.

CS3-4

Epidemiology and measures of surgical site infection following arthroplasty

Toshinori Masaoka, Kosuke Kubo, Kengo Yamamoto
Dept. of Orthopedic Surgery, Tokyo Medical University

Quality of life (QOL) of the patients suffering from joint disease has been remarkably improved with development of arthroplasty and its popularity. However, there is always a risk of surgical site infection which can be considered as one of the critical complication. Because the large foreign object is inserted into the body in arthroplasty, it is obvious the operation has a high risk of the serious infection. With this in mind, we consider extreme perioperative care should be taken. The research by The Japanese Orthopaedic Association reported that operative infection rate following arthroplasty was 1.3% and listed its risk factors as follows: Sexuality (male), weight, disease (tumor), complicating diseases (diabetes, osteoporosis, immune disorders), antibiotics use within 3 months preoperatively, history of preoperative steroid injection, low in protein and/or in albumin, years of operative experience of the surgeon, type of prosthesis, use of bone cement, allogeneic bone transplantation, operation time, blood loss, allogeneic transfusion, the use of pulsing irrigation, use of double surgical suit, preoperative hospitalization period, and antibiotics infusion period after the operation. Rheumatoid arthritis is reportedly considered as one of the risk factor of arthroplasty, because it causes skin fragility, and immunosuppressive drug is used for its treatment, though, JOA research found the infection rate in rheumatoid arthritis patients was 1.4%, which was not significantly different compared to the rate in the patients with other diseases. Some studies showed TNF inhibitor raised postoperative infection rate in rheumatic patients. Currently, there has been no report reached a firm conclusion regarding TNF inhibitor effect on the infection. Since TNF- α plays an important role in infection defense, there is a concerns to the use of the inhibitor which may cause postoperative infection, and we consider further research on TNF inhibitor effect might be needed.

CS3-5

Influence of biologics for spinal surgery

Hiroshi Takahashi, Akihito Wada, Ayako Kubota, Yuichiro Yokoyama, Fumiaki Terajima, Keiji Hasegawa, Takashi Saito, Takashi Arai, Toru Suguro
Toho University School of Medicine, Department of Orthopaedic Surgery

Objective

In recent years, biologics such as TNF- α inhibitors (infliximab and etanercept) and an IL-6 receptor antibody (tocilizumab) have been used to treat rheumatoid arthritis (RA). However, the effects of these biologics on postoperative complications have not been studied. Therefore, we examined complications in a group of patients after spinal surgery.

Subjects and Methods

The subjects were 59 patients with RA who underwent surgery after 2001. Among the subjects, 48 did not take a biologics, while 1 received tocilizumab and 10 took etanercept. The patient who took tocilizumab and those treated with etanercept underwent surgery on day 22 and from days 8 to 14, respectively, after the final drug administration. The same protective antimicrobial agent was administered postoperatively in all 59 patients, in accordance with our standard medication manual. Wound healing and surgical site infection (SSI) were examined in all subjects.

Results

Prolonged wound healing was observed only in the patient treated with tocilizumab. SSI was not detected in any of the 59 patients.

Discussion

The effects of biologics on postoperative complications are unclear. Prolonged wound healing observed in the patient who received tocilizumab was induced by pressure exerted on the wound site due to an unfavorable body position; therefore, the wound site was sutured again under local anesthetic and the body position was changed frequently, resulting in rapid recovery. Thus, we cannot be certain that this complication was associated with the biologics. However, the findings of the study suggest that unexpectedly few complications develop when spinal surgery is performed within an appropriate period after final biologics administration. Evaluation of data for more cases is required to confirm these findings.

CS3-6

Infection and Infecting Organisms associated with Rheumatoid Arthritis Patients-Effective Treatment and Infection Control Measures from Standpoints of Characteristics of Pathogens-

Kazuhiro Tateda

Department of Microbiology and Infectious Diseases, Toho University School of Medicine, Tokyo

It is well known that rheumatoid arthritis (RA) patients are susceptible to several infectious diseases. Particularly, RA patients receiving biologic agents, such as infliximab and etanercept, were tend to be suffered from bacterial pneumonia. Those patients were susceptible to a variety of respiratory pathogens including *Legionella* spp, *Streptococcus pneumoniae* and *Staphylococcus aureus*, in addition to *Mycobacterium tuberculosis* and *Pneumocystis jirovecii*. In this presentation, the important pathogens for RA patients will be reviewed in their bacteriological characteristics, simultaneously with effective treatment and infection control measures. Especially, topics and some pitfalls of above organisms will be briefly discussed. In addition, appearance and spreading of antibiotic resistant organisms, in particular community-acquired methicillin-resistant *S. aureus* (CA-MRSA), will be focused. CA-MRSA is known to be a cause of necrotizing pneumonia and refractory soft-tissue infections, even in healthy individuals. Other important antibiotic-resistant organisms include multiple-drug resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in patients with ventilator and post-operative situations. In particularly RA patients after operation for synthetic bones and joints, biofilm formation by bacteria is a critical factor for treatment failure and prognosis of patients. Bacteria will form microcolony on surfaces of artificial materials that frequently demonstrate tolerance to antibiotic killing effects and resistant to host anti-bacterial defenses. How to cope with biofilm-forming bacteria and prevention of biofilm is the most crucial factor for those patients with transplantation of synthetic medical devices in RA patients. Recently, the new insight was reported in biofilm research demonstrating that bacteria are communicating each other by production of small molecules named autoinducers, which enabled bacteria regulate and coordinate virulence factors expression and biofilm formation. This new critical mechanism was referred to quorum-sensing in bacteria. In this presentation, several topics of important organisms for RA patients, especially bacteriological characteristics, pathogenesis of infection and biofilm formation, in addition to effective antibacterial chemotherapy and infection control measures will be presented and happy to discuss with audiences.

CS4-1

Disease-specific iPS cells for modeling of autoinflammatory syndromes

K Megumu Saito

Center for iPS cell research and application (CiRA), Kyoto University, Kyoto, Japan

Besides for regenerative medicine, human induced pluripotent stem (iPS) cells, developed by Dr. Shinya Yamanaka, et al., are also an attractive technology for accelerate disease understanding and drug innovation. It has been difficult for investigators to perform experiments with patient-derived tissues or cells because of unavailability or poor reproducibility. However, by using iPS cells, this problem can be overcome. Now you can obtain cells for iPS-cell generation from patients at the bedside, then differentiate them into cells of interest and perform investigation at the lab bench, and finally bring the results back to the bedside. In this presentation, I will introduce our current study on disease modeling by using patient-specific iPS cells, and discuss future perspectives.

CS4-2

Rheumatoid arthritis and osteoimmunology

Tomoki Nakashima^{1,2,3}, Hiroshi Takayanagi^{1,2,3}

¹Department of Cell Signaling, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan, ²Japan Science and Technology Agency (JST), Explorative Research for Advanced Technology (ERATO) Program, Takayanagi Osteonetwork Project, ³Global Center of Excellence (GCOE) Program, International Research Center for Molecular Science in Tooth and Bone Diseases

The interaction between the immune and skeletal systems has long been acknowledged, but investigation into rheumatoid arthritis (RA) as well as the various bone phenotypes found in mice deficient in *immunomodulatory molecules* has highlighted the importance of the dynamic interplay between the two systems. This has led to the recent emergence and subsequent rapid evolution of the field of osteoimmunology. In the bone destruction associated with RA, IL-17-producing helper T cells (Th17) play a major role by inducing receptor activator of nuclear factor- κ B ligand (RANKL). RANKL stimulates osteoclastogenesis through nuclear factor of activated T cells cytoplasmic 1 (NFATc1), which is well known as a crucial regulator of immunity. In addition to cellular interactions via cytokines, the immune and skeletal systems share various molecules, including transcription factors, signaling molecules and membrane receptors. The scope of osteoimmunology has grown to encompass a wide range of molecular and cellular interactions, the elucidation of which will provide a scientific basis for future therapeutic approaches to diseases of both the immune and skeletal systems.

CS4-3

Divergent Roles of Smads in Arthritogenic T Helper 17 Cells

Mizuko Mamura

Lee Gil Ya Cancer and Diabetes Institute, Gachon University of Medicine and Science, Korea

Transforming growth factor- β (TGF- β) is a pivotal cytokine to induce interleukin 17-producing T helper cells (Th17), which play pathogenic roles in murine collagen-induced arthritis (CIA). On the other hand, TGF- β is known to be the most potent immunosuppressive cytokine to inhibit the differentiation and functions of inflammatory effector cells as well as to induce Foxp3⁺ regulatory T cells.

However, the molecular mechanisms of complex functions of TGF- β remain unknown.

We found that TGF- β receptor-activated Smads (R-Smads), Smad2 and Smad3 exerted the opposing effects on Th17 differentiation and the pathogenesis of CIA. Smad2 deficiency attenuated CIA by suppressing Th17, whereas Smad3 deficiency exacerbated CIA by enhancing Th17. Notably, Smad2 and Smad3 acted on Stat3 activation in Th17 development through distinct mechanisms despite their high homology. Smad2 bound with Stat3 to enhance transcription of IL-17A and ROR γ t, whereas Smad3 targets transcription of JAK/STAT inhibitors, such as SOCS3 and SHP1/2 to regulate phosphorylation of Stat3.

Divergent functions of Smad2 and Smad3 in Th17 regulation imply that the functional complexity of TGF- β is intrinsic to its canonical signaling pathway and R-Smads could be possible therapeutic targets for rheumatoid arthritis (RA).

CS4-4

A "two-receptor" model: integrins and growth factor receptors

Jun Saegusa^{1,2}

¹Department of Clinical Pathology and Immunology, Kobe University School of Medicine, Kobe, Japan, ²Department of Evidence-based Laboratory Medicine, Kobe University School of Medicine, Kobe, Japan

Fibroblast growth factor (FGF) and insulin-like growth factor (IGF) play important roles in the pathogenesis of rheumatoid arthritis because they have growth-promoting and anti-apoptotic effects on synovial cells, and are also involved in the angiogenesis in inflamed synovial tissue.

Integrins are a family of $\alpha\beta$ heterodimeric transmembrane molecules that mediate cell-extracellular matrix and cell-cell adhesion. Growing evidence suggests that integrins mediate signal transduction through interaction with multiple cellular or extracellular matrix ligands.

FGF and IGF act through binding to the FGF receptors (FGFR) and IGF receptors (IGFR), respectively. It had been proposed that cross-talk between "outside-in" integrin signaling and FGFR/IGFR signaling plays a critical role in FGF/IGF signaling, but the specifics of the cross-talk was unclear. By using docking simulation and mutagenesis, we found that both FGF-1 and IGF-1 directly and specifically bind to integrin $\alpha\beta$ 3. In both cases, the ternary complex of integrin $\alpha\beta$ 3-FGFR-FGF-1 or integrin $\alpha\beta$ 3-IGFR-IGF-1 was formed. Interestingly integrin-binding-defective mutants (FGFR^{R50E} and IGFR^{R36E/R37E}) showed markedly reduced ability to induce cell proliferation and migration, whereas they bind to FGFR/IGFR. Investigations on cell signaling revealed that FGF^{R50E} did not induce sustained ERK activation, and IGFR^{R36E/R37E} did not induce IGFR phosphorylation.

Taken together, our results generated an alternative evidence of the role of integrin $\alpha\beta$ 3 in FGF and IGF signaling, in which FGF-1 and IGF-1 directly bind to integrin $\alpha\beta$ 3 in addition to FGFR/IGFR on cell surface. It has been traditionally believed that the binding of FGF to FGFR or IGF to IGFR is sufficient to induce cell proliferation. However we have demonstrated that the simultaneous binding of FGFR/IGFR and integrin $\alpha\beta$ 3 to FGF-1/IGF-1 occurs during FGF/IGF signaling. We propose this novel concept as a "two-receptor" model.

CS4-5

Synovialin and Rheumatoid arthritis

Naoko Yagishita¹, Toshihiro Nakajima²

The symptoms of rheumatoid arthritis (RA) are based on the many processes; chronic inflammation, overgrowth of synovial cells, bone and joint destruction and fibrosis. To clarify the mechanism of outgrowth of synovial cells, we carried out immunoscreening using anti-rheumatoid synovial cell antibody, and cloned 'Synoviolin'. Synoviolin was highly expressed in the rheumatoid synovium, and confirmed that this molecule is one of the causative factors of arthropathy. Further analysis using gene targeting approaches showed that in addition to its role in RA, Synoviolin is essential for embryogenesis. Synoviolin deficient mice (*syno*^{-/-}) exhibited severe anemia caused by enhancement of apoptosis in fetal liver, and the results suggested that the liver is sensitive organ for Synoviolin. Next, to understand the role of Synoviolin in fibrosis, we explored the involvement of Synoviolin in liver fibrosis because of simplicity of its development. We applied the CCl₄-induced hepatic injury model to synoviolin heterozygote (*syno*^{+/-}) mice, and demonstrated that these mice are resistant to onset of liver fibrosis. This result suggests that Synoviolin is involved in not only overgrowth process of synovial cells but also fibrosis process.

CS5-1

Validation of 2010 ACR/EULAR classification criteria for RA using five cohorts

Masayoshi Harigai^{1,2,7}, Yuko Kaneko^{3,7}, Atsushi Kawakami^{4,7}, Shigeto Tohma^{5,7}, Ayako Nakajima^{6,7}

¹Department of Pharmacovigilance, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, ²Department of Medicine and Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, ³Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, ⁴Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki Graduate School of Biomedical Sciences, ⁵Sagamihara National Hospital, National Hospital Organization, ⁶Institute of Rheumatology, Tokyo Women's Medical University, ⁷The committee on the evaluation of new diagnostic criteria for RA of Japan College of Rheumatology

Advances in the treatment of rheumatoid arthritis (RA) compelled the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) to develop new, recently published, classification criteria for RA. The aim of the new classification criteria is to identify patients with newly developed arthritis for whom the risk of symptom persistence or structural damage is sufficient to be considered for intervention with disease-modifying anti-rheumatic drugs (DMARDs). In addition to those newly presenting patients, the application of the criteria to patients with erosions typical for RA or with longstanding disease was also considered and defined. The JCR committee for evaluation of the 2010 ACR/EULAR classification criteria installed a working group for cohort analysis and ordered the validation of the new criteria through an analysis of five cohorts in Japan; the SAKURA cohort from Keio University (analyzed by Y. Kaneko), the Nagasaki early arthritis cohort from Nagasaki University (analyzed by A. Kawakami), the IORRA cohort from Tokyo Medical and Dental University (analyzed by A. Nakajima), the SACRA cohort from Sagami National Hospital, National Hospital Organization (analyzed by S. Tohma), and the REAL cohort from Tokyo Medical and Dental University (analyzed by M. Harigai). Thus far, findings of these analyses have revealed that sensitivities of the new criteria were distributed from ~60 to ~80%, and specificities were ~60 to ~70%. Classi-

fication values of the new criteria are strongly affected by the inclusion and exclusion criteria, the definition of the gold standard for RA, and percentages of patients with erosions typical for RA or long-standing diseases. We have to take these conditions into account to fully evaluate the results of the validation and to apply the criteria to the clinical diagnosis of RA.

CS5-2

From expert validation group perspective - analysis summary

Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University

【Purpose】To validate the new RA classification criteria by ACR/EULAR. **【Methods】**JCR committee for validation of the new criteria by experts was organized by 10 rheumatologists in university hospitals (4), general hospitals (4) and private clinics (2), included equal numbers of internists and orthopedists. Committee members evaluated independently the 56 case scenarios established by cohort analysis group, and recorded the likelihood for RA from 1 (the least likely) to 10 (the most likely) together with the occasion to prescribe methotrexate. **【Results】**Among 56 case scenarios, 45 cases who are available to score by new/old criteria were analyzed. Those cases included 26 cases with RA as the final diagnosis, and 19 with non-RA (SLE 4, UA 4, PsA 2, RS3PE 2, SjS 2, gout, OA, PM, sarcoidosis and PR 1). 28 females and 10 males, average age 51.1 ± 15.4 years old, (21–80), disease duration was 12.4 ± 19.4 months (0.1–63 months). Sensitivity and specificity of the new criteria by the final diagnosis were 53.8% and 63.1%, whereas those of 1987 criteria were 23.1% and 63.1%, respectively. False positive cases by the new criteria were 2 SLE, one each with SjS, RS3PE, PsA and PR. Correlations between scores of the new criteria and the likelihood for RA were $R^2=0.3027$ in RA and $R^2=0.03$ in non-RA. Likelihood distributed widely among committee members, but no relationship was found between subspecialty or the hospital they belongs. Methotrexate was recommended in 48 occasions (13.8%), and the sensitivity and the specificity of this criteria for MTX use were 72.9% and 61.8%. **【Discussion】**This study was conducted using case scenario documents, thus, we should consider whether this might be relevant to the real world events or not, nonetheless, our findings indicated the new criteria are valid to apply in daily clinical settings. **【Conclusion】**New criteria can be used in daily practice in Japan, however, we should be careful that this will not certificate the diagnosis of RA.

CS6-1

Influence of organ comorbidities on therapeutic course in patients with RA.

Yoshie Kusunoki, Hirahito Endo, Shinichi Kawai
Toho University Omori Medical Center

Recently therapeutic goal of rheumatoid arthritis (RA) is a remission by useful therapeutic tools, biologics such as anti TNF therapy. But in RA patients with functional impairments needs surgery for functional recovery. Recently rheumatic medical care was done in the Rheumatic Center. We also do rheumatic medical care in the collaborative relationship that orthopedics, internal medicine are mutual as rheumatic collagen disease center in this hospital. Because some therapeutic stances for RA being different in each specialists, it is difficult to decide allotment of a role in rheumatic medical care. RA patients usually had multiple organ complications as well as orthopedic disorders. Several organ complications might influence methods and how to lead orthopedics therapy. To evaluate the complications to influence RA therapy, we analyzed the frequency of

other complications, cardiovascular disorders, respiratory disorders, and metabolic disorders using Charlson Comorbidity Index (CCI) in our hospital. Previous reports show that RA having a complication occupies higher than half in the RA patient in the department concerned, a complication need for therapy of internal medicine was found in 54% of patients with RA. It was hypertension 27.9%, diabetes mellitus 12.3%, hyperlipemia 11.7%, respiratory tract disease 7.5%, cardiovascular disease 6.6%, and malignant tumor 6.6%. Organ involvements have an influence on a function of the patient regardless of disease activity of RA by a case. We report cooperation to aim at thought patient QOL amelioration on collaborative relationship of internal medicine and orthopedics in a RA medical care system.

CS6-2

Joint replacement when using biologic agents in the patients with rheumatoid arthritis

Ayako Kubota¹, Toru Suguro¹, Masayuki Sekiguchi¹

¹Department of Orthopaedic Surgery, Toho University School of Medicine, ²Tsuchida clinic

The drug therapy for rheumatoid arthritis (RA) has dramatically improved the outcomes with the advent of methotrexate and biologics. In our hospital, the drug therapy for RA is performed in both Departments of Rheumatology Center and Orthopedic Surgery. Some reports have indicated a decrease in the number of orthopedic operations due to biologics; however, the operations which use biologics have increased at our department since 2006.

RA patients on whom the Department of Internal Medicine requests us to perform operations account for many cases of advanced bone destruction of lower extremity, such as hip and knee joints. A lot of our patients consult their physicians on their gait disturbance, and then see the orthopedic doctors. Some reports have indicated that effects of biologics to suppress the progression of bone destruction of lower extremity cannot be achieved, unless the Larsen grade is below 2 at the time of introducing biologics. It is considered that surgeries are often applied to cases where bone destruction has already progressed at the time of starting biologics.

For the purpose of improving walking ability, orthopedic doctors often give priority to lower extremity in proposing operations to RA patients. However, in recent years, there has been an increase in operations to reconstruct upper extremity function, such as total elbow arthroplasty and finger replacement arthroplasty. About 98% of the RA patients whom our department carried out surgeries while using biologics, were female. As a result of the advancement in implants, it has become possible to ameliorate worries which are peculiar to women and different from pain, such as impaired daily activities (e.g. washing face and hair) and grooming of fingers which has been given up. In addition, the RA patients, who control their disease activity well, actively participate in physical therapy, have their outcomes stabilized after the reconstructive surgeries of upper extremity. It is expected that there will be more surgical cases of upper extremity in the future.

Many female patients who account for the majority of RA patients judge female doctors as easy to talk at medical examinations and considerate in treatments. Conversely, it is assumed that female doctors, from the position of the same gender, can understand the symptoms of female patients more easily and give consideration to treatments.

Collaboration between rheumatology and orthopedic surgery is essential to achieve higher QOL among RA patients, and it is hoped that more female doctors will be active.

CS6-3

Optimizing the timely surgical intervention for RA (ortho-surgeons' perspective)

Natsuko Nakagawa

Kohnan Kakogawa Hospital, Department of Orthopaedic Surgery

As we are in the new era of the treatment of rheumatoid arthritis (RA), we cannot have any strategy without biologics. Therefore the orthopaedic surgeries for RA patients will have to evolve. We are going to talk about the timing of the surgery for RA patients, and the way of cooperation of surgeons and physicians from female's point of view. In our hospital, surgeons and physicians see RA patients in neighboring consulting room, and exchange views with each other. The consultations regarding surgeries of RA patients are one of the most important role for us. The three main purposes of surgeries for RA patients are 1) pain relief, 2) functional recovery, and 3) cosmetic improvement. Some surgeries are requested by patients themselves, others are recommended by doctors. In terms of 1) pain relief, both patients and doctors have to think about the surgical intervention in cases that the conservative treatment is no more effective. In terms of 2) functional recovery, the problem is more difficult. Planning functional recovery as a total, sometimes the orthopaedic decision of priority is required. When physicians consult surgeons about the problems of RA patients, surgeons explain to the patients the details of the surgery and the indication for it. For 3) cosmetic improvement, presumably, there are wide variability among RA patients about the its importance. Surgeons would like to improve the cosmetic standpoint for the RA patients who don't know the possibility of cosmetic improvement by surgery. In future female doctors may be more needed for the care and treatment of RA patients as most of the patients are female. Female doctors' capability must be one of the most important points for planning the surgery, the consultation for the problems of the daily life (especially life regarding female), the challenge of easy fitting splints and braces. The cooperation of physicians and orthopaedic surgeons will be also more important in future.

CS6-4

When should internists consult an orthopedist about surgery for RA patients?

Miki Murata

Rheumatic disease center, Konan Kakogawa Hospital

Most of the Japanese rheumatologists feel some difficulty to decide when to consult an orthopedist about surgical indications, joint injections, physical therapies, and prosthetics for patients with rheumatoid arthritis. Fortunately, the rheumatologists and the orthopedists in our rheumatic disease center are working together for outpatients at the same location, therefore they can consult each other easily. However, in general, it is not easy for rheumatologists to consult an orthopedist when they are not confident for surgical indications. Moreover, rheumatologists may be afraid that patients make questions about surgeries not easily answered by them. Even if rheumatologists know the basic knowledge of surgical indications including difficulty walking, severe joint space narrowing, or uncontrollable pain continuing for more than six months, they cannot match the orthopedists who made the final judge of operations. Therefore I prefer to consult a little preliminarily rather than behind. Nevertheless, rheumatologists are responsible for reducing useless or unmatured consultations to orthopedists.

The attendees will learn a lot of surgical indications from the presentations by the orthopedists in this symposium, meanwhile I will show the several cases experienced in our center, including the oper-

ated and unoperated cases with proper, unmatured, and late consultation to discuss the best timing of consultation to orthopedists.

CS6-5

Role of biological agents in total knee arthroplasty

Kazue Hayakawa¹, Hideki Date¹, Mitsuhiro Morita¹, Harumoto Yamada¹, Yachiyo Komatsu², Yuzuru Nishino², Kenichi Kato², Shusaku Fukaya², Shunji Yoshida², Kenji Nakagawa³

¹Department of Orthopedic Surgery, Fujita Health University School of Medicine, Toyoake, Japan, ²Division of Infections Diseases and Rheumatology, Department of Internal Medicine, Fujita Health University School of medicine, ³Nisshin Orido Hospital

We studied the relation between total knee arthroplasty (TKA) and BIO in this department after the appearance of BIO and examined the cooperation between the departments of internal medicine and orthopedic surgery involving BIO. In the period from 2002 until December 2010 when BIO were on the market, TKA for RA was performed on 200 knees in 148 patients in this department. The Bio introduction group consisted of 68 knees in 48 patients with Bio introduced at any time. The timing of introduction of BIO was before TKA in 23 knees (18 in the department of internal medicine and 5 in other hospitals), within one year after TKA in 12 knees (2 in the department of internal medicine, 6 in the department of orthopedic surgery and 4 in other hospitals) and more than one year after TKA in 33 knees (16 in the department of internal medicine, 10 in the department of orthopedic surgery and 7 in other hospitals). 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. 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. RA treatment in the group not administered BIO was often performed in the department of internal medicine, but this appeared to be because many RA patients were outpatients in the department of internal medicine from beforehand. Involvement of both the department of orthopedic surgery and the department of rheumatology in RA treatment is considered to be very beneficial for the patient.

CS6-6

Difference of physician's specialty and cooperation in treatment of RA

Ayako Nakajima, Shigeki Momohara, Atsuo Taniguchi, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University

It has been recognized that cooperation in treatment of rheumatoid arthritis (RA) by both internist and orthopedist is more required since the use of biologics became popular. However, there has not been a study that put focus on difference of treatment between internist and orthopedist. Institute of Rheumatology, Tokyo Women's Medical University is the institute where internists and orthopedists cooperatively treat RA patients from the beginning of its foundation. Internists and orthopedists belong to one medical office and work side by side at outpatients' clinic and ward. IORRA is an observational RA cohort study conducted in such institute.

We investigated whether there is a difference in background and treatment of RA patients among physician's specialty or gender by using IORRA database. In the survey in April 2009, the patients

treated by orthopedists were older (62.6 ± 12.0 y.o. vs 59.0 ± 13.2 y.o., $p < 0.001$), had longer disease duration (16.5 ± 9.9 y vs 12.5 ± 9.4 y, $p < 0.001$), high disease activity (DAS28: 3.4 ± 1.1 vs 3.3 ± 1.2 , $p < 0.001$) and worse physical function (J-HAQ: 0.92 ± 0.87 vs 0.67 ± 0.72 , $p < 0.001$) than the patients treated by internists. The patients treated by orthopedists were treated with corticosteroid more frequently (52.7% vs 45.2% , $p < 0.001$) but with less dose (3.8 ± 2.5 mg/d vs 4.3 ± 3.0 mg/d, $p < 0.001$) and treated with methotrexate equally (65.8% vs 67.9% , $p = 0.174$) but with less dose (6.9 ± 2.8 mg/w vs 8.2 ± 3.2 mg/w, $p < 0.001$) than the patients treated by internists. The patients treated by orthopedists reported presence of interstitial lung disease and diabetes mellitus less frequently than the patients treated by internists (2.7% vs 1.7% , 4.3% vs 3.2%), respectively. These differences detected between male physicians and female physicians were smaller than those between internists and orthopedists.

These differences seem to be the reflection of the medical condition expected in each specialty where internists and orthopedists treat RA patients cooperatively.

CS6-7

Coordination of orthopedic surgery and internal medicine to rheumatology.

Closing Remarks

Kazuko Shiozawa

Konan kakogawa hospital. Rheumatoid disease center.

I will report on the current status of female doctors. As viewed from the licensure who passed medical examination, a third is occupied by female doctors. One out of 6 doctors is female. The number of female doctors is increasing annually by 6%. Proportion of female doctors is large especially in young generations. In Japan College of Rheumatology, female doctors occupied 1,122 (12.4%) in 9,059 members, the percentage of female doctors is especially high ratio 35.8% at twenties, 23.5% at thirties, 11.3% at forties, 6.0% at fifties, 3.0% over 60 years old. In Konan Kakogawa hospital Rheumatic Disease Center, 3 of 6 rheumatic physician are female, 2 of 3 female doctors had children, so we made a rule of free night duty and emergency duty and offered good working environment under male doctor's understanding and cooperation. Rheumatoid arthritis is a multi-organ disease involving lung, kidney and others. The knowledge required for the practice in rheumatology is wide and also deep. Since female are a little more well-studied and good at gathering many knowledge than male doctors, we may say that female doctors are a good candidate for good rheumatologist. Especially female have a little more sympathy on patients as compared to male doctors, and thus they may contribute nicely to the treatment and care of rheumatic disease patients. I hope that more female doctors try to be a physician and orthopedist in rheumatology.

CS7-1

Long-term results of resection arthroplasty for rheumatic forefoot deformities

Junya Mibe¹, Yasutaka Watanabe¹, Ryouhei Kouno¹, Seiichirou Egawa¹, Hiroyuki Hattori², Kengo Yamamoto²

¹Department of Orthopedic surgery, Tokyo Metropolitan Ohtsuka Hospital, Tokyo, Japan, ²Department of orthopedic surgery, Tokyo Medical University

[purpose] Various kinds of operation methods have been reported for rheumatic forefoot deformities. Mainly we performed resection arthroplasty for the first to fifth metatarsal bone, and we present

the results.【subject and methods】We intended for 55 feet that were performed resection arthroplasty from the first to the fifth metatarsal heads until from 1993 to 2005 and were able to followed up more than five years. It was two men (3 feet), 31 women (52 feet). The age was 36-73 years old (an average of 58.5 years old), a postoperative

CS7-2

Resection arthroplasty for rheumatoid forefoot deformities

Taku Kawasaki¹, Katsuhisa Kikuchi², Noriaki Okumura¹, Naruhito Kodama¹, Yoshitaka Matsusue¹

¹Department of Orthopaedic Surgery, Shiga University of Medical Science, Otsu, Japan, ²Department of Rehabilitation, Shiga University of Medical Science, Otsu, Japan

BACKGROUND: The purpose of this retrospective study was to assess the results of reconstruction of the rheumatoid forefoot with resection arthroplasty of the metatarsal heads. The use of K-wires following resection has been reported to improve the cosmetic appearance, to simplify postoperative management, and to decrease recurrence of deformity. In this study, we report the results of resection arthroplasty without K-wires fixation.

METHODS: A retrospective study of twenty-two consecutive patients (thirty-six feet) with severe rheumatoid forefoot deformities was performed. The results of resection arthroplasty for forefoot deformities were evaluated clinically and radiologically. The average age at surgery 62.2 years old, the average of follow up after surgery was 45.6 months. 2-5th metatarsal heads were resected through a planter approach (Lelievre method). After the resection arthroplasty resected bones were corrected by bandage fixation for two weeks without transfixing by Kirshner wire.

RESULTS: In spite of the partial recurrence of toe deformity, this operation produced high patient satisfaction. No patient sought additional surgical treatment for the feet.

CONCLUSIONS: Metatarsal head resection is a simple procedure that gives long-term pain relief in most of the patients who have rheumatoid forefoot deformities. The results were satisfactory without K-wires fixation.

CS7-3

Rheumatoid forefoot reconstruction. Fusion or Swanson implants for 1 MTP joint.

Tae Hyun Lee¹, Tadashi Tsukeoka¹, Hiroaki Tsuruoka¹, Masahiko Suzuki²

¹Department of Orthopaedic Surgery, Chiba Rehabilitation Center, Chiba, Japan, ²Department of Orthopaedic Surgery, Chiba University, Chiba, Japan

Management of the patient with rheumatoid forefoot deformity requires a multidisciplinary integrated approach for a successful outcome. Despite recent advances in the pharmacological management of rheumatoid arthritis and its impact upon disease progression, forefoot deformity and pain remain common manifestations requiring input from orthopaedic surgeons. First we did fusion of the 1st MTP joints with lesser MTP joint excision arthroplasty and since 1992 used a swanson flexible hinge toe implant with or without grommet for the 1st MTP joints. A total of 115 feet with RA foot reconstructions were undergone in our department since 1983. Of those cases 30 feet were reviewed through a detailed questionnaire, clinical examination, standardized radiographs, and pedobarographic analysis.

CS7-4

Mid-term results of arthroplasty for rheumatoid forefoot deformities by a shortening oblique osteotomy

Hiroshige Sano^{1,2}, Tadamasa Hanyu²

¹Department of Orthopedic Surgery, Niigata Prefectural Tokamachi Hospital, ²Department of Rheumatology, Nagaoka Red Cross Hospital

Background: This study aimed to evaluate joint preserving procedures by a shortening oblique osteotomy (SOO) for rheumatoid forefoot deformity and their functional outcomes in the mid-term. **Method:** Fifty-one feet in 37 patients who had rheumatoid arthritis were observed after an operation on the forefoot that included a SOO of the metatarsal neck of the lateral toes. In addition, patients underwent either flexible hinge toe implant arthroplasty, Mitchell's osteotomy or desis in the first metatarsophalangeal joint. **Results:** American Orthopaedic Foot and Ankle Society (AOFAS) score improved from 32.4 points pre-surgery to 74.7 points at the latest follow-up. At the follow-up, 57% patients were pain-free, 78% patients wore off-the-shelf shoes. The mean HVA decreased significantly from 37.7 degrees to 16.5 degrees postoperatively. M1M2 angle and M1M5 angle also decreased postoperatively. Recurrence of callosities with moderate pain occurred in 7 feet, bony ankylosis at metatarsal joint in 4 feet, delayed union at osteotomy site in 1 foot and infection in 2 feet. **Conclusion:** As shown in this series, the improvement in deformities, function, and cosmesis of metatarsophalangeal joint preservation was satisfactory in SOO. Because of the development of combined drug therapy, the benefits of synovectomy, osteotomy, and shortening in length should be reconsidered. The author's study suggests that the shortening oblique osteotomy should be considered one of the surgical reconstruction options for patients with rheumatoid arthritis who have forefoot deformities.

CS7-5

Metatarsal shortening oblique osteotomy for rheumatoid forefoot deformities

Isao Nakasone¹, Shigeki Sekiya², Kazumasa Hayashi¹, Kazutoshi Sakaeda¹, Hiroya Sakai¹

¹Department of Orthopaedics Surgery, Saitama Medical Center, Saitama, Japan, ²Department of Orthopaedics, Sekishindo Hospital

Background: The purpose of the present study was to assess the results of metatarsal shortening oblique osteotomy for rheumatoid forefoot deformities.

Methods: Thirty-four feet in 23 patients with rheumatoid forefoot deformities for which a shortening oblique osteotomy of the metatarsal neck of the lateral toes was performed between 1998 and 2010 were examined for an average of 58.7 months (range, 5-156 months) after surgery. There were 19 women (30 feet) and 4 men (4 feet) with a mean age at surgery of 59.1 years (44-79 years). For the deformity of the great toe, resection arthroplasty or modified Mann osteotomy was performed. Postoperatively, the MTP joints of lateral toes were temporarily fixed by K-wires. K-wires were removed at 3 weeks, since when full weight bearing with insole was allowed. American Orthopaedic Foot and Ankle Society (AOFAS) score was used for the clinical assessment, and radiological assessment was done according to modified Sharp score, excluding the score in hand, the first MTP joint and IP joint.

Results: The average of AOFAS score was improved from 32 points preoperatively to 79.7 points postoperatively. The average of modified Sharp score was improved 20.8 to 16.5 points.

Discussion: Resection arthroplasty for rheumatoid forefoot deformities have been commonly done for these feet. However, treatment of

rheumatoid arthritis has improved with the introduction of disease modifying anti-rheumatic drugs and biological agents, which are recently reported to bring about the repair of bony erosion and the improvement of subchondral bone structure, which encourages us to perform joint preservation surgery.

Conclusion: Metatarsal shortening oblique osteotomy for rheumatoid forefoot deformities produced successful clinical and radiological results. This procedure was considered beneficial for the deformities of the forefoot in patients with rheumatoid arthritis.

CS7-6

Radiological issues after joint-preserving surgery against RA forefoot deformity

Makoto Hirao¹, Kenrin Shi¹, Hideki Tsuboi², Akihide Nampei³, Hideki Yoshikawa¹, Jun Hashimoto¹

¹Department of Orthopaedics, Osaka University Graduate School of Medicine, ²Dept. of Orthopaedics, National Hospital Organization Osaka Minami Medical Center, ³Dept. of Orthopaedics, Osaka Rosai Hospital

With progression of RA drug therapy, the importance of joint-preserving surgery against forefoot deformity has been recognized in recent years. We also preserve MP joints since 2000, however some issues occur including ankylosis of MP joint, non/mal-union in bone cutting site, and recurrence of the dorsal displacement. In this study, the frequency of such failures was surveyed. Thirty one cases of joint-preserving surgeries (shortening osteotomy in II-V metatarsal bone) were evaluated (21: proximal shortening osteotomy in 1st metatarsal bone, 10: distal one). In these cases, non union was occurred in 4 cases, recurrence of the displacement was in 1 case, and ankylosis of MP joint was in 3 cases. To avoid ankylosis, now we are shortening the duration of joint fixation after surgery.

CS8-1

Risk and benefit of Joint Surgery for the patients with rheumatoid arthritis

Toshihisa Kojima, Masatoshi Hayashi, Koji Funahashi, Daizo Kato, Hiroyuki Matsubara, Naoki Ishiguro

Department of Orthopedic Surgery, Nagoya University School of Medicine, Nagoya, Japan

Rheumatoid arthritis causes joint distraction, followed by loss of physical function and mental distress, such as depression. Joint replacement therapy can improve function of damaged joints and control local inflammation in the joints. The patients with progressive disease need systemic control and recovery of damaged joint function by surgical procedures. Now, we will show the combined beneficial effects of drug therapy and surgical procedure. What kind of patient needs the surgical procedures? About 30 % of the patients with surgical procedures in our department were treated with biologics. Half of the patients with arthritis in knee joints at the initiation of biologics have damaged (Larsen III-IV) joints. In these patients, during 1.5 years, the damaged knee joints needed joint replacement surgery while 15 % of not damaged joints (Larsen 0-II) needed surgery during 3.0 years. Summary of the profile for the patients who need surgical procedures are following; The patients have damaged joints, 1) Without sufficient systemic control of inflammation, caused by insufficient response to the treatment or other complications in kidney, lung and so on. 2) With good control of systemic inflammation and only one or two active arthritis in damaged large joint (knee hip, elbow) The patients in category 2), could reach very good condition (remission or low disease activity) after the operation. Recovery from surgical intervention in patients treated with

biologics was better than in those treated with other DMARDs. Deep infection of prosthesis is one of the most important complications. It has been reported that the biologics could be risk factor for the infection. However, the rate of infection is about 1 %, Therefore, precise assessment of the risk should be very difficult. Surgical procedure should be indispensable for the patients with established and progressive disease. Risk management of surgical procedures should be needed to maximize their beneficial effects.

CS8-2

Perioperative medication management for patients with rheumatoid arthritis

Masayoshi Harigai^{1,2}, Kaori Watanabe^{1,2}

¹Department of Pharmacovigilance, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, ²Department of Medicine and Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University

A new therapeutic strategy and biological disease-modifying anti-rheumatic drugs (biologics) have significantly improved functional outcomes of rheumatoid arthritis (RA) patients. Most RA patients, however, have to continue their RA medications and may receive various surgical procedures during their clinical course. In these cases, the proper management of medications, including methotrexate (MTX), biologics, and corticosteroid (CS), are necessary. Several randomized clinical trials (RCTs) and cohort studies with an appropriate comparator group have been conducted to assess the safety of MTX in the perioperative period. A systematic literature review (SLR) revealed no association of MTX use with increasing risk of surgical complications, but a significant association with fewer RA flares (Clin Exp Rheumatol 2009). Other studies also support the lack of association between continuing MTX use in the perioperative period and risks for postoperative complications and surgical site infections. The safety of biologics in RA patients undergoing orthopedic surgery was reported in a prospective cohort study (Foot Ankle Int 2004), a retrospective cohort study (J Rheumatol 2007), and a case-control study (Rheumatol 2010). In the cohort studies, continued use of TNF antagonists was not associated with risks for complications of wound healing or surgical site infection. In the case-control study, however, TNF antagonist use was identified as a significant risk factor for surgical site infection and deep vein thrombosis; controversy remains in this research field. An SLR by Marik *et al.* on requirement of perioperative stress doses of CS in patients given long-term CS therapy (Arch Surg 2008) contained 2 RCTs and 7 cohort studies. Neither RCT revealed differences in the hemodynamic profile between patients given stress doses of CSs compared with those given their usual daily dose. The optimal management of these medications based on the latest clinical evidence will be discussed.

CS8-3

Postoperative Complications in RA relevant to the treatment with biologic agents

Masahiko Suzuki¹, Hiroshi Inoue², Satoshi Soen³, Kenji Takagishi⁴, Keiichiro Nishida⁵, Tsukasa Matsubara⁶, Yuichi Mochida⁷, Shigeki Momohara⁸, Toshihito Mori⁹, Toru Suguro¹⁰

¹Research Center for Frontier Medical Engineering, ²Inoue Hospital, Japan, ³Department of Orthopaedic Surgery and Rheumatology, Nara Hospital, Kinki University School of Medicine, Japan, ⁴Department of Orthopaedic Surgery, Graduate School of Medicine, Gunma University, Japan, ⁵Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Science, Japan, ⁶Matsubara Mayflower Hospital, Japan, ⁷De-

partment of Chronic Intractable Disease Center, Yokohama City University Medical Center, Japan, ⁸Institute of Rheumatology, Tokyo Women's Medical University, Japan, ⁹Department of Orthopaedic Surgery, Sagami Hospital, National Hospital Organization, Japan, ¹⁰Department of Orthopedic Surgery, Toho University Omori Medical Center, Japan

(Purpose) The number of orthopaedic surgery under treatments with biologic agents has been increasing in Japan. However, whether biologic agents cause the increase of postoperative complications or not is still unknown. The Rheumatoid Arthritis Committee of the Japanese Orthopaedic Association investigated the postoperative complications of rheumatoid arthritis patients in teaching hospitals. (Methods) The surveillance form about medications and surgeries in patients with rheumatoid arthritis between January 2004 and November 2008 were sent to 2019 teaching hospitals. Data was analyzed by the Rheumatoid Arthritis Committee. (Results) Biologic agents were administered to patients with rheumatoid arthritis in 632 of the 1,245 hospitals (50.8%) and 430 of the 1,245 hospitals (34.5%) required surgical intervention under treatment with biologic agents. The number of surgeries under treatment with biologic agents was 3,468 and the incidence of infection was 1.3% (46 cases). The incidence of infection was 1.0% (567 procedures) in 56,339 procedures under treatment with non-biologic disease modifying anti-rheumatic drugs. There were no significant differences between biological and non-biological treatment groups in the infection rate. In the joint arthroplasty group, the numbers of procedures under biological and non-biological treatments were 1,626 and 29,903, and the incidences of infection were 2.1% (34 procedures) and 1.0% (298 procedures) respectively. There was a significant difference between two groups. The odds ratio was 2.12 (95%CI: 1.48 – 3.03, $p < 0.0001$). (Conclusion) The odds ratio of biological treatment in joint arthroplasty was more than two-fold greater in the patients with SSI compared to those that were treated with non-biologic agents. Caution and prudence should be required for operative procedure, perioperative course, and consent in joint arthroplasty of patients with rheumatoid arthritis under biological agents.

CS8-4

The perioperative use of biologic agents in patients with RA - IORRA study-

Katsunori Ikari, Kosei Kawakami, Atsuo Taniguchi, Hisashi Yamanaka, Shigeki Momohara
Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

The appropriate use of biologic agents in rheumatoid arthritis patients in perioperative period of orthopedic surgery remains controversial. In this symposium, we will discuss the perioperative use of biologic agents in RA patients as one of the priority issues in the biologic era.

CS8-5

Biologics and RA-related surgery -A report from a nationwide database (NinJa)-

Jinju Nishino¹, Sakae Tanaka², Toshihiro Matsui³, Keita Nishimura⁴, Yuho Kadono⁵, Tetsuro Yasui², Toshihito Mori², Shigeto Tohma⁶
¹Nishino Clinic Orthopedics and Rheumatology, ²Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan, ³Department of Rheumatology, Sagami Hospital, National Hospital Organization, Kanagawa, Japan, ⁴Department of Orthopaedic Surgery, Teikyo University School of Medicine, Tokyo, Japan, ⁵Department of Orthopedic surgery, Saga-

mihara National Hospital, National Hospital Organization, Kanagawa, Japan, ⁶Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami Hospital, National Hospital organization

Common uses of Biologic agents in the treatment of rheumatoid arthritis (i.e. RA) have brought us the inhibition of synovial inflammation and joint destruction. The controlled disease activity may lead to the lower incidence of surgical interventions. However, Biologics also may bring us the infection risk, the delay of wound healing and diagnostic difficulty of infection. "The JCR Guideline of Biologics usage" indicated the peri-operative drug withdrawal. In the cases that abided by JCR guideline, many cases of peri-operative flare-up of RA inflammation were reported. Therefore, we need the revised and renewal guideline based on evidences collected from clinical practice in Japan. We examined the frequency of RA-related surgery, the procedures composition and the incidence of infection using data from National Database of Rheumatic Diseases (i.e. NinJa), also investigated the effect of biologics to the diagnosis of infection using Bone and Joint Infection Study Network (i.e. BJ IN). The frequency of Biologic use increased sequentially and reached 20.7%. The incidence of surgery in patients with biologics was above 10%, higher than in patients with conventional DMARDs, however, decreased to 5.6% in 2009. The surgical procedures proportion and the frequency of infection did not show statistically significant changes. However, the ratio of musculoskeletal infection has increased. In the patients (i.e. pts) with conventional DMARDs, CRP, and WBC count presented significant differences between the pts with infection and without infection, whereas pts using Biologics presented no significant differences between the groups. Diagnostic difficulty may increase by Biologics generalization. Either biologics efficacy or the mildness disease activity of administration subjects may cause the incidence decrease of surgery. We discuss the usefulness of neutrophil CD64 in diagnosis of infection and the adjustment of peri-operative biologics withdrawal through case presentations.

CS8-6

Preliminary recommendation for perioperative use of biologics in RA patients

Satoshi Soen^{1,2}, Masahiko Suzuki², Keiichiro Nishida², Hiromi Oda², Hiroshi Inoue², Atsushi Kaneko², Kenji Takagishi², Takaaki Tanaka², Tsukasa Matsubara², Naoto Mitsugi², Yuichi Mochida², Toshihito Mori², Shigeki Momohara², Toru Suguro²

¹Department of Orthopaedic Surgery and Rheumatology, Nara Hospital, Kinki University School of Medicine, ²Rheumatoid Arthritis Committee of Japanese Orthopaedic Association

Perioperative guidelines or recommendations have never been well established for a majority of the traditional antirheumatic drugs in use today. Recommendations for the perioperative use of nonsteroidal anti-inflammatory drugs and glucocorticoids have the most evidence-based support. Data for the use of methotrexate are also available from which to generate reasonable guidelines; however, for the remaining antirheumatic drugs in current use, the available data cannot support any clear evidence-based recommendations. To provide reasonable guidelines for the use of the biologics, perhaps the best we can do is to extrapolate from the large surveillance data. The Rheumatoid Arthritis Committee of the Japanese Orthopaedic Association investigated the post operative complications of rheumatoid arthritis patients in teaching hospitals. In the joint arthroplasty group, the numbers of procedures under biological and non-biological treatments were 1,626 and 29,903, and the incidences of infection were 2.1% (34 procedures) and 1.0% (298 procedures) re-

spectively. The odds ratio of biological treatment in joint arthroplasty was more than two-fold greater in the patients with SSI compared to those that were treated with non-biologic agents. Caution and prudence should be required for operative procedure, perioperative course, and consent in joint arthroplasty of rheumatoid arthritis patients under biological agents. With a multitude of additional biologics on the horizon, we are soon to be further challenged in providing well-founded, evidence-based recommendations for the perioperative management of the biologics response modifiers. We ultimately need more detailed data addressing these problems to formulate more definitive recommendations. Additional investigation is now proceeding.

CS9-1

History of a Total Knee Arthroplasty (TKA)

Shaw Akizuki

Center of Reconstructive Surgery for Arthritis

Total Knee Arthroplasty (TKA) is an excellent treatment that can be reconstructed three joint features as exception of pain, stability and mobility, but still in developing product. A history of TKA begins on 1861 by Fergason as resection arthroplasty. Afterwards in 1940 to 1960 McKeever and Macintosh made metal tibia spacers. On 1969, Gunston FH made Polycentric Knee composed of metal runner and tibial pedestal made by polyethylen. This knee is the roots of modern knee arthroplasty. But all these prosthesis failed in clinically. A truly practical TKA was Total Condylar Knee Prosthesis (TCP) that was made by Insall JN and Walker PS on 1973. Afterwards, TKA developing with those of research of normal knee joint kinematics, materials and operative technique. In this symposium, I will give an outline of a history of development of Total Knee Arthroplasty.

CS9-2

Issues of knees with RA and operative solution

Ryuji Nagamine

Sugioka Memorial Hospital

There are many concerns during TKA in patients with RA. The patients are relatively young and therefore, operative technique to obtain long-term survival is necessary. In some cases with RA, knees may have severe valgus deformity with instability. CCK system may be necessary in such cases. Knees may have severe bone destruction and/or bone defects, flexion contracture or stiff condition. Therefore, all knowledge and technique about TKA are necessary, those being; exposure of joint, obtaining correct alignment of the components and obtaining correct soft tissue balancing. For the exposure, Rectus snip, turndown or lateral para-patellar approach may be necessary. First, synovectomy should be done. To obtain correct soft tissue balancing, we use modified gap control technique. Posterior clearance is also important. Posterior condyle that is not covered with the femoral component should be resected so as not to induce impingement against the posterior lip of the tibial articular surface. PS system should be selected in cases with degeneration of PCL. In cases with severe instability or/and bone defect, CCK should be backup. At that time, distal femoral cut should be set at 7 degrees valgus and the tibial posterior slope should be 0 degrees. In cases with severe flexion contracture, soft tissue release especially in the posterior cavity may be necessary prior to TKA. In cases with stiff knees, we intentionally create wider flexion gap than extension gap by means of modified gap control technique. In cases with bone defect, bone grafting is necessary. The direction of screws that fix the grafted bone should be planed before TKA. After components

are inserted, the tourniquet is released and hemostasis should be done. Finally, capsule is closed. If VY quadricepsplasty is done, modified Pennington suture that is used to reattach the tendon in hand surgery is useful.

CS9-3

In vivo kinematic analysis of TKA with RA patients

Tetsuya Tomita¹, Kazuma Futai¹, Norimasa Shimizu¹, Masahiro Kurita¹, Takaharu Yamazaki¹, Kunihiro Kawashima¹, Yasuo Kunugiza², Kazuomi Sugamoto¹

¹Department of Orthopaedic Biomaterial Science, Osaka University Graduate School of Medicine, ²Department of Orthopaedics, Osaka University Graduate School of Medicine

Objective: To investigate the effect of inflammatory disease on in vivo kinematics of TKA. **Patients and Methods:** We analyzed 14 TKA in RA and 30 TKA in OA. All the TKAs were clinically successful. We recorded the deep knee bending motion under weight bearing condition using fluoroscopy. In vivo kinematic analyses were performed by 2D/3D registration technique. There were 7 NRG-PS (12 in OA), 5 RP-F (9 in OA), and 2 Vanguard RP (9 in OA). Three LCS meniscal bearing TKAs followed more than 20 years were investigated using the same methods.

Results: There is no significant difference in TKA kinematics among recent three PS TKAs. Kinematic pathways are different due to the implants design, however, among the same design TKA, the kinematic pathway is same pattern. On the other hand, the long-follow up LCS TKA demonstrated the different kinematic pathway due to the individuals.

Discussion: Inflammatory disease did not effect on the recent PS TKAs kinematics at short-term follow-up. In this point, we have to analyze the more longer term follow-up cases in future. In long-term follow-up LCS TKAs, the soft tissue obtained during operation might change during long follow-up. One of the causes should be control of disease activity after operation.

CS9-4

CR type TKA in the RA patients

Koh Shimizu

Institute of Orthopaedics, Chiba Rohsai Hospital, Ichihara, Japan

[Purpose] In the RA patients, PS type TKA with cement has been recommended because of weakness of bone and soft tissue caused by inflammation. However, in recent years, bone weakness is not so severe due to better control by MTX and biological medicine, compared to steroids. Furthermore, evidence of problems including wear of the post, dislocation, and tolerance has been observed in PS type TKA. At our hospital, CR type TKA has been used in the majority of RA patients; and the purpose of this study is to investigate the results of the CR type TKA in the RA patients.

[Materials and Methods] The study group included 147 CR type TKA (122 cementless and 25 cement) performed in RA patients, and 588 CR type TKA (559 cementless and 29 cement) performed in OA patients. Average age at surgery was 58 years in RA patients and 73 years in OA patients, and average follow up period was 7 years and 1 month in RA patients and 7 years and 8 month in OA patients, respectively. Clinical results, flexion angle, and radiographical findings were investigated accordingly.

[Results] Good clinical results were observed in RA patients with cementless CR type TKA and in RA patients with cemented CR type TKA, same as OA patients. Postoperative flexion angle was best in the medial constraint type, followed by constraint type and flat type. Furthermore, this angle was observed to be better in RA

patients compared to OA patients, due to lesser osteophyte and ligament contracture in RA patients. Incidents of loosening was almost equivalent between RA cases with cementless TKA and OA cases; and sinking was very rare except in cases in which smaller size or incorrect angle of the implant was used..

[Conclusion] In the RA patients, surgical results of the CR type TKA was sufficient except cases with severe PCL disorder. CR type cementless TKA is one of the recommended surgical methods for the RA knee, especially for younger patients, except cases with severe bone atrophy or defect.

CS9-5

Clinical results of simultaneous bilateral total knee arthroplasty

Yoshiyasu Miyazaki, Kazuaki Tsuchiya, Takashi Nakamura, Hideyuki Aoki, Ayako Kubota, Minoru Tsukagoshi, Muneki Saito, Keitaro Yamamoto, Toru Suguro

Department of Orthopaedic Surgery, Toho University School of Medicine.

Rheumatoid arthritis (RA), osteoarthritis (OA) for total knee arthroplasty (TKA) due to dysfunction is doing a common surgical technique, joint symptoms of pain and instability an improvement. Simultaneous bilateral TKA in selected patients doing, RA and OA are reported with clinical outcome and complications were compared and divided. For 40 patients with 80 bilateral TKA was performed end of October 2010.the case RA was 9, OA was 31cases. RA patients with mean age at operation was 59.6 years. The clinical investigation. Knee extension range of motion preoperation average -23.1 °, 104.2 ° flexion when the study was -2.2 °, 123.9 ° has been improved. Outcome criteria in rheumatoid arthritis knee score average 87.8 points preoperatively to 44.4 points at the survey confirmed the therapeutic effect of TKA.The four patients with no history included (44.4%), but postoperative complications in four patients with symptomatic deep vein thrombosis (44.4%), and delayed wound healing, brisement force '4 those who underwent arthritis (44.4%), respectively. While the examination of patients with OA was performed, the mean age at surgery had been 75.5 years. Knee extension range of motion preoperative average -9.6 °, 111.9 ° flexion when the study was -0.4 °, 124.8 ° and improved the average outcome criteria in the preoperative knee joint deformity of 45.5 points When the survey was 84.5 point gain. The nine patients without the past history (29.0%), and postoperative complications in nine patients with symptomatic deep vein thrombosis (29.0%), two patients with delayed wound healing (6.5%), symptomatic pulmonary embolism was one case. RA patients with simultaneous bilateral TKA in the preoperative state of the OA is often compared with no problem, often in difficult surgical technique, perioperative addition, it is also necessary postoperative care It was suggested that.

CS9-6

Long-term results of total knee arthroplasty in patients with rheumatoid arthritis

Toshihiro Ohdera

Fukuoka Orthopaedic Hospital

We investigated long-term results of total knee arthroplasty (TKA) in patients with rheumatoid arthritis (RA). Between 1978 and 2010, we performed 2807 TKAs in our hospital. Initially we adopted the CR type prosthesis (PCA type 274, Omnifit type 274, Dltafit type 207, Duracon type 292) and we changed to the PS type (LPS-Flex type) from the CR type since 2000 due to several reasons. Among these TKAs, arthroplasties in RA was 266 joints, 9.5% and 122 patients with over 10 years follow-up were reviewed. The CR

type implant was selected in these patients. Most of cases revealed posterior instability in 90 degrees of flexion. A mean flexion of the knee was 102 degrees. Two TKAs were revised due to aseptic loosening and one infected TKA had several revisions. There are some disadvantages of the posterior cruciate ligament (PCL) preservation. Roll back motion the PCL leads is doubtful. The strength and function of the PCL will deteriorate after TKA, especially in RA patients. There are several articles describing that the CR type TKA is not suitable for RA patients. At present, we use the PS type TKA and replace the patella in RA patients for better long-term results. The implants are fixed with bone cement. Furthermore, better durability of the polyethylene, for example highly cross-linked polyethylene, will be needed for the implant longevity over 20 years.

CS10-1

The history of weekly methotrexate pulse therapy in Japan

Shinichi Kawai

Rheumatic Disease Center, Toho University School of Medicine, Tokyo, Japan

The history of weekly methotrexate (MTX) pulse therapy for patients with rheumatoid arthritis (RA) in Japan will be introduced in my presentation in this symposium. The weekly MTX pulse therapy for patients with RA was approved by the Japanese regulatory authorities in 1999, however, the highest doses was restricted as 8 mg/week which was much less than those (20-30 mg/week) in other countries even in Asia. This highest approved dose was decided by only the results of a clinical trial for New Drug Application (NDA) conducted in Japan. After approval of this extra-low doses of MTX pulse therapy, physicians have demanded a proposal of the higher doses of MTX to be approved without doing a new clinical trial for NDA. Very recently, 16 mg/week of MTX as the highest dose of MTX pulse therapy was just approved by the Japanese regulatory authorities in January 2011.

CS10-2

An appropriate use of MTX - To select the right patients for MTX treatment -

Takao Fujii¹, Hideto Kameda²

¹Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, ²Division of Rheumatology, Department of Internal Medicine, School of Medicine, Keio University

The new ACR/EULAR classification criteria for rheumatoid arthritis (RA) has been published in 2010 and the "treating to target strategy" for achieving remission should be indicated against "definite RA" patients. Because patients who met the new criteria will develop persistent or erosive arthritis, the most common disease-modifying anti-rheumatic drugs (DMARDs) choice may be methotrexate (MTX) because of well-understood long-term efficacy and toxic profile.

The JCR guideline for MTX use in patients with RA demonstrates that MTX should be initiated when the standard dose of other chemical DMARDs fails to show adequate response within a few months. This statement is based on the Japanese regulation of MTX treatment. For patients with risk factors of disease progression, however, MTX can be used as the first chemical DMARDs. The presence of rheumatoid factor and/or anti-citrullinated peptide/protein antibodies, bony erosion, high disease activity (by EULAR), high value of HAQ-disability index, and extraarticular disease (by ACR) have been reported as the poor prognostic factors. Actually, the majority of RA patients have some of these factors, MTX administration should be

considered for patients with few risk factors of MTX-associated adverse reactions.

MTX is contraindicated for patients with severe complications because of its toxicity. Treatment with MTX should be avoided for patients with pregnancy, allergic reaction to MTX, and severe organ diseases (e.g., pleural effusion or ascites, active infectious diseases, hematological disorder, liver dysfunction, chronic renal disease, and pulmonary disease).

Unfortunately, there are the right patients for MTX treatment who has not started MTX, and the wrong patients who take MTX in Japan. In the near future, more increased dose of MTX will be used for a larger number of RA patients. For the best use of MTX, we would like to show the right patients for MTX treatment.

CS10-3

How to use MTX as anchor drug - Dosing, administration and folate prescription

Yasuo Suzuki

Division of Rheumatology, Department of Internal Medicine, Tokai University School of Medicine, Kanagawa, Japan

A recent paradigm shift of the treatment of rheumatoid arthritis is to aim for remission by the tight control strategy using disease modifying anti-rheumatic drugs (DMARDs) as early as possible in the disease process. Among the DMARDs, methotrexate (MTX) is considered the anchor drug and should be used first in patients at risk of developing erosive and persistent arthritis. The Japan College of Rheumatology (JCR) has demanded improving dosage of MTX for several years and there was a significant progress in the application for increasing the upper limit of MTX dose in 2010, and an increase in dose of MTX up to 18mg/week is now under deliberation by the board of review. The JCR published Recommendations for the Use of Methotrexate in the Treatment of Rheumatoid Arthritis on September 21, 2010. MTX should be started at 6mg/week, with escalation at least up to 8mg/week but should be determined considering risk/benefit ratio in each patient. If poor prognostic factors, such as high disease activity, early erosions, and positive anti-CCP antibodies/RF, are present, starting MTX with a higher dose should be considered. If the treatment target is not achieved with 8mg/week of MTX, further improvement could be obtained with increasing doses up to 16mg/week. Single oral weekly doses of MTX could be given once weekly, but divided oral dosages at 12 hour intervals for 2-3 doses given as a course once weekly are recommended when higher doses of MTX with more than 10mg are prescribed. In patients responding insufficiently to MTX monotherapy, combination of MTX plus other DMARDs or biologics should be considered using the same doses of MTX as those in monotherapy. Prescription of folic acid 5mg or less/week with MTX reduce the risk of liver and gastrointestinal toxicity and cytopenia and is strongly recommended for patients taking higher doses of MTX or with risk factors of side effects.

CS10-4

Risk management of methotrexate therapy in patients with rheumatoid arthritis

Masayoshi Harigai^{1,2,5}, Ayako Nakajima^{3,5}, Takao Fujii^{4,5}

¹Department of Pharmacovigilance, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, ²Department of Medicine and Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, ³Institute of Rheumatology, Tokyo Women's Medical University, ⁴Department of Rheumatology and Clinical Immunology, Graduate

School of Medicine, Kyoto University, ⁵The committee on MTX guideline of Japan College of Rheumatology

Methotrexate (MTX), an anchor drug for treating rheumatoid arthritis (RA), is a disease-modifying anti-rheumatic drug with good efficacy and safety profiles. To maximize its therapeutic potential, proper screening prior to MTX treatment, patient education and prophylactic measures at the start of MTX treatment, and continuous monitoring thereafter are needed. Risk management of MTX therapy will become more important after official approval of a higher dosage of MTX for RA. Chapter 10 of the Japan College of Rheumatology (JCR) guidelines for MTX therapy begins with patient education, one of the most important issues for prevention, early diagnosis and treatment of adverse drug reactions (ADRs). It is strongly recommended that every patient given MTX learns about its ADRs and when and how health care professionals should be contacted. Bone marrow suppression, interstitial pneumonia (MTX lung), and infection are the top three causes of death for which causal relationships with MTX cannot be denied. Prompt diagnosis and proper treatment, including immediate discontinuation of MTX, are required when these ADRs develop. Bone marrow suppression, a serum concentration-dependent ADR, is often associated with over-dosage, renal dysfunction, and dehydration. MTX lung, a dose-independent ADR, often develops early in the course of treatment and is associated with pre-existing interstitial pneumonia. Pneumocystis pneumonia, tuberculosis, bacterial pneumonia, and sepsis are relevant infections in RA patients given MTX. MTX lung, pulmonary infection, and rheumatoid lung should be included as differential diagnoses in RA patients given MTX presenting with respiratory manifestations. Risk factors, prevention, and management of liver toxicity, gastrointestinal tract symptoms, and lymphoproliferative disorders are also included in the JCR guidelines for MTX therapy. The guidelines will help to implement more efficacious and safer MTX therapy for RA patients.

CS10-5

Recommendations for the use of methotrexate in rheumatoid arthritis -perioperative period of orthopaedic surgery, pregnancy, breast feeding, and combination therapies-

Tetsuya Tomita¹, Ayako Nakajima², Katsuaki Kanbe³

¹Department of Orthopaedic Biomaterial Science, Osaka University Graduate School of Medicine, ²Institute of Rheumatology, Tokyo Women's Medical University, ³Department of Orthopaedic Surgery, Tokyo Women's Medical University, Medical Center East

Recommendations for the use of methotrexate in rheumatoid arthritis.

-Perioperative period in RA patients undergoing orthopaedic surgery-

Methotrexate can be safely continued in the perioperative period in RA patients undergoing orthopaedic surgery. However, there is no studies concerning the non-orthopaedic surgery or the high dose usage over 12.5mg/week.

-Pregnancy and breast feeding-

Methotrexate should not be used for at least 3 months before planned pregnancy for men and women and should not be used during pregnancy or breast feeding.

CS11-1

Lupus nephritis

Ken-ei Sada, Hirofumi Makino

The renal involvement in SLE called 'lupus nephritis' affects 50-80% of patients with SLE and the morphological changes observed in the kidney show a great diversity. In order to standardize definitions, to emphasize clinically relevant lesions, and to improve interobserver reproducibility, the ISN/RPS 2004 classification was proposed. Recently, several retrospective validation studies concerning utility of ISN/RPS classification, especially among class IV, were performed. In these reports, reproducibility is almost improved by the definition of diagnostic term, but the outcome related with classification, especially in class IV, is controversial. We also showed that histological predictors (e.g. necrotic lesion, sclerotic lesion) were similarly observed between IV-G and IV-S. The more qualitative categorization by the response to standard treatment may need to emphasize clinically relevant lesion related to renal outcome. Although the combination treatment of corticosteroid and cyclophosphamide (CY) is global standard for induction remission of lupus nephritis, current status of treatment for lupus nephritis in Japan is unknown. Because the usage of CY and azathioprine (AZA) for treatment of lupus nephritis had approved by the Ministry of Health and Welfare in Japan, increase the frequency of concomitant usage of these immunosuppressants is predicted. We should reconfirm appropriate dose adjustment of CY for renal function and age. Additionally usage of CY often increase risk for ovarian toxicity, so alternative drug have been asked for. Although remission induction study for lupus nephritis did not meet its primary objective of showing that mycophenolate mofetil (MMF) was superior, the maintenance study for lupus nephritis have revealed efficacy of MMF superior to AZA recently. Different treatment response cause from pathological diversity of lupus nephritis may make difficult to show the efficacy of several drugs in clinical study.

CS11-2

Best clinical practice for systemic sclerosis

Masataka Kuwana

Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

Systemic sclerosis (SSc) is an intractable disease characterized by fibrosis of the skin and various internal organs, microvascular damage, and production of anti-nuclear antibodies. Modest improvement of long-term survival has been reported in SSc patients over past 20 years, while this is primarily attributable to introduction of supportive therapies, such as ACE inhibitors for renal crisis and prostanoids for pulmonary arterial hypertension. The only drug that has been proved to prevent progression of organ involvement in SSc patients is cyclophosphamide, but serious side effects such as carcinogenesis limit long-term use of this drug. In contrast, there are a number of drugs that failed to show the disease modifying effects in SSc patients, including D-penicillamine, IFN-gamma, minocycline, relaxin, type I collagen oral tolerance, etanercept, anti-TGF-beta1 antibody CAT-192, and rituximab. In EULAR 2009 recommendations for management of SSc, methotrexate is recommended for treatment of skin thickening although current evidence is weak. Ongoing clinical trials for early diffuse cutaneous SSc or interstitial lung disease include autologous hematopoietic stem cell transplantation, imatinib, abatacept, and mycophenolate mofetil. Recently, early aggressive treatment has been shown to improve functional outcomes in patients with rheumatoid arthritis, resulting in proposal of entirely new classification criteria for detection of rheumatoid arthritis

as early as possible. Early intervention should be also effective for SSc since fibrosis and microvascular damage would be irreversible one established. Based on this concept, diagnostic criteria for early SSc have been proposed, and include Raynaud's phenomenon, nailfold capillary changes, and SSc-specific autoantibodies. Best clinical practice for SSc using currently available diagnostic tools and drugs is discussed in this symposium.

CS11-3

Vasculitis

-ANCA associated vasculitis-

Yoshihiro Arimura

First Department of Internal Medicine, Kyorin University, School of Medicine

Vasculitic syndrome (Systemic vasculitis) involves all vessels from the aorta to the vena cava via capillaries and venules. Vasculitic syndrome is classified into two types: large vessel vasculitis and small vessel vasculitis. Microscopic polyangiitis (MPA), Wegener's granulomatosis and Churg-Strauss syndrome in small vessel vasculitis were further classified into a group known as anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis after the discovery of ANCA. Although, the prognosis of these diseases has improved gradually due to wide-spread use of ANCA measurement and recognition of the disease entities, their mortalities remain high. Early diagnosis and development of new treatments are needed to improve the survival rate. Problems related to early diagnosis are as follows: 1) Differentiation of ANCA-associated vasculitis from ANCA-positive diseases without vasculitis, such as infectious diseases, especially bacterial endocarditis. 2) Differentiation from ANCA-positive collagen vascular diseases without vasculitis, glomerulonephritis, drug induced vasculitis and tumor related vasculitis. 3) Distinction of MPA, MPO-ANCA-positive Wegener's granulomatosis, ANCA-negative Churg-Strauss syndrome and single organ involved-ANCA associated vasculitis. 4) Understanding the role of re-elevation of the ANCA titer at the remission stage for early detection of relapse and the method of detecting ANCA-negative relapse. 5) Improvement of ANCA measurement including the capture ELISA system. Several prospective, randomized controlled studies to determine the efficacy and safety of new immunosuppressive treatments for ANCA-associated vasculitis have ended and related reports have appeared recently in Europe and North America. In Japan, intravenous immunoglobulin therapy for steroid-resistant nervous disorder of CSS was covered by the national insurance in 2010. Cyclophosphamide and azathioprim for vasculitic syndromes will be also covered in Japan. We will discuss recent progress in the early diagnosis and new treatments for ANCA-associated vasculitis in this symposium.

CS11-4

Sjögren's syndrome

Hisanori Umehara

Kanazawa Medical University, Department of Hematology and Immunology

Sjögren's Syndrome (SS) is one of autoimmune diseases, with dry eyes and dry mouth and a 9:1 Female predilection. While the hallmark features of SS are related to exocrine gland dysfunction, SS has also various extra gland symptoms including arthritis, lymphadenopathy, Raynaud's phenomenon, chronic thyroiditis, interstitial pneumonia, interstitial nephritis, atrophic gastritis, autoimmune hepatitis, primary biliary cirrhosis, etc. No less than 10 sets of diagnostic/classification criteria for SS such as European-American criteria and Japanese criteria have been applied since 1965, but none

have been universally adopted or accepted by the American College of Rheumatology. These criteria have often identified patients with similar clinical features, but not necessarily with a common disease process. There is scant longitudinal data on SS. The absence of recognized classification criteria contributes to delays in diagnosis for individual patients and hampers research into SS due to small sample sizes and heterogeneously diagnosed patient populations. To address these issues, the ongoing Sjögren's International Collaborative Clinical Alliance (SICCA) was funded under a US National Institutes of Health contract beginning in 2003. SICCA is an ongoing longitudinal multi-site observational study to establish the international criteria for SS. Data from 1490 patients enrolled in SICCA revealed female (95%), positive ocular staining for KCS (72%), positive labial salivary gland biopsy (42%), positive serum anti-SS-A and/or -B (39%). Based on the computer analysis of these data, primary Sjögren's syndrome will be classified when at least 2 of the following are present: 1) SICCA ocular surface staining grade ≥ 3 2) Focal lymphocytic sialadenitis in LSG biopsy with FS > 1 3) Serum antibodies against Ro(SS-A) or La(SS-B), or RF with ANF This criteria has been submitted to ACR as the international diagnostic criteria of Sjögren's syndrome.

CS11-5 **polymyositis • dermatomyositis**

Hidehiro Yamada

Division of Rheumatology and Allergology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan

There are several risk factors for the poor prognosis of patients with inflammatory myopathies, which include delay in the initial treatment by more than 6 months, severe muscle weakness at the presentation, dysphagia/respiratory muscle weakness, serious complications such as interstitial lung disease, malignancy and cardiac involvement. Recognition of these prognostic factors and the development of novel therapeutic strategies for these complications may improve quality of life of these patients.

CS12-1 **Extensor tendon rupture in the rheumatoid hands - minimum 10-year follow-up -**

Hiroyasu Ikegami¹, Takashi Ishiguro², Yukio Horiuchi³, Toshiyasu Nakamura¹, Kazuki Sato¹, Yoshiaki Toyama¹

¹Department of Orthopaedic Surgery, School of Medicine, Keio University, Tokyo, Japan, ²Ishiguro Seikeigeka, Kanagawa, Japan,

³Department of Orthopaedic Surgery, Kawasaki Municipal Hospital, Kanagawa, Japan

Objectives

At 46th Annual Meeting in 2002, we had reported the treatment using tension-reduced early mobilization for reconstruction of extensor tendon rupture in the rheumatoid hands. This time, we report the results of the patients who have passed ten years and more from the operation.

Methods

20 patients (all females) were the cases passed 10 years and more from the operation among 65 cases we have treated since 1987. The age at the operation were 34 to 72 years old (the avg.59). The operation consists of synovectomy, capitulum ulnae treatment (Sauvé-Kapandji's or Darrach's Method), and the reconstruction of the extensor tendon. Active exercise of the fingers was started in the tension-reduced position immediately after the surgery. We studied patients' satisfaction, the range of motion of MP joints, deformity of fingers,

and re-rupture of the extensor tendons.

Results

The patients' satisfaction was "good" or "excellent" in 18 cases (90%). A reduction in the extension angle of MP joints was mostly 10 degrees at the point of 1 year after the operation. There were 7 cases whose extension lags of MP joints were more than 30 degrees at the time of examine. The causes were such as collapse of the carpal bones, volar dislocation of MP joints, and ulnar deviation of MP joints. Two among 10 cases of the extensor tendon rupture of the 4th and 5th fingers showed dislocation of the extensor tendon of the 3rd finger toward ulnarside on the MP joints. However, there was no case that caused re-rupture of the extensor tendons.

Conclusions

Since RA is a progressive disease, the long-term progress is not always good, and there is a tendency that limited extension of the MP joints increases. However, the patients have almost no difficulty in physical movements in everyday because our treatment does not have a risk of the limitation of flexion.

CS12-2 **Reconstruction of the rheumatoid wrist including DRUJ and extensor tendons**

Asami Abe, Hajime Ishikawa, Akira Murasawa, Kiyoshi Nakazono, Satoshi Ito, Hiroshi Otani, Hiroe Sato, Daisuke Kobayashi

Niigata Rheumatic Center

With the recent advance in the medical treatment of RA, disease activity is well-controlled. However, many patients with wrist disabilities still remain. Reconstruction of the rheumatoid wrist is performed in the patients with difficulties in the daily activities due to persisting pain, swelling, deformity and restricted forearm rotation for more than 6 months despite current conservative treatments, and in the patients with sudden loss of hand function due to tendon rupture.

Operation for the radiocarpal joint (RCJ): Ulnar carpal shift progresses after synovectomy of the rheumatoid wrist combined with Darrach procedure. For the unstable RCJ with ulnar shift, volar subluxation, radial rotation and supination, carpal reduction and radiolunate arthrodesis are indicated, if the midcarpal joint (MCJ) remains. If there is no space in the MCJ, Clayton tendon transfer is alternatively indicated. In Sauvé-Kapandji (SK) procedure, the preventive effect on the progression of instability at the RCJ is weak. For the palmo-ulnarly subluxated RCJ, total wrist arthrodesis using an intramedullary rod is indicated.

Operation for the distal radioulnar joint (DRUJ): For the unstable DRUJ, Darrach procedure is indicated if the ulnar head is obviously deteriorated. If its deterioration is mild, SK procedure is performed. In either procedure, stabilization for the unstable ulnar stump is required using the pronator quadratus muscle, or the extensor carpi ulnaris tendon, or the flexor carpi ulnaris tendon.

Operation for the extensor tendon rupture: Reconstruction of the ruptured tendon is usually performed combined with synovectomy and flattening of the gliding floor. Preoperative 3D-CT images of the wrist deformity and the extensor tendon rupture are utilized for preoperative planning. Tendon transfer or end to side suture is performed on the wrist, in which rupture was left unreconstructed for more than 2 or 3 months with myostatic contracture of the proximal muscles.

CS12-3 **Surgical efficacy of limited wrist fusion for the treatment of RA wrists**

Norimasa Iwasaki, Akio Minami

Radiolunate fusion is a limited wrist fusion procedure for the treatment of RA wrists. The main purpose of this study is to evaluate the surgical efficacy of radiolunate fusion for RA wrists. Radiolunate fusion had been carried out in 19 RA wrists of 16 patients. All cases were simultaneously performed with Darrach procedure. According to the modified Larsen's classification of radiographic stage, preoperative patient group included one hand in stage 2, 15 hands in stage 3, and three hands in stage 4a. Postoperative clinical evaluation was based on the Stanley's classification. At follow-up, all cases were graded as excellent (63%) or good (37%). Postoperative wrist ROM significantly decreased, compare with preoperative one. The progression of the radiographic stage was found in only two cases. On the basis of these results, we may conclude that radiolunate fusion is effective procedure for the treatment of RA wrists. However, surgeons must consider a decrease in wrist ROM after this procedure.

CS12-4

Surgical treatment for thumb boutonniere deformity in rheumatoid arthritis

Takuji Iwamoto, Katsunori Ikari, Shigeki Momohara

Institute of Rheumatology, Tokyo Women's Medical University

Objective: The boutonniere deformity is the most common thumb deformity in rheumatoid arthritis. Clinical staging of the deformity as early, moderate, or severe is dependent on the extent to which the deformity is passively correctable, but in all cases, reconstruction of the extensor mechanism is necessary. The purpose of this study was to describe the results of our modified EPL rerouting procedure.

Methods: Seventeen fingers (early 3, moderate 9, severe 5) with an average age of 67 years and an average follow-up period of 13 months were included in this study. Following MP joint synovectomy or arthroplasty (and IP joint fusion in four of the severe cases), we sutured the EPL tendon firmly to the dorsal base of the proximal phalanx and transferred the EPB to the distal portion of the EPL tendon to extend the IP joint.

Results: Mean MP joint range of motion increased from 19.6° to 46.9°. Mean MP joint extension remarkably improved from -59.8° to -17.7° while IP joint extension remained adequate. Thumb appearance improved in 16 cases, and patient satisfaction was high.

Conclusion: It is difficult to improve the thumb boutonniere deformity with conservative treatment even after the synovitis are diminished by pharmaceutical therapy. Our EPL rerouting procedure reinforced MP joint extension while at the same time preserving the extension of IP joint.

CS12-5

Clinical Outcome of Finger Joint Arthroplasty for Rheumatoid Arthritis

Yoshiya Arishima¹, Yoshitaka Minamikawa², Nobuhiko Sunahara¹, Yasuhiro Tsuneyoshi³, Kaneyuki Tsuchimochi¹, Eiji Taketomi¹, Hitoshi Hirota¹, Hideo Ohtsubo¹, Masaki Akimoto¹, Sanae Ohkura¹, Takemasa Matsuda¹, Setsuro Komiya³

¹The Center for Rheumatic Diseases, Kagoshima Red Cross Hospital, Kagoshima, Japan, ²Tokyo Hand Surgery and Sports Medicine

Dislocation and ulnar drift of the metacarpophalangeal joints are common problem in patients with rheumatoid arthritis. Swanson Metacarpophalangeal Joint Arthroplasty (SMPA) is most common procedure, which provides good alignment of the fingers and improves the activities of daily living. However, SMPA has some problems such as limitation of range of motion, breakage, sinking and osteolysis caused by foreign-body granulation. Self Locking Finger Joint (SLFJ), (Nakashima Medical, Okayama, Japan) is a cementless implant which is aimed to reduce these problems. In this series we analyzed short-term results of SLFJ for the finger deformities in patients with RA. Twenty-eight patients with 87 joints were reviewed after a minimum follow-up period of 1 year (average, 2.6 y; range, 1-4y). Patients were all female, and average age at surgery was 60 years (range, 33-77y). In radiographic evaluation, none of the prostheses had mechanical loosening. Periprosthetic radiolucent zone was observed in seven prostheses at proximal phalanx, and nine prostheses at metacarpal. All radiolucent zone was observed around the screw, but not around the part of joint anchor. Five prostheses had mechanical sinking at proximal phalanx, but none of prosthesis sank at metacarpal. Any breakage of prosthesis was not observed. Three prostheses with two patient were dislocated, and only one patient with persistent of flexion contracture needed revision surgery. In clinical evaluation, four patients with fourteen joints recurred ulnar drift, but they did not wished revision surgery because of no complaint in their daily use. Delayed infection was occurred in one prosthesis which needed removal. These short-term results suggest that the Self Locking Finger Joint may be resolve some problem of Swanson silicon implant, and considered as an option of finger joint prostheses in patients with rheumatoid arthritis.

CS12-6

Examination of Total Finger Arthroplasty with FINE® Total Finger System

Masayuki Sekiguchi, Kazuaki Tsuchiya, Yoshiyasu Miyazaki, Yoshiyuki Ohikata, Ayako Kubota, Hirofumi Kawakami, Keiji Hasegawa, Toru Suguro

Department of Orthopaedic Surgery, Toho University School of Medicine

[Introduction] As one of deformities of rheumatoid hand, palmar dislocation of MP joints occur in high rate. Total finger joint arthroplasty using various types of implants have been performed as reconstructive surgery for rheumatoid hand. However, surface replacement system has the problem of postoperative palmar dislocation of basal phalanx. In additionally, the rigid joint system has a high possibility of causing breakage of implant, and loosening. We developed FINE® Total Finger System which assisted the function of reconstructed soft tissue and could control palmar dislocation of the base phalanx to solve these problems. Clinical application of this system has been started from April 2004. [Method] The number of cases was twenty five (both hand six cases). All cases were females. Age was an average of 63.2 years old. The stage of RA was Larsen's Grade IV or V. The arthroplasty with FINE® Total Finger System was performed for 101 fingers. Both implants were fixed with bone cement. Range of motion was measured as a clinical evaluation, and the presence of a clear zone surrounding the implant was checked with X-ray image. [Result] The postoperative extension angle of MP joints was an average of -19.5 degrees and the flexion angle was an average of 70.2 degrees. All patient were very much satisfied, in order to be able to perform skill movements, such as writ-

ing a character and using chopsticks. Severe case of the ulnar drift deformity of MP joints or the case whose have severe palmar dislocation, showed poor extension in ring finger and little fingers. [Conclusion] The period after an operation was seven years also with the case in which progress was the longest. However, implant showed no damage or deformation, a lot of satisfaction of patients was high. Progressive destruction of the radiocarpal joint and carpal collapse was thought to be one of the factors affecting postoperative results.

CS13-1

Evaluation of plain radiographs with rheumatoid arthritis - Upper Extremity

Takaya Mizuseki, Yasuo Kurose

Hiroshima Prefectural Rehabilitation Center

In imaging joints destruction of rheumatoid arthritis (RA), plain radiography (XP), computed tomography, MRI and ultrasonography are available. Detection of early joint deterioration became possible thanks to recent development of MRI and ultrasonography. Yet, plain radiography remains major tool in diagnosis and decision making of surgery because it enables long time followup of multiple joints and because of simplicity and low cost. [Joint destruction] Joint destruction is represented by joint space narrowing and erosion. Narrowing occurs after destruction of cartilage, while erosion occurs when pannus invades into bare area of subchondral bone. In order to express degree of destruction, Steinbrocker's staging and Larsen's grading system are well known. Elbow synovectomy is usually indicated until Larsen's grade III. After grade IV, total elbow arthroplasty is preferred. In choosing types of arthroplasty, the degree of joint absorption and derangement are taken into consideration. Wrist synovectomy is not limited by the stage of destruction, but in early cases, ulnar stabilization procedure, such as ulna head preservation or Sauve Kapandji procedure should be added. In grade V wrists, immobilization procedure should be added to prevent further collapse. [Joint deformity and dislocation] Joint deformity caused by loosening of soft tissues are another serious problem. In wrists with longstanding synovitis, the TFCC, the DRUJ become attenuate and the ECU tendon subluxates volarly, thus causing ulnar head dorsally dislocate. The carpi volarly subluxate. The DRUJ synovitis erodes radius sigmoid notch, making "scallop sign". This sign is known for impending extensor ruptures. On the radial side, the RSC ligament becomes loose, causing the scaphoid flex. As a result, the carpi rotate radialward. The MP joint synovitis causes the joint volarly subluxate and extensors ulnarly dislocate. Intrinsic muscles become tight. All of them act fingers to drift ulnarward.

CS13-2

What should be evaluated on the plane radiographs of lower extremities?

Yoichi Taneda

Department of Orthopaedic Surgery, Kasugai Municipal Hospital

Plane radiographs are the most basic diagnostic imaging for the rheumatic joint diseases. They have so much information that we need a high resolution monitor under the filmless circumstances. First, radiographs should be read macroscopically namely the shape of the joint head and joint cavity, their alignment and the joint space that means the thickness of joint cartilage. Next, more detailed observations should be needed in terms of bone sclerosis, erosion, osteophyte formation, calcinosis and free bone fragments. In addition some kinds of stress radiographs would be applied for the assessment of joint instability especially in the lower extremities. For example anterior drawer and posterior drawer in the knee joint and

valgus and varus stress in the knee and the ankle joint would be usually used for the diagnosis of post traumatic instability. The combination of those findings lead to the diagnosis of arthritis or arthrosis or other specific joint diseases.

In the hip joint assessment should be done on the CE angle of acetabulum, roundness of femoral head, joint space narrowing, shape of the femoral neck, medial or lateral migration of the femoral head and crystal deposition on the acetabulum cartilage or on the soft tissues around the hip joint. In the knee joint the shape of femoral condyle and tibial condyle and its alignment, knee joint space, the shape of patella and its proximal or distal shift and the shape of the tibial tuberosity would be assessed. The above-mentioned stress tests would be assessed in some cases. The crystal deposition on articular cartilage or meniscus would be important findings.

It is difficult to assess the hind foot on the plane radiographs because of its complex structures. The learning curve of a lot of film reading enables to find out the abnormalities and leads to the next step examinations. When a patient complains an ankle pain, a talocalcaneal joint should be checked along with a talocrural joint because they demonstrate similar pain around an ankle.

CS13-3

Evaluation and Measurements Taken Using the Plain Radiograph : Spine

Takashi Kaito, Kazuo Yonenobu

Department of Orthopaedic Surgery, National Hospital Organization Osaka Minami Medical Center

Spinal involvement in severe rheumatoid arthritis (RA) is not always properly evaluated during the neurologic exam due to concomitant joint deformities and loss of muscle strength caused by diffuse atrophy and neuropathy. However, the reported incidence of spine lesions in RA is high (40-80%). The development of the surgical management of joint replacement of the extremities has led to a growing importance of spinal lesions in predicting prognosis and mortality. Spinal lesions have two aspects. One is a locomotory disability caused by the destruction of spinal joints and ligaments and the other is nerve root and/or spinal cord compression caused by deformity and instability of the spine. The upper cervical spine is a characteristic focus in RA and deterioration can be lethal due to static and dynamic compression of the spinal cord and brainstem. Radiographic signs of cervical involvement can be classified into three types. The most common type is atlanto-axial subluxation (AAS), which is horizontal (especially antero-posterior) instability subsequent to laxity or rupture of the transverse, alar and apical ligaments. Vertical subluxation (VS) occurs as a consequence of the destruction of lateral atlanto-axial joints and atlanto-occipital joint. Subaxial subluxation (SS) is anterior or posterior vertebral subluxation as a result of destruction of facet joints, and ligamentous structures attached to the spinous process and vertebral disc. The thoracic and lumbar spine is also affected in same fashion as the subaxial cervical spine. Typical radiographic findings are vertebral subluxation, disc narrowing without osteophyte formation and vertebral compression fractures. In this lecture, the basic anatomy, characteristic radiographic findings and evaluation methods of spinal lesion in RA will be discussed. The possible impact of biological agents in the treatment of cervical lesions will also be discussed.

CS13-4

Cervical spine surgery using CT based navigation system for RA patients

Akihito Wada, Hiroshi Takahashi, Yuichiro Yokoyama, Fumiaki Terajima, Yasuaki Iida, Toru Suguro

Pedicle screw fixation is gaining popularity in various type of cervical spine conditions. Not only three column control of the vertebrae and segmental anchorage points, it should achieve better deformity collection and rigid fixation compared with other anchoring system. Although posterior instrumentation surgery using pedicle screw is an effective manner in the collection and fusion, there are potential risks of misplacement of pedicle screw and neuro-vascular injuries. The purpose of this study is to evaluate the efficacy of the computed tomography (CT) based navigation surgery for screw placement in posterior cervical spine surgery for rheumatoid arthritis. A total of 9 patients were studied, which included 1 male and 9 females. The average age at the time of surgery was 55 years old. Preoperative diagnosis of the type of RA was MES in 7 and MUD in 2 patients. Preoperative CT taken with 1.00 mm axial slice of the spine were obtained for all patients and analyzed for surgical planning. The data were transferred into a computer work station and re-constructed into 2 and 3 dimensional images of the vertebrae, and appropriate diameter screws were set to pass through the pedicles on the computer screen before surgery. Using postoperative CT scan, screw placement was evaluated. The use of CT based navigation system for the screw placement of the cervical spine not only effectively reduced the screw mal-position and surgical complication in patients with RA, but also reduce the intra-operative radiation exposure.

CS13-5

Evaluation with ultrasound

Kei Ikeda

Department of Allergy and Clinical Immunology, Chiba University Hospital, Chiba, Japan

Musculoskeletal ultrasound depicts a range of pathologies in and around joints by illustrating soft tissue and bone surface. In rheumatoid arthritis (RA), synovial inflammation, subsequent structural damage, and differential causes of symptom can be assessed with ultrasound. Evaluation of synovial inflammation with ultrasound, especially, allows accurate diagnosis and activity assessment, and therefore, contributes to better clinical outcome. Synovitis is depicted as either synovial hypertrophy or increased synovial fluid with B-mode ultrasonography. Although these two findings are often indistinguishable from each other in small joints, synovial hypertrophy is more specific to synovitis. Particularly, synovial hypertrophy accompanied by increased Doppler signals represents ongoing synovial inflammation, therefore, synovial Doppler flow is very important in the assessment of disease activity of RA. However, it should be noted that the assessment of synovial blood flow could be influenced by many factors, such as instrument, setting, transducer, or gel temperature. Different joints should be assessed differently for accurate estimation of inflammation according to their synovial shape, threshold for increased blood flow, and normal vessel distribution. We reported the benefit of ultrasound in evaluating drug response in RA at the JCR meeting last year and we will report our study addressing the benefit of ultrasound in RA diagnosis combined with ACR/EULAR criteria. In addition to these benefits, performing ultrasound improves skills in clinical joint examination, needle aspiration, injection, and X-ray reading, by giving feedback with accurate morphological information.

Next Decade Symposium

NDS1-1

How to start and continue biologics safely?

Toyomitsu Tsuchida

Institute of Rheumatic Diseases, Tsuchida Clinic

The specialty of Rheumatology was established fifteen years ago. Since then, treatment for Rheumatoid Arthritis (RA) had advanced dramatically, initiated with MTX, followed by Infliximab, the first biologics in Japan. Series of advancement require more experts on these treatments. Recently we see multiple titles used for rheumatologists. I propose the new title 'Specialized Rheumatologist', who is dedicated to RA management and whose clinical practice is mainly (minimum 80%) devoted to RA patients.

I report how I use biologics safely. Among 1,870 RA patients in my clinic, 540(28.9%) of them are on biologics. Among these 540, more than 520 patients are on Etanercept delivered subcutaneously. As of December 2010, 360 patients (61.2%) are still on Etanercept. The most common side effect is respiratory infection such as bacterial pneumonia. We experienced two Tuberculosis reactivation, with one death. The second most common side effect is dermatological disorders, especially herpes zoster. These side effects are commonly seen in other biologics as well.

I emphasize that it is extremely important to provide team-approach care with pulmonologists, in order to minimize side effects. I am located in Chiba and my patients come from all over Chiba. I make a map to show them where pulmonologists are located. I always refer patients on biologics to a pulmonologist in the area. I routinely look for any respiratory abnormalities for patients on biologics. I check blood test results within forty minutes to identify any abnormalities before infusion. I take the same approach for subcutaneous biologics. Though we take such a thorough approach, we had one case of pyogenic vertebral osteomyelitis.

Subcutaneous biologics are relatively safe and straightforward. In contrast, intravenous biologics are more laborious and not recommended for every rheumatologist. I propose that routine outpatient follow-up with Specialized Rheumatologist every three month, in order to properly use biologics.

NDS1-2

Early Diagnosis and Treatment Strategy of Rheumatoid Arthritis using High Resolution Radiograph (HRR).

Kuniomi Yamasaki

Shin Yokohama Yamasaki Clinic

Early diagnosis and treatment is the most important to stop joint destruction and to induce the functional and structural remission in rheumatoid arthritis (RA). According to a study by Yamasaki, M. (St. Marianna Univ. ;n=104) comparing the 4 criterias: 1987ARA, Japanese Ministry of Health & Welfare (JMHW, Yamasaki), 2009 and 2010ACR/EULAR (A/EU) criterias, sensitivity and specificity are 67.3 and 95.2%, 91.8 and 96.2%, 93.8 and 100%, 69.3 and 100% respectively. JMHW and 2009A/EU criterias are useful, but 2010A/EU criteria is not useful for diagnosing early RA because 1. Several cases scoring <6 (5 points: 5 cases, 4 points: 5 cases, 3 points: 2 cases) have erosion in radiograph. 2. These cases with erosion in X-ray tend to have lower titer or negative on serology (p<0.001). 3. Differential diagnosis is important. Only 3 diseases are written in 2010A/EU. DIP joints are omitted to count, but 14% of early RA (<1 year) and 70% (>10y) showed erosion. High Resolution Radiograph (HRR; mammography films and cassettes, an ordinary X-ray apparatus: 50kV, 100mA, 0.04sec. for hands 0.06sec. for feet) is very useful for detecting synovial and periarticular bone changes in the early

stage and evaluating the therapy as well. For the treatment strategy, MTX is the first line DMARD, but the dose is limited to 8mg/w in Japan. 2008EULAR recommendations propose to start from 10~15mg/w and augment up to 20~30mg/w. 2008ACR guideline recommend to use a TNF-inhibitor for the highly active pt. onset within 3 months if they have no economic problem. Many Japanese pt. cannot afford expensive biologics (Bio), but many can be treated successfully with GST or Bucillamine+/-MTX>8mg/w. 2010JCR guideline recommends to use Bio if the image shows erosion which is the most important point. Joint destruction may progress even if CRP,ESR,RF and CCPab are negative. DAS28 without foot joints leads mistake. In conclusion, tight control using HRR is the most useful way to maintain remission and stop the joint damage.

NDS2

inflammatory synovitis: rheumatoid arthritis and its related disorders

Masataka Uetani, Yasuo Kido

Nagasaki University, Graduate School of Biomedical Sciences, Department of Radiological Science

Synovitis can be seen in many arthritic disorders, including rheumatoid arthritis. Conventional radiography of the joints is considered the standard method for detecting and quantifying joint damage in RA. However, radiographs cannot directly demonstrate synovitis and only show late disease manifestations as joint space narrowing and bone erosions. Magnetic resonance (MR) imaging is increasingly being used in the assessment of rheumatoid arthritis due to its capacity to help identify the key pathologic features of this disease entity at presentation. MR imaging has demonstrated greater sensitivity for the detection of synovitis and erosions than either clinical examination or conventional radiography and can help establish an early diagnosis of rheumatoid arthritis. It also allows the detection of bone marrow edema, which is thought to be a precursor for the development of erosions in early rheumatoid arthritis as well as a marker of active inflammation. In this presentation, we outline the role of MRI in the work-up of rheumatoid arthritis and related disorders and discuss its strengths and limitations with the help of representative examples.

NDS3

Morning conference—Keep in mind diseases that mimic RA

Mitsumasa Kishimoto¹, Atsushi Hashimoto², Yasuhiro Suyama¹, Shinichi Nogi², Noboru Hagino³, Kota Shimada⁴, Yohei Seto⁵, Yasuaki Okuda⁶

¹Section of Allergy and Rheumatology, St Luke's International Hospital, ²Department of Rheumatology, National Hospital Organization Sagami National Hospital, ³Department of Allergy and Rheumatology, ⁴Department of Rheumatology, Tokyo Metropolitan Tama Medical Center, ⁵Institute of Rheumatology, Tokyo Women's Medical University, ⁶Center for Rheumatic Diseases, Dohgo Spa Hospital

What is the difference in clinical education between Japan and the US? In the US, trainees are expected to elicit a detailed history from the patient, then a thorough physical examination, both of which lead to a reasoned plan for basic management with the appropriate studies. This training in clinical reasoning starts during medical school in the United States through active discussions of patients during case presentation, between the resident and the attending physician. In Morning report (Case Conference) a case presentation is actively done on nearly a daily basis. Not only the presenter but also the participating audience—both residents and students—are encouraged to think about the possible differential diagnoses by

understanding the condition from a certain chief complaint, history, and physical as if they were actually looking at the patient. After this process, the assessment and plan is formulated, and necessary studies are reviewed. In this way, the reasoning and logic behind ordering any studies is explained, rather than on the basis of routine. In this morning session, we will present eight cases which mimic rheumatoid arthritis and discuss the differential and how we can discriminate between them.

NDS4-1

Overview: The pathogenesis of rheumatoid arthritis and the targeted therapies

Kazuhiko Yamamoto

Department of Allergy and Rheumatology, The University of Tokyo Graduate School of Medicine

Regarding the pathogenesis of Rheumatoid arthritis (RA), several genetic susceptibility loci have been reported. *HLA-DRB1* is the strongest, but other genes are also associated. On the other hand, a gene-environment interaction has been also suggested. In fact, smoking and periodontitis are strongly associated with seropositive RA. It is estimated that smoking or periodontitis triggers the production of anti-citrullinated peptide antibodies (ACPAs) in individuals who carry the HLA-DR shared epitope. In established RA, the synovial membrane is infiltrated with several different inflammatory cells. It is clear that T cells are important. In particular, T_H17 cells may enhance synovitis and damage of the joint through interactions with other cells. Macrophages are also important mainly by secreting crucial pro-inflammatory mediators. The success of B cell-specific antibody therapy suggests the importance of B cells. Synovial fibroblasts are also key players in joint damage through the secretion of matrix metalloproteinases and other enzymes. Initially, these fibroblasts appear to be activated by the inflammatory microenvironment but subsequently become semi-autonomous. Bone damage is caused by osteoclasts that are induced by several inflammatory signals in the joints. Understanding the pathogenesis of joint inflammation and destruction in RA involves dissection of the cellular and molecular interactions in the synovial tissue. Development of effective targeted therapies has been achieved by such understandings. Novel therapies include biologics that target several inflammatory cytokines, T cells, or B cells and small compounds that inhibit signal pathways in the cells. However, more specific approaches should be further pursued from fine insights of cellular and molecular pathways. These approaches will lead to more rational and safer treatments.

NDS4-2

New inhibitors of osteoclasts: anti-RANKL antibody and cathepsin K inhibitor

Toshio Matsumoto

Department of Medicine and Bioregulatory Sciences, University of Tokushima Graduate School of Medical Sciences

There has been a rapid increase in our understanding of the regulatory mechanism of osteoclastic bone resorption. Expression of receptor activator of NF- κ B ligand (RANKL) is enhanced in stromal cells of osteoblast lineage under stimulation by bone resorptive factors. With the binding of RANKL to its receptor, RANK, on the surface of monocytic cells of osteoclast lineage, multinucleated osteoclasts are formed. Osteoclasts thus formed adhere to bone surface via binding of α v β 3 integrin with matrix proteins, and form a sequestered environment called resorption lacunae. Osteoclast membrane facing lacunae forms ruffled border on which vacuolar type H

$^{+}$ -ATPase and Cl^{-} channel, CCL7, are expressed. With the secretion of HCl and cathepsin K, an osteoclast-specific lysosomal enzyme with collagenolytic activity under acid pH, osteoclasts are able to resorb bone. Each of these molecules essential for osteoclastic bone resorption has been considered as a candidate for osteoclast inhibitor. Among them, inhibitors of RANKL-RANK system and cathepsin K have been thought as most promising candidates for new anti-resorptive agents. A fully human monoclonal antibody against human RANKL, denosumab, binds RANKL and inhibits the formation and activity of osteoclasts, and has been shown to have a superior effect in the treatment of tumor-induced bone destruction and osteoporosis. Cathepsin K inhibitors do not inhibit the formation or activity of osteoclasts but block cathepsin K activity to inhibit collagen degradation. Interestingly, clinical studies with a cathepsin K inhibitor, odanacatib, demonstrated that, while it strongly inhibited bone resorption, only a slight suppression of bone formation was observed with a robust increase in bone mineral density in osteoporotic patients. There is also a report to suggest a direct inhibitory effect of a cathepsin K inhibitor on autoimmune inflammation. These new osteoclast inhibitors will be reviewed and discussed.

NDS4-3

-p38 inhibitor-Feedback from analysis of p38-related genetically engineered mice

Yoshitoshi Kasuya

Department of Biochemistry and Molecular Pharmacology, Graduate School of Medicine, Chiba University, Chiba, Japan

p38, one of MAPK family is activated by stress and proinflammatory cytokines and also called stress-activated protein kinase (SAPK). Originally, p38 was identified as a kinase activated in response to endotoxin and osmolarity shock and a target molecule of cytokine-suppressive anti-inflammatory drugs (CSAIDs). As a Ser/Thr protein kinase, activated p38 phosphorylates two groups of substrates: other protein kinases (MAPKAP-K2/3, PRAK, MSK1/2 and MNK1/2) and transcriptional factors (ATF2, MEF2A/C, Gadd153, p53, Elk-1/TCF, SAP-1a, CHOP, Max, etc.) and produces various cellular outputs. Especially, p38 is closely related to inflammatory diseases by regulating production and signaling of cytokines. Thus, p38 is widely noticed as a target molecule in the therapy for inflammatory diseases. It has been 15 years since one class of p38 inhibitor compounds, the pyridinyl-imidazoles were discovered. To date, a number of orally-available small-molecule p38 inhibitors were developed by many pharmaceutical companies, and some of these have advanced to clinical studies to explore those potential for the treatment of rheumatoid arthritis, psoriasis, Crohn's disease, COPD, and so on. Several p38 inhibitors expected therapeutic benefit were discontinued in phase II and III trials, indicating that p38 inhibitors have safety issues to solve. However, the fact that new p38 inhibitors are entering human clinical trials one after another clearly suggests the high potential of p38 as a target of anti-inflammatory strategy.

We now investigate the pathophysiological role of p38 in various diseases by using genetically engineered mice (p38 α -KO mice and p38-TG mice). Elucidation of a new concept for p38-regulated pathological development may lead to the extension of p38 inhibitors application for diseases. In this presentation, I will overview p38 inhibitors and a new mechanism for p38-regulated inflammatory diseases through analysis of p38-related genetically engineered mice.

NDS4-4

Anti-rheumatic drug targeting Janus kinase; the next generation for RA treatment

Kunihiro Yamaoka, Yoshiya Tanaka

The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan

Treatment of rheumatoid arthritis (RA) with biologics has brought a paradigm shift. Previous medications controlling symptoms for improvement of quality of life (QOL) have resulted in continuation of aggressive bone destruction with poor outcome in QOL. Whereas 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, even with these biologics, ~30% of patients poorly respond to treatment and due to parenteral administration and expense, patients with difficulties in inducing or continuing biologics is not rare. Cytokines bind to their cognitive receptor and activate tyrosine kinases to transduce intracellular signaling to exert its original biological function. Recently, inhibitors targeting tyrosine kinases have achieved attention, based on the clinical efficiency on RA patients. Among the tyrosine kinase inhibitors, CP690,550 targeting Janus kinase (JAK) has shown dramatic effect with similar efficiency with biologics on patients resistant to MTX or biologics. In addition, efficacy and safety was reported to be maintained up to 6-12 months at the American college of rheumatology 2010. 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 which was the best result among the clinical studies with CP690,550. At the same meeting, INCB28050 specifically targeting JAK1/2 was also reported to be as effective as CP690,550. These compounds are small molecule compounds, orally available with short half life and depending on the process of synthesis, it is expected to be less expensive compared to biologics. Therefore, small molecule compounds possess the possibility to solve the problems with biologics and provide another paradigm shift in treatment of RA.

In this symposium, recent advance in JAK inhibitors for RA will be reviewed and discuss on the possible mechanism of action

NDS4-5

Syk inhibitors

Kiyonao Sada^{1,2}

¹University of Fukui, Faculty of Medical Sciences, ²University of Fukui, OLSAP

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 Fukui Medical School. Syk is activated by various physiological stimulations, and is required for the activation of mast cells, macrophage, osteoclasts, and B cell development. In addition, Syk is involved in the pathogenesis of leukemia, autoimmune diseases fungus and virus infection. Recently, novel Syk inhibitors (R112, R406, R788) were developed and its usefulness has been evaluated in the treatment of allergic rhinitis and rheumatoid arthritis. In this session, I will introduce the structure and function of Syk, and then review the classical and novel Syk inhibitors and their current status.

NDS4-6

New anti-cytokine (IL-15, IL-17, IL-12/23 inhibitor, anti-TNF ligand superfamily

Isao Matsumoto

The understanding of the pathogenesis and optimal therapeutics for rheumatoid arthritis (RA) has advanced remarkably over the last decade. Especially, prognosis for RA patients has significantly improved with the recent use of biologics targeting tumor necrosis factor alpha and interleukin 6. In this talk, recent progress of new therapeutic target for RA, focusing on IL-15, IL-17, IL-12/23, TNF-ligand superfamily, will be discussed. **IL-15** IL-15 is expressed primarily by macrophages, fibroblast like synoviocytes, and relates to the maintenance, differentiation, activation and induction of T and NK cells. IL-15 is found at elevated levels in the serum and synovial fluid of RA patients. Human studies targeting IL-15 (AMG714 formerly known as HuMax-IL-15) shows encouraging early results. **IL-17** The discovery of interleukin (IL)-17 and its major cell source, the type 17 T-helper (T_H17) lymphocyte, has been linked to several autoimmune diseases. The pathological evidence of IL-17 in murine arthritis is clearly defined, although in human is still in debate. Observations from phase I trials show that signs and symptoms of RA are significantly suppressed following treatment with anti-IL-17 antibodies, without notable adverse effects. **IL-12/23** Importance was confirmed by murine arthritis, a third Phase III trial of anti-IL-12p40mAb (ABT874) ustekinumab has been done in the treatment of psoriasis. This trial found clinical response with ustekinumab over the 12-week study period. Potent and orally active inhibitor of the cytokines interleukin-12 (IL-12), and interleukin-23 (IL-23) production, STA-5326 has been in clinical trial of Crohn's disease. **TNF ligand superfamily** Abnormal levels of soluble and membrane BAFF and resulting B-Cell elevations have been implicated in a number of autoimmune diseases including systemic lupus erythematosus (SLE), Sjogren's Syndrome and RA. Anti-BAFF mAb (Belimumab) shows good clinical response to SLE, and TACI-Ig shows good clinical response in RA.

NDS5-1

Musculoskeletal ultrasonography

Shigeru Ohno

Center for Rheumatic Diseases, Yokohama City University Medical Center, Yokohama, Japan

Over the last decade, musculoskeletal US (MSUS) has become an important tool in clinical practice in rheumatology, especially in Europe. MSUS can detect subclinical synovitis which can not be evaluated by clinical examination, and it also detects bone erosions which can not be revealed by conventional radiography. MSUS gives us various important information necessary for the early diagnosis, the accurate evaluation of disease activity and prediction of the prognosis of RA, as well as those for the guidance of dynamic treatment strategies. MSUS is one of the clinical tools necessary for tight control of RA and its clinical use can even improve the long-term prognosis of RA patients. MSUS has also demonstrated its value across a range of rheumatic conditions.

There are some frequently asked questions about MSUS.

I don't need MSUS. I can judge by clinical evaluation or CRP.

MRI is more clinician-friendly and accurate.

MSUS is operator dependent and inaccurate.

Can RA be diagnosed solely with MSUS?

MSUS is time-consuming.

Should I change the treatment by the findings of MSUS?

Who should perform MSUS?

How many joints should be examined?

In this symposium, I would like to answer these FAQs showing im-

ages and existing evidence. At this moment, MSUS is not widely used in Japan compared with European countries, but it will become an important clinical tool for all the Japanese rheumatologists in the next decade. We are entering a new stage of the management of rheumatic diseases with treatment strategies such as 'tight control' and 'treat to target'. I would like to discuss the importance of MSUS in the clinical practice in rheumatology.

NDS5-2

MRI diagnosis of rheumatoid arthritis

Takeshi Suzuki, Masanobu Horikoshi, Makoto Sugihara, Hiroto Tsuboi, Hiroshi Ogishima, Isao Matsumoto, Takayuki Sumida

Division of Clinical Immunology, Major of Advanced Biochemical Applications, Graduate School of Comprehensive Human Science, University of Tsukuba

Recently, it is well known that a therapeutic window of opportunity exists in the early stage of rheumatoid arthritis (RA) and starting of treatment in this time is important for prevention of joint destruction. Thus developing better methods for the early diagnosis and treatment of RA is the prime objective for rheumatologists, and a new imaging diagnostic tool such as ultrasounds and MRI are getting attention. The major observations found by MRI are bone erosion, bone edema, synovitis and tenosynovitis. While bone erosion can be detected by radiography and synovitis and tenosynovitis by ultrasounds, bone edema can be found by only MRI.

Hence, one of the meanings of MRI in daily practice is evaluation of bone edema. Bone edema is defined as a lesion within the trabecular bone with ill-defined margins and signal characteristics consistent with increased water content which show high signal intensity on STIR and low signal intensity on T1 weighted image. In general, bone edema exists alone or exists adjacent to MRI bone erosion. Because MRI bone edema predicts a total Sharp, bone edema is known as a predictor of erosive change. Hence, the precise estimation of not only synovitis but also bone edema is important for the improvement of joint prognosis of RA. Hence, periodical MRI estimation is expected. In the case of MRI estimation of bone edema is important, swollen joint is improved but tender joint isn't, serological inflammatory markers is higher compared with physical finding and joint destruction is proceeding even if under low clinical activity. In these cases, bone edema is still remained strongly even if synovitis is improved. However MRI is not widely spread in daily practice because of some limitations. Low-field extremity MRI (lfMRI) has been recently developed to address these limitations and our university has developed new lfMRI. In this presentation, I introduced our lfMRI and the patients for which MRI estimation of bone edema is important.

NDS5-3

Conventional Radiography is the gold standard method for joint involvements in RA

Atsushi Kaneko

Department of Orthopaedic surgery and Rheumatology, Nagoya Medical Center, NHO, Nagoya, Japan

In spite of the fact that numerical parameters for clinical, structural and functional remission have been internationally agreed upon and also that MRI and ultrasound of joints of patients in remission have revealed subclinical synovitis, why is it that large scale clinical trials still depend on scoring systems based on plain X rays? This is because, unlike DAS 28 and HAQ scores that can provide only a snapshot of the disease state, a plain X ray can reveal the entire course that the disease has gone through, particularly the scale and

speed of disease progression. Even though MRI can reveal the details of deformity of one particular joint, it is not suited to capture the state of all the joints in the body. Furthermore, the availability of MRI infrastructure is also limited. Ultrasound Sonography can reveal synovial proliferation and hypertrophy, vascularity of synovitis near the bedside teaching, but it is poor in reproducibility. But a plain X ray can comprehensively and sequentially capture the extent of destruction of small, mid, large joints and vertebrae. Hence it can be argued that in large scale RCTs, plain X-ray, along with scoring systems like modified Total Sharp Score will continue to be used as a major parameter in joint assessments.

Larsen's grade classification (1977), which was also used is widely employed for evaluating large joints. However, this classification was developed assuming the aggravation and progression of lesions, and not their improvement, as is observed with biological DMARDs. We develop the new scoring system "X- ray evaluation criteria of RA large joints, allowing for joint remodeling", a set of evaluation criteria developed by the clinical research group of which the author is a member, called ARASHI (Assesment of Rheumatoid Arthritis by Systemic Histological and radiological Imaging) sponsored by the MHLW Health Research Group. In this symposium, I would like to introduce ARASHI new scoring system.

International Symposium

IS-1

G-CSF & GM-CSF as therapeutic targets in autoimmune inflammatory diseases

Ian P Wicks^{1,3}, Brent S McKenzie², Ann L Cornish¹, Ian K Campbell^{1,2}

¹Walter & Eliza Hall Institute of Medical Research and Royal Melbourne Hospital, Melbourne, Australia, ²CSL Ltd, Bio21 Institute, Melbourne, Australia, ³University of Melbourne, Victoria, Australia

Granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) are well-recognised haemopoietic regulators and are used clinically as growth factors to enhance myelopoiesis. Although generally well tolerated in cancer treatment, administration of G-CSF and GM-CSF can exacerbate underlying autoimmune conditions. G-CSF and particularly GM-CSF are widely produced, pleiotropic cytokines that regulate the production, differentiation and activation of a variety of myeloid cells. Enhanced myelopoiesis accompanies acute and chronic inflammatory disease responses. Endogenous G-CSF and GM-CSF also have effects on cells outside of the bone marrow. These effects may amplify maladaptive immune responses in autoimmunity, including the Th17 pathway. We postulate that antagonism of G-CSF and/or GM-CSF could represent novel therapeutic approaches for a variety of autoimmune diseases that cause sterile tissue inflammation, including rheumatoid arthritis (RA). This presentation will review pre-clinical evidence for this approach in murine models of disease and considerations in moving into the clinic.

IS-2

Therapeutic potential of PI3K inhibitors for rheumatoid arthritis and other rheumatic diseases

Naoto Tamura

Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo, Japan

Small molecule compounds that target components of signal transduction pathways are attractive therapeutics of chronic inflammatory diseases, including rheumatoid arthritis (RA), because they are orally bioavailable and potentially cheaper to manufacture than biologics. Class I phosphatidylinositol-3 kinase (PI3K) is an enzyme that phosphorylates phosphoinositides in response to extracellular stimuli and regulates cellular activation, proliferation, and migration, in a variety of cell types, suggesting that it plays a critical role in the development of inflammation. In patients with RA, recent reports have shown convincing pathogenic evidence for the involvement of PI3K and Akt signaling pathways in synovial inflammation. We have demonstrated anti-rheumatic effects of a novel PI3K-specific inhibitor, ZSTK474, in autoimmune arthritis models. Administration of ZSTK474, even if started after the development of arthritis, ameliorated rat adjuvant-induced arthritis (AIA) and mouse collagen-induced arthritis (CIA) with no apparent adverse effect. Proliferation of B lymphocytes and synovial fibroblasts from AIA rats were inhibited by ZSTK474 *in vitro*. ZSTK474 reduced weight of the peripheral lymph node in AIA rats. Production of prostaglandin E2 in the synovium was also decreased. Moreover, ZSTK474 suppressed osteoclast formation *in vitro* and also in the joints of CIA mice. Levels of serum biomarkers of systemic bone resorption reduced in ZSTK474-treated groups. Therefore, ZSTK474 might possibly suppress joint destruction in RA.

Furthermore, activation of PI3K/Akt pathway was also reported in lupus-prone MRL-lpr mice and selective inhibition of PI3K gamma reduced the disease incidence and severity. More recently, the ki-

nome array analysis revealed particular upregulation of PI3K in B cells from patients with SLE in comparison with matched controls. These findings indicate that PI3K might be a potential therapeutic target of RA, other choric arthritis, and SLE.

IS-3

Regulation of T helper cell differentiation and function by microRNAs

Stefan A Muljo

National Institutes of Health, NIAID, Laboratory of Immunology, Bethesda, Maryland, USA

Eukaryotes possess microRNA (miRNA) genes that encode a class of evolutionarily-conserved small untranslated RNAs capable of regulating gene expression at the post-transcriptional and translational level. They are initially expressed as long primary RNA transcripts that form characteristic stem-loop structures, which get recognized and cleaved by the RNaseIII-like enzymes Droscha and Dicer to generate small RNA duplexes 19-23 nucleotides in length. These miRNAs are not translated into protein in order to function, but instead physically interact with complementary nucleic acid sequences and Argonaute (Ago) protein complexes called RNA-induced silencing complexes (RISC) to mediate sequence-specific gene silencing. As such, they utilize the endogenous RNA interference machinery, a novel pathway for genetic regulation. Due to their small size and inability to code for protein, miRNAs were overlooked until recently. Nowadays, their ability to regulate gene expression programs and consequently a diverse array of cellular processes such as signal transduction, cell cycle, apoptosis, pluripotency, differentiation, and transformation is well appreciated. Using genetically engineered mice harboring a conditional allele of Dicer to specifically ablate miRNA biogenesis in T cells, we previously observed that T cell development was impaired and CD4⁺ T helper cell differentiation was aberrant. To identify miRNAs that may control T helper cell differentiation, we performed a miRNA expression profiling screen of four well-characterized subsets: Th1, Th2, Th17 and iTreg. As a result, we identified subset-specific miRNA expression profiles. We will describe one example of a miRNA that is highly-expressed in Th17 cells, and our ongoing exploration of its role in T helper cell differentiation and function.

IS-4

Role of TGF- β -Smad2/3 signaling in helper T cell function and differentiation

Akihiko Yoshimura, Kenji Ichiyama

Department of Microbiology, Keio University School of Medicine

Th17 cells have been implicated in autoimmune disease models including collagen-induced arthritis. The transforming growth factor- β (TGF- β) has been shown to play pivotal roles in Th17 differentiation. However, TGF- β also is involved in iTreg induction and immune suppression, and signaling mechanisms by TGF- β for these various functions has not been well understood. In this study, we generated T cell specific Smad2/3 knockout (cKO) mice. In vitro analysis indicate that both Smad2 and smad3 were redundantly essential for the induction as well as maintenance of Foxp3 by TGF- β . Smad2/3 were also redundantly essential for the suppression of IL-2 and IFN- γ production from naïve CD4⁺T cells. Consistent with these data, Smad2/Smad3-double knockout mice, but not single knockout mice, develop fatal inflammatory diseases with higher IFN- γ . Smad2-cKO mice were resistant against Th17-mediated autoimmune disease, suggesting that the Smad pathway is involved in Th17 differentiation. However, ROR γ t, the master regulator of Th17

differentiation, was normally induced in the absence of Smad2/3. Thus, Smad2/3 indirectly regulate Th17 development through suppressing anti-Th17 cytokine (IL-2, IL-4 and IFN- γ) production. Last important question is what is the Smad-independent pathway and how it upregulates ROR γ t. We identified several genes regulated by Smad-independent pathway using Smad2^{-/-}Smad3^{-/-} T cells. We found that the expression of Eomesodermin (Eomes) is strongly suppressed by TGF- β 1 through the Smad-independent, JNK/c-Jun-dependent pathway. Overexpression of Eomes significantly suppressed the Th17 differentiation, while knockdown of Eomes expression replaced TGF-beta in primary T cells. Blockage of the JNK pathway abrogated Eomes repression and reduced Th17 differentiation. Thus, suppression of Eomes by TGF- β 1 is suggested to be one of the mechanisms for Smad-independent Th17 differentiation.

IS-5

Assessing progression of osteoarthritis

David J Hunter

University of Sydney, Sydney, Australia.

Accurate, highly reproducible and responsive measures of the rate of disease progression are a prerequisite for assessing structural change in clinical trials. As osteoarthritis is typically a very slowly progressive condition, one can optimize trial efficiency by finding more responsive endpoint/s and or stratifying the study sample to further enhance efficiency. Traditionally measurement of OA structural change has been performed using radiographs. Due to inherent limitations in plain radiograph technology, further research and development has investigated other techniques that may improve the assessment of disease, its early development and its progression. Foremost among these is Magnetic Resonance Imaging (MRI), a non-invasive three dimensional method for assessing joint morphology that may supplant the widespread use of plain radiographs in clinical trials. Broadly speaking, MRIs of OA structure can be measured semi-quantitatively or quantitatively, and either morphological or compositional measurements of articular cartilage can be obtained. Whilst MRI has enormous potential, recent studies provide a note of caution for its immediate ability to supersede the weight-bearing radiograph. The responsiveness of different measures of cartilage morphometry may not be as great as early data suggested. Conservative study designs based on large MRI progression series currently in the public domain require large sample sizes, if quantitative cartilage morphometry measures are used as the endpoint. If one could confidently design studies based on smaller sample sizes and/or shorter study durations, this would, greatly reduce the resource implications for MRI based interventional studies.

IS-6

In vivo three dimensional imaging system for the analysis of joint function

Kazuomi Sugamoto

Orthopedic Biomaterial Science, Osaka University Graduate School of Medicine, Osaka, Japan

Thousand of cadaveric studies were already reported but those may differ from in vivo condition for lack of ligamentous or muscular effect. Plain X-ray only gives us two dimensional information and it is not sufficient for the 3D analysis. 3D CT or MRI are only the device to visualize the structure under the static conditions. Development of in vivo 3D kinematic analysis system are really needed. Two systems were developed in our institute. One is a system using 3D CT or MRI and the targeted joint is placed in serial positions of the motion plane to evaluate 3D kinematic of the motion

and the images are obtained in each position. The data are saved and transmitted to a computer workstation, where image processing such as segmentation and volume registration are performed using a software program developed in our laboratory. Segmentation is defined as extracting the contour of the bone required for processing, which is semi-automatically segmented by intensity thresholding techniques. Volume registration is an image processing method for matching volume images based on voxel values. Kinematic variables are measured by automatically superimposing segmented 3D CT or MRI of the bones in the neutral position over images for each position using this method of registration. The correlation coefficient is used as a method of measuring similarity of voxel values for registration. With this method of measuring, a matrix that allowed for the maximal correlation of the two images is calculated. Animations of the joint movement are created from the calculated motions and surface bone models that were reconstructed from #D-MRI data using the marching cubes algorithm in the Visualization Toolkit (VTK). This method is available for the in vivo 3D kinematics after the arthroplasty. The 3D pose-estimation technique is built on a 2D/3D registration algorithm, which determines the spacial pose for each component from the implant contours and CAD models of the implant.

Educational Lecture

EL1

Skilled directions for DMARDs

Takaaki Fukuda

Center for Rheumatic diseases, Kurume University Medical Center

We have a strong therapeutic procedure of biologics for the treatment of rheumatoid arthritis(RA). But, A clinical remission is very possible so far even by basic nonbiologic DMARDs treatment.

It is most important thing for the management of RA is early diagnosis and starting DMARDs earlier. DMARDs are a medicine that controls the RA inflammation by modifying the immune abnormality of RA. The Ministry of Health, Labor and Welfare research group made a diagnosis and treatment manual of the RA (revised edition) in 2004. The DMARDs has been summerised in Chapter 5. Also, ACR announced the RA treatment guideline in 2002. The feature are ?DMARDs beginning within three months ?Continuance or the change and the addition are examined the effect judgment in month third or more ?The anchor drug of DMARDs is a methotrexate ?The use of biologics was considered in cases of DMARDs failure. Afterwards, ACR 2008 Recommendations concerning the use of low molecular DMARDs and biologics was announced. The recommendations made in the text for when to start or resume a therapy are discussed predominately by drug. Further, when different drugs were similarly recommended for a particular clinical circumstance, their order of presentation was alphabetical and listed in a specific order of preference. After establishing a diagnosis of RA, risk assessment is crucial for guiding optimal treatment. Recommendations for non-biologic therapy are divided into those patients with RA of varying disease duration, as defined by duration of <6months, 6-24months, and >24months and be showed by figures. In the EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs, ?Treatment with synthetic DMARDs shuld be started as soon as the diagnosis of RA is made. ?MTX shuld be part of the first treatment strategy in patients with active RA. are stated. I would like to do explicate of DMARDs.

EL2

Lung infections during the treatment of rheumatoid arthritis

Hitoshi Tokuda

Social Insurance Central General Hospital

Biologic agents, including TNF inhibitors and IL-6 receptor antibody, have been widely introduced as therapeutic tools for rheumatoid arthritis and have obtained a great success in disease control. However various infections emerged at considerable rate as adverse effects of these new treatments. Lung infections are the most important because of their diversity, difficulty of diagnosis, and disease severity. We shall discuss lung infections in 5 categories, 1) bacterial pneumonia, 2) organizing pneumonia 3) Pneumocystis pneumonia (PCP), 4) drug induced acute lung injury in necessity of distinction with PCP, 5) Mycobacterial infection. Bacterial pneumonia in RA patients somewhat differ from ordinary community acquired pneumonia in healthy people. Often its causative agents includes Pseudomonas, originating from concomitant lung diseases such as bronchiectasis and fibrosis. Antibiotics should be chosen taking into consideration these unique spectrum of bacteria species. Organizing pneumonia in RA resembles bacterial pneumonia but does not respond to antibiotics. It only respond to corticosteroid therapy. Currently this disorder is tend to be classified as interstitial lung disease, bot some people assume that it is a failure of resolution of infectious pneumonia. PCP is relatively rare but sometimes fatal complication.

In RA patients, the diagnosis is often difficult because of small amount of the organism. The treatment is also difficult. The pathogenesis of PCP has been clarified as augmented immune response evoked by this organism. Treatment should be constituted based on these knowledge, including corticosteroid therapy. Mycobacterial infection includes tuberculosis (TB) and non-tuberculous Mycobacteriosis (NTM). The prophylaxis of TB has been established but the proper criteria for the selection of candidates remains unsolved. As for NTM no treatment or prophylactic strategy has been established because of its resistance to antibiotics.

EL3

The new evolution of autoinflammatory syndrome

Tomoyuki Imagawa

Department of Pediatrics, Yokohama City University School of Medicine

The autoinflammatory syndrome includes various disease that cause the inflammation, and each mechanism of inflammation has become clear gradually by clarifying the disease gene in recent years. Moreover, the biologics where pro-inflammatory cytokine such as IL-1 β and TNF α is obstructed has come to be introduced in the treatment. It has come to obtain the improvement of a long-term prognosis by preventing the sequela such as amyloidosis that happen in succession to the improvement and that of the inflammation by clarifying therapeutic targets more than the inflammation conditions when treating to the autoinflammatory syndrome, and selecting the remedy. Abnormality of the gene that controls the inflammatory cytokine production, the secretion, and it like IL-1 β and TNF α , etc is clarified by the inflammatory condition. It is significant to consider the understanding of the inflammation condition to be treatment to consider the inflammatory condition of the autoinflammatory syndrome.

EL4

Radiographic features and treatment for spinal lesions of rheumatic diseases

Junichiro Nakamura

Yokohama City University Medical Center

The upper cervical spine is often affected in rheumatoid arthritis (RA), where neck pain and spastic quadriplegia are primary symptoms. Atlantoaxial subluxation (AAS) and vertical subluxation (VS) are well-known conditions of RA. Single-plane lateral radiography of the cervical spine is simple and effective for detecting spinal lesions. An atlantodental interval of more than 3 mm indicates AAS, and if the space available for the spinal cord is less than 14 mm, myelopathy is a risk. Subaxial lesions have a stepladder appearance. Magnetic resonance (MR) imaging of the spine is indispensable for evaluation of the spinal cord in RA patients. Some patients with AAS or VS complain of vertebrobasilar insufficiency symptoms such as vertigo, double vision and dizziness. MR angiography or enhanced computed tomography as well as angiography of the vertebral artery should be performed for such patients. Severe neck pain or myelopathy are considered surgical indications. Spondyloarthritis (SpA) and ankylosing spondylitis (AS) are considered to have a low prevalence in Japan. Recently however, the prevalence of SpA has been reported to be the same as that of RA. The various symptoms include back pain, morning stiffness, weight loss, general fatigue and peripheral joint pain. AS often overlaps with psoriasis, inflammatory bowel disease, or with uveitis or iritis. NSAIDs are commonly used for the treatment of AS and SpA. Sulfasalazine is effective for peripheral arthritis of AS. Anti-TNF-alpha blockers are now

also used for the treatment of AS and related diseases. Early diagnosis of SpA is required for a good response to anti-TNF-alpha agent therapy. MRI of the sacroiliac joint can detect early-stage sacroiliitis of SpA. While fludeoxyglucose positron emission tomography is expensive and not covered by health insurance, it is however sometimes useful for diagnosing undifferentiated SpA. Surgical treatment (spinal osteotomy and THA) are also performed as required.

EL5

Imaging examination for rheumatoid arthritis

Isao Matsushita, Hiraku Motomura, Tomoatsu Kimura

Department of Orthopaedic Surgery, Faculty of Medicine, University of Toyama

Early diagnosis and tight control of disease activity are essential for the management of rheumatoid arthritis (RA). To obtain better clinical outcome, it is important to use appropriate imaging modalities as a guide for 'treat to target'. Plain radiographic examination is a basic tool to assess joint damage in RA. Early radiograph shows soft tissue swelling and bone atrophy around joints. Pocket erosion in bear areas, joint space narrowing and roughness of subchondral bone are detected at progressive stage in RA. Modified Sharp score is a useful method for the evaluation of small changes of joints in early stage of RA. However, only small joints in hands and feet are assessed by this scoring system. We developed ARASHI scoring system for the evaluation of large joint damage in RA. This scoring system is well related to Larsen grade and further detail of large joint changes can be evaluated. Ultrasonographic (US) examination in RA is a very useful tool to make early diagnosis and to evaluate efficacy of treatment. Thickness of synovium and effusion are detected using gray scale method of US, and abnormal vascular signal can be detected by power Doppler method. Using US, sensitivity and specificity for detecting synovitis is as high as MRI. MRI can identify bone lesion associated with RA which cannot be visualized by radiographic technique. Bone marrow edema has been described as an ill-defined area of abnormal signal intensity. The presence of bone marrow edema can be a marker of inflammatory activity of RA and be defined as a pre-erosive lesion which enables us to predict joint damage. MRI erosion is detected as a well-defined area of abnormal signal. MRI is more sensitive than conventional radiography in detecting bone erosions in early RA. Here, I report on the usefulness and pitfall of imaging examination in rheumatoid arthritis using cases we have followed.

EL6

Skin manifestations in collagen-vascular and rheumatic diseases

Hikaru Eto

St. Luke's International Hospital

There are so many skin manifestations expressed in collagen-vascular and rheumatic diseases. In SLE, disease specific skin manifestations are, 1. Acute or subacute cutaneous lupus, 2. Chronic cutaneous lupus, 3. Oral/Nasal ulcers, and 4. Nonscarring alopecia. There are many non-specific skin manifestations as Raynaud's phenomenon, acrocyanosis, pernio-like erythema, and livedo reticularis. These symptoms are important for diagnosing SLE. In systemic sclerosis (SSc), skin sclerosis and insufficient peripheral blood circulations are major cutaneous signs. When we come-across to skin sclerosis without Raynaud's phenomenon, we have to differentiate it from adjuvant disease, diabetic digital sclerosis, or drug-induced skin sclerosis. In dermatomyositis, heliotrope-like erythema, Gottron's sign, periungual erythema, poikiloderma are major skin manifestations, and they are especially important for diagnosing

amyopathic dermatomyositis. In ARS antibody syndrome, mechanic's hands are specific skin manifestations that correlate with interstitial lung disease (ILD). Some ARS antibody syndrome cases may be included among those previously diagnosed as ILD. Since mechanic's hands are clinically similar to hand eczema, skin biopsy should be taken in suspicious cases. In Sjogren syndrome, dry skin, annular erythema, insect-bite like erythema, urticarial erythema, erythema nodosum, hyper gamma-globulinemic purpura, pernio-like erythema can be seen. In rheumatoid arthritis, necrobiotic skin lesions, vasculitis, neutrophilic dermatosis are frequently associated. Recent increase of psoriatic arthritis became major target for anti-TNF therapy, which is important differential diagnosis in sero-negative arthritis.

EL7

Evaluation and treatment of rheumatic disease-related lower limb joint lesions

Ryota Teshima

Department of Orthopedic Surgery, Faculty of Medicine, Tottori University, Yonago, Japan

The lower limbs play an important role in the preservation of the standing position and gait. The healthy condition of the bilateral lower limbs facilitates gait. The unaffected limb's compensatory function does not act, differing from the upper limbs. Therefore, the development of lower limb joint lesions affects basic ADL including gait even when they are mild, markedly reducing the QOL; it is necessary to accurately and promptly evaluate and treat the condition. Physicians should observe patients' gait and posture on entering the consultation room, and evaluate the grade of pain and gait disorder. Physicians should concretely ask about the type/grade of pain to objectively evaluate the type (resting pain, starting pain, pain on motion, and nocturnal pain) and grade (persistent, transient, severe, and dull) of pain. The presence or absence of resting pain is important for evaluating the condition. Usually, its presence suggests pathologically marked inflammatory/destructive conditions.

After identifying the localization of a lesion, patients should be examined to evaluate the condition. Flare, heat sensation, swelling, tenderness, and joint mobility must be assessed in comparison with the unaffected side. Based on these physical findings, the anatomical/histological localization of the lesion should be estimated. Subsequently, to verify a tentatively diagnosed disease, hematology and imaging procedures should be performed.

Based on physical and laboratory findings, it should be verified whether the tentatively diagnosed disease is appropriate, and treatment must be performed in accordance with the disease. For diagnosis, referred pain, lumbar/root pain, neuralgia, and malignant tumors should be considered. For treatment, it is important to maintain/improve the walking function.

EL8

Current evaluation of joint function for treatment of joint disease

Takashi Nakamura

Department of Orthopaedic Surgery, Graduate School of Medicine, Kyoto University

The basic function of joint consists of the three elements, stability, mobility and painless. While the functional evaluation of joint includes the range of motion, the muscle strength and assessment of joint function is possible by using advanced image technology and biochemical analysis of joint fluid or blood

In this lecture normal joint function will be reviewed from the view

point of lubrication of articular cartilage. The surface of articular cartilage and joint fluid play key roles for the good lubrication of joint. The sliding surface of the joint becomes important for boundary lubrication and joint fluid is essential for liquid lubrication. Lubricin and hyaluronic acid are key molecules for joint lubrication.

The second topics of this lecture will review the advanced imaging for the functional assessment. MRI and CT in recent years show a remarkable progress and are applied for the joint evaluation. Contrasted MRI of cartilage is possible using Gd which is trapped in cartilage matrix by ionic charge. It is called as dGEMRIC (delayed phase imaging cartilage MRI). Additionally it is known that the mechanical properties of cartilage can be measured with the use of ultrasound. Ultrasound or OCT will be used new technique for evaluation of cartilage.

EL9

Adipokines in Rheumatic Diseases

Shinichi Kawai

Rheumatic Disease Center, Toho University School of Medicine, Tokyo, Japan

Adipose tissue has long been known as a structural component of many organs and a site for energy storage. Recently, *in vitro* and *in vivo* studies have demonstrated that the major cellular component of adipose tissue, the adipocyte, has the ability to synthesize and release various physiologically active molecules, including adiponectin, leptin, resistin, and visfatin as well as cytokines like interleukin (IL)-6 and tumor necrosis factor α . They are called as adipokines or adipocytokines. Initial reports about adipokines were focused mainly to insulin resistance in diabetics and atherosclerosis, however, some reports raised our interest with respect to the role of adipokines in inflammation and immunity. In addition, dyslipidemia and immature atherosclerosis in rheumatic diseases such as RA and SLE have been reported as major complications in these diseases. We have reported that the serum levels of resistin, leptin, and adiponectin were all associated with CRP level in patients with rheumatoid arthritis (RA). We also revealed that adiponectin stimulates the productions of IL-8 and prostaglandin E_2 by RA synovial fibroblasts in a receptor-dependent manner, suggesting that some adipokines may act as pro-inflammatory cytokines in RA. Furthermore, it is demonstrated that resistin is one of the key adipokines in systemic rheumatic diseases such as systemic lupus erythematosus, systemic vasculitis syndrome, and Kawasaki syndrome. These results suggest that some adipokines may play an important role at least in part in pathophysiological conditions of various rheumatic diseases.

EL10

Interstitial lung disease in rheumatoid arthritis

Sakae Honma

Department of Respiratory Medicine, Toho University Omori Medical Center

Interstitial lung disease (ILD) is a frequent extraarticular manifestation of rheumatoid-arthritis (RA). The existence of ILD can be clarified by the introduction of HRCT. It is classified into two categories which consisted of primary lung lesions caused by RA itself and secondly associated lung lesions such as drug-induced pneumonitis or opportunistic infection. The reported prevalence of ILD in patients with RA is 10 to 50%. Several studies have reported smoking, male gender, and longstanding RA to be risk factors for the development of ILD. Patients with RA-ILD most often present with chronic cough and exertional dyspnea. A physical examination may reveal inspiratory fine crackles, and pulmonary function tests dem-

onstrate restrictive impairment with a reduced diffusing capacity. The serum levels of damaged-pneumocyte markers (KL-6 and surfactant proteins A and D) are frequently increased. HRCT scanning is generally sufficient to confirm the diagnosis of ILD, although in a minority of cases, surgical lung biopsy may be required. The histopathologic and radiographic appearance of RA-ILD is heterogeneous and primarily mimics the patterns seen in the idiopathic interstitial pneumonias such as usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP) and organizing pneumonia (OP). While the NSIP pattern predominates in most forms of connective tissue-associated ILD, studies in patients with RA-ILD suggest that the UIP pattern is more common in this patient population. UIP pattern appears to predict worse survival in RA-ILD patients. Moreover, preexisting ILD is a well-known risk factor for drug-induced ILD. It is important to distinguish drug-induced pneumonitis or opportunistic infection from primary RA-ILD lesions. We should make a treatment for RA patients according to the cause of each lung lesions.

EL11

A treatment for an intractable organ involvement for collagen diseases

Hirahito Endo

Toho University School of Medicine, Ohmori Medical Center, Department of Rheumatology

Severe organ involvements include in many collagen diseases. Although recent progress on therapy of collagen diseases with severe organ involvements the prognosis of these patients did not improve until now. There are still many intractable involvements that are resistant to the conventional therapy using corticosteroids and immunosuppressive drugs. Such treatment resistant disorders include interstitial lung disease in inflammatory myositis, severe lupus nephritis, and pulmonary arterial hypertension etc. Recently, several new approaches to treat the severe intractable complications of patients with collagen diseases reported. These new therapeutic approaches were involved new biologics such as rituximab, targeting small molecules such as BlyS antagonist, and intravenous immunoglobulin therapy in vasculitis or interstitial pneumonitis. However corticosteroids and immunosuppressive drugs is still a basic for the treatment of collagen diseases. The advance effects of therapeutic drug such as corticosteroids and immunosuppressive drugs sometimes become a problem. It is important that we prevent treatment adverse drug reactions. These severe advance effects were serious infectious diseases and aseptic necrosis etc. This lecture will give you information about a standard strategy and topics of therapy for several severe organ involvements with collagen diseases. I will discuss the treatment of the intractable severe organ involvements of patients with connective tissue diseases.

EL12

Latest New Evidences of TNF Inhibitor

Yutaka Kawahito

Kyoto Prefectural University of Medicine

As a TNF inhibitor, etanercept and adalimumab were approved since the use of infliximab was enabled in Japan in 2003. The disease activity of patients with rheumatoid arthritis (RA) decreased, and ADL followed by life expectancy improved. On the other hand, these TNF inhibitors were used for psoriasis, psoriatic arthritis, and ankylosing spondylitis. Infliximab was also adapted to the intractable uveitis of Behcet's disease, and the treatment of the refractory rheumatic diseases is enabled. The benefit to the treatment of these

TNF inhibitors is very big for rheumatology. In recent years the recommendation of the treatment of RA is published by ACR and EULAR, and the clinical remission is a realistic goal for the treatment of RA which is suggested by Treat to Target (T2T). Furthermore, the definition of the remission announced by ACR/EULAR in ACR 2010 was severer than a conventional remission standard. Thus the treatment of RA moved to the new change period. The post marketing surveys (PMS) of TNF inhibitors are almost finished. Based on these Japanese evidences, how we should treat RA patients to aim at the continued remission is an important problem now. In this lecture we want to talk about the treatment approach to clinical remission and the application of new TNF inhibitors such as certolizumab and golimumab which will be approved for the treatment of RA in the near future.

EL13

Laboratory tests to evaluate the prognosis of rheumatoid arthritis

Yoshinari Takasaki

Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine

Rheumatoid arthritis is known to be an autoimmune disease which is characterized by progressive-destructive arthritis, and patients with RA develop seriously decreased QOL (quality of life) without adequate treatments in the early stage of disease. Therefore the main purposes of the treatment for RA are to prevent bone/cartilage destruction, to improve QO of patients, and to improve prognosis. From this perspective, it is required that disease-modifying antirheumatic drugs (DMARDs) and biologic agents, which prevent or delay bone/cartilage destruction, must be started immediately after diagnosis of RA. But the selection of the drugs is not always easy because of adverse reactions of these drugs. Therefore, the evaluation of prognosis in each patient has become an important factor to determine the strategy for the treatment. It is known that serological factors such as anti-cyclic citrullinated peptide (CCP) antibody and IgM-rheumatoid factor (RF) are useful to evaluate the prognosis of RA, in addition to the diagnosis. Not only autoantibodies i, but also some parameters for inflammation such as MMP-3 are also known to be useful for the evaluation of the prognosis n RA patients. In this session, laboratory tests to evaluate the prognosis of rheumatoid arthritis as above mention will be discussed.

EL14

Indications of biologics and its proper use in rheumatoid arthritis

Nobuyuki Miyasaka

Department of Medicine & Rheumatology, Tokyo Medical & Dental University

Rheumatoid arthritis is characterized by persistent and destructive arthritis and often involves systemic organs. Introduction of biologics has dramatically changed its outcome and early intervention of the disease together with tight control enables us to achieve not only clinical remission, but also structural remission and functional remission. However, there is always a negative side of the coins, which are the adverse effects of biologics, especially if not used properly. It is therefore essential for rheumatologists to know both indications and contraindications of biologics. Postmarketing surveillance study of biologics in Japan clearly identified the risk factors for serious infection, i.e. advanced age, preexisting lung diseases and long-term steroid use. Screening of latent tuberculosis and other types of infections prior to the use of biologics should be per-

formed and anti-tuberculous drug, i.e. isoniazid should be administered prophylactically prior to the commencement of biologics. Development of *Pneumocystis jiroveci* pneumonia (PCP) during biologics treatment has drawn the attention in Japan and rheumatologists should master how to prevent, diagnose or treat this potentially fatal complicated condition. Vaccination against influenza should be done periodically and pneumococcal vaccine is indicated for elderly patients or those having risk factors for infection. Proper use of biologics to treat rheumatoid arthritis will be discussed.

EL15

Recent progress in surgical treatment for cervical spine lesions in rheumatoid arthritis patients

Masashi Yamazaki

Department of Orthopaedic Surgery, Chiba University Graduate School of Medicine

Cervical spine lesions in rheumatoid arthritis (RA) patients include atlantoaxial subluxation, vertical subluxation and subaxial subluxation. When compression to the spinal cord occurs and myelopathy progresses, gait disturbance and clumsiness of hands become prominent. Previous reports have shown evidence that once myelopathy develops, patient life expectancy is poor if they are not treated surgically. However, conventional surgical techniques such as decompression and bone grafting are insufficient for treating destructive RA in the cervical spine. Recent advances in spinal instrumentation have enabled us to perform rigid internal fixation. Thus, reconstruction surgery for RA in the cervical spine has been increasingly performed.

Occipitocervical (O-C) posterior fusion and atlantoaxial posterior fixation have been performed using anchors such as C1–C2 transarticular, pedicle, and lateral mass screws. By using spinal instrumentation, we can treat RA spine patients with a postoperative rehabilitation program earlier. However, risk of vertebral artery (VA) injury at the insertion of screws is a major problem. Therefore, surgeons must consider how to safely and effectively insert screws, and accurate preoperative surgical planning is required. 3D CT angiography is a useful tool for evaluating the course of VAs. Preoperative surgical simulation and intraoperative navigation using 3D full-scale models can improve the safety of surgery.

When neck is fixed at kyphotic alignment for O-C fusion, the risk of development of dysphagia increases. The O-C2 angle is a useful marker for evaluating the upper cervical alignment. Negative change of the O-C2 angle after O-C fusion is associated with the development of dysphagia.

In RA patients with an upper cervical lesion, sleep apnea syndrome (SAS) frequently develops. It has been believed that compression of the brain stem by a vertically subluxed axis causes central apnea. However, our report has recently shown that most SAS in RA patients is the result of obstructive apnea, and O-C fusion with correction of kyphosis at the craniovertebral junction has the potential to improve SAS.

EL16

Assessment of upper limb functions for total management of rheumatoid patients

Michiaki Takagi

Department of Orthopaedics, Yamagata University Hospital

In total management of RA patients, drug therapy, surgery, rehabilitation and care play major roles. The aim is to improve ADL and QOL. Physical, mental and social factors are essential for better management. Many medical professions participate in the process

and their minute cooperation is indispensable.

Adequate evaluation can help better management, especially in new era of RA therapy. Patient-based evaluation and outcome analyses are important. Various functional assessment of upper limb are applied not only by restricted manners, but also under general consideration for QOL. Upper limb function mainly consists of reach, grasp, skill of hand and adjusting arm direction. Disabilities of upper limb is caused by pain, swelling, abnormal range of motion and instability of joints, which are often combined with muscle weakness, musculoskeletal imbalance, neuropathies, and vasculitis. It is also affected by systemic disease state, other joints and their inabilities. It is important to recognize that disability of the upper limb can appear even in the initial stage, and that compensatory function by neighboring sites and opposite limb may mask the disability.

Together with better understanding of anatomy and exercise physiology, intimate inquiry and consideration regarding basic evaluations, i.e., muscle power, range of motion, perimeter, length of limb, deformity, instability and neural function, as well as objectively detailed evaluations, i.e., DASH, STEF, Hand 20, score for shoulder and elbow (JOA), and that for wrist (PRW, JSSH), are desirable. It would be also referred to and/or combined with items of upper limb described in related ADL and QOL analyses. Such strategy and the outcome assessment may contribute to evaluation of upper limb function, thus leading to more substantial total management of RA patients.

Rising & Achievement Seminar

RA1

How to use practical biologics in rheumatoid arthritis

Katsuaki Kanbe

Department of Orthopaedic Surgery, Tokyo Women's Medical University, Medical Center East

It is reasonable to induce early remission and continue it for long term even remission criteria of ACR was changed recently. Biologics is possible to continue remission stably and long period with inhibition of progression of joint destruction. However biologics have sometimes limitation of inhibition of all joint swelling and tenderness. We found the relationship between disease duration and HAQ under biologics treatment. Therefore biologics can decrease HAQ in early stage RA on the other hand it was limitation in progressive RA even treatment of biologics. Here I would like to talk about practical use of biologics by experience more than 850 cases of biologics. There are methods to treat tolerated cases with biologics such as MTX increasing, steroid i.v., dose increase of biologics, addition of DMARDs, switching to other biologics. We reported previously that arthroscopic synovectomy was useful for tolerated cases of biologics and good indication was no wait for treated cases with joint swelling especially knee joints. In general, cases of Larsen grade III-IV is suitable for arthroplasty in lower limb, however in upper limb including hand, elbow and shoulder, arthroscopic synovectomy is effective to improve ROM with capsular release and mild manipulation. After looking at cytokine expression pattern of TNF- α and IL-6, the decision of biologic choice and increase of rate of remission were performed. However serum expression pattern of TNF- α and IL-6 were different between practical clinic and logical theory in biologics. Further topics of orthopaedics surgery and biologics including infection rate or timing of operation are addressed in this seminar.

RA2

Metalloproteinases in destruction of articular cartilage in rheumatoid arthritis

Yasunori Okada

Department of Pathology, School of Medicine, Keio University

Synovial joint is composed of articular cartilage, synovial membrane and joint cavity. Once joint receives injuries, synovial membrane can be completely repaired, whereas articular cartilage results in irreversible damage because of its poor repair ability. In RA (rheumatoid arthritis), which is characterized by chronic proliferative synovitis, articular cartilage and bone are targeted for the destruction, but synovial membrane can be escaped from the destruction. Members of the MMP (matrix metalloproteinase) and the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) gene families are believed to play a central role in the destruction of articular cartilage by degradation of the extracellular matrix in the cartilage. Degradation of aggrecan (a major proteoglycan in cartilage) is ascribed mainly to ADAMTS4 and 5 (aggrecanase-1 and 2) and collagens are degraded by collagenolytic MMPs (MMP-1, 8, 13 and 14). Destruction of articular cartilage by these metalloproteinases in RA is considered to be through three pathways: synovial membrane-derived proteinases in synovial fluids, chondrocyte-produced proteinases and direct contact of proteolytic synovial membrane and pannus tissue. RA synovial membrane is known to produce MMP-1, 2, 3, 8, 9 and 14 and ADAMTS4 as well as TIMP-1, 2 and 3. Most of these MMPs and ADAMTS4 are secreted to synovial fluid and attack surface areas of the articular cartilage. Among them, MMP-3 levels in the synovial fluid are 50–100-

fold higher than other MMPs in RA patients and the data of serum levels are clinically used as a prognostic marker for joint destruction and for monitoring the effects of target therapies on rheumatoid synovitis such as anti-TNF- α antibody therapy. Other drugs used for treatment of arthritides such as high-molecular-weight hyaluronan and COX-2 inhibitors are also reported to down-regulate the expression of ADAMTS4 and some MMPs. In this Rising & Achievement Seminar, I will briefly mention on the basic structure and function of synovial joints, and then review the recent progress on the importance of the metalloproteinases in cartilage destruction based mainly on our data.

RA3

Drug therapy for patients with rheumatoid arthritis in pregnancy

Atsuko Murashima^{1,2}

¹Department of Women's Health, National Center for Child Health and Development, ²Drug Information Institute in Pregnancy

Patients with rheumatoid arthritis (RA) must become pregnant under good conditions to get good results. So, the teratogenicity of the drugs is a very important theme. Some cases taking these medicines worsen while they discontinue those to try pregnancies. We suggest continuously uses of medicine until becoming pregnant based on "all or none" theory to balance pregnancy with treatment while monitoring a menstrual cycle. Among Disease Modifying Anti Rheumatic Drugs (DMARDs), salazosulfapyridine is thought to be the safest for pregnant woman and bucillamine is thought to be safe by experience. Anti-TNF including infliximab, etanercept, and adalimumab are thought to be relatively safe by some researches and are able to be used until becoming pregnant. Of course, it should be carried out after taking the informed consent well. We cannot deny that the Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) which most of the RA patients take influence ovulation and placentation. We may reduce of NSAIDs by using of DMARDs and it may improve sterility. Some studies have shown that steroid has a risk of cleft-lip/palate in slight degree. Tacrolimus is judged relatively safe by the reports of the patients after the transplant. "Risk communication" is most important in drug therapy for patients in pregnancy.

RA4

Launching pad for next paradigm of rheumatology

Kusuki Nishioka

Institute of Medical Science, Tokyo Medical University

Recent advance of molecular targeting strategy has been developing and outstanding progress in the treatment of various intractable inflammatory disorders. Current advance for biology research, together with progress of research environment, we proposed here Bio-Rheumatology on new research launching pad, following 1st Bio-Rheumatology International Congress (BRICs) will be held in Tokyo 14/Nov to 16/Nov. The basic concept of "Bio Rheumatology" is aimed at the formation of new scientific field which embraces "exit" as novel innovation of fusion between "quantum biology" and "cell biology", by end-cutting formation forward and catastrophe of joint-microcosm.

RA5

Total joint arthroplasty of the upper extremities for rheumatoid arthritis patients

Masayuki Sekiguchi

The disease activity fell by MTX and biologics having been introduced into the treatment of rheumatoid arthritis. Moreover, ADL has improved and the life prognosis has also been improved further. However, there are some cases from which the effect of the expected biologics is not acquired. Furthermore, there are also still many cases in which joint destruction already advanced. For these cases, total joint arthroplasty is an indispensable functional reconstruction way. Total joint arthroplasty maintains a patient's ADL and QOL, and improves them. As compared with THA or TKA, the histories of TEA and TFA for rheumatoid arthritis are short, and generally, in order to improve the patient's walk ability first, THA or TKA is performed preferentially. In the Japan market size investigation report in 2009, the total number of total joint system is 171,825 units (106% compared with last year). However, the number of the total joint system of the upper extremities is less than 3% of the total number of artificial joints. If the patient's elbow or finger joints are destroyed, they will receive severe restriction in ADL. For example, washing their face, taking meal, performing hygiene and writing, etc. If the patient's disease activity improves and their life are extended by using the biologics, it will be expected increasing the need of the joint arthroplasty of the upper extremities aiming at an improvement of a upper-extremities function. In Japan many total joint systems of elbow and finger joints are developed and the clinical results of the good short period and the middle have been reported. We developed the original unique total joint system (FINE® Total Joint System series) of the elbow, the finger, the knee, and the ankle joint. Clinical application of TEA was started from 2000, and clinical application of TFA was started in 2004. The characteristic of these systems, operation adaptation, the operation method, postoperative results, etc. are reported in this lecture.

RA6

State of the art surgical treatment for rheumatoid foot

Yasuhiro Tanaka

Department of Orthopaedic Surgery, Nara Medical University

The foot is most frequently affected by rheumatoid arthritis. Even if activity of rheumatoid arthritis is well controlled by biologics, activity of daily living in some patients is severely limited by foot pain. Mild foot deformities or synovitis in few joints causes pain at a walk. The benefit has a big not only patient satisfaction but also medical care economy without increasing drugs if we can operate patients with minimum invasive surgery. Recent advancement of orthopaedic surgery in the foot and ankle field will be mentioned in this lecture. For the forefoot, we treat patients aiming at joint preservation as much as possible. Our study showed that morphological characteristic in rheumatoid hallux valgus are similar to general hallux valgus. Therefore, osteotomies should be indicated for rheumatoid hallux valgus, if articular cartilage did not much affected. For the midfoot and hindfoot, we can treat lesions using arthroscopic or endoscopic approach with benefit of progress of the arthroscope technology. Perfusion and traction work well for obtaining good arthroscopic views. Arthroscopic synovectomy is indicated for synovitis in not only the ankle but also Chopart joint, the hallux MTP joint and tenosynovitis around the ankle. On the other hand, terminal stage of foot deformities are difficult to be treated by drugs even if the paradigm shift of the treatment occurs. There are lesions to require resection arthroplasty and arthrodesis, and total ankle replacement still more. For the severe forefoot deformities, MTP arthrodesis or resection arthroplasty is performed. Partial tarsal fusions are se-

lected for limited parts of tarsal joints. In addition, ankle fusion or total ankle arthroplasty is chosen for the ankle in terminal stage. A balanced treatment system of orthopedics treatment and systemic control by drugs is necessary for patient satisfaction.

RA7

Total Knee Replacement for Rheumatoid Arthritis Patients

Takashi Nakamura

Toho University Orthopedics

Joint problems in the knees due to rheumatoid arthritis (hereinafter referred as RA) are seen often. Articular cartilage is destroyed from proliferative synovitis and causes deformation such as bow-legs, knock-knees and fixed flexion. As the articular destruction progresses, it accompanies restricted articular motion and joint instability and makes standing and walking difficult. For those symptoms, total knee replacement (hereinafter referred as TKA) is performed. Although it is generally performed for patients with Larsen Grade IV or above, it is performed for patients with Larsen grade III if there is severe pain and instability. Recently, due to improved artificial joint material and design, and surgical techniques, TKA has long term stability in postoperative results. However, there are a few problems in performing TKA for RA patients. Those are decrease in bone quality, multiple joint diseases, severe bow-legs and fixed flexion, severe bone defect, arthritis mutilans, and weakened resistance for infections due to medications. For those problems, they necessitate certain measures. One is humane intraoperative maneuvering. If the patients have multiple joint disorders or have deformation especially in the hip joint or leg joint, they must get measured sufficiently because there are enough landmarks for checking alignment. Also, joint surgical treatment is selected for patients with severe deformation. Furthermore, the biological drug usage is showing a large development in RA treatment. While administering biological drugs, withdraw time must be set for each drug and thorough perioperative care is necessary. It is extremely important to sufficiently understand the problems for each patient's symptoms for planning a TKA operation for RA patients properly. This time, I report the summary of clinical results for TKA for patients with RA conducted in our clinic and the problems as well as the measures.

RA8

Antiphospholipid syndrome diagnostic testing and new emerging Markers

Tatsuya Atsumi

Department of Medicine II, Hokkaido University Graduate School of Medicine

Although the original concept of antiphospholipid antibodies (aPL) considers that those antibodies were directed against anionic phospholipids, evidence has shown that phospholipid-binding plasma proteins such as b2-glycoprotein I (b2GPI) and prothrombin are the dominant antigenic targets recognized by aPL in patients with antiphospholipid antibodies (APS). Anticardiolipin antibodies (aCL), anti-b2GPI antibodies and lupus anticoagulant (LA) are the laboratory tests considered in the revised criteria for the classification of the APS. However, a number of issues regarding the definition of 'aPL positive' are on discussion. For example, there would be many *in vitro* false positives in LA in daily practice (laboratorial false positive). In addition, LA was found in patients with a variety of disease, such as infectious, malignant or autoimmune diseases (clinical false positive). Further, there are many patients, strongly suspected to have APS by their clinical phenotype, but negative for any current aPL (false negative). For the better recognition of APS

patients, we investigators have to keep our effort to polish the modality to identify 'true aPL'. Recently, Scientific and Standardisation Committee of the international society of thrombosis and haemostasis (SSC-ISTH) revised the guideline to detect LA. The recommended procedures are clearer and more simple than the previous ones. This recommendation would be helpful not only for the research but also for the daily practice of LA, despite the evidence level is not high. We reported the clinical utility of phosphatidylserine dependent antiprothrombin antibody (aPS/PT) assay for the diagnosis of APS. The aPS/PT strongly correlate with the presence of LA and both sensitivity and specificity of aPS/PT were demonstrated to be comparable to that for aCL; moreover, most of the APS patients with aPS/PT had positive LA. These data suggests that aPS/PT may also be one of the 'confirming' assays for APS-associated LA.

RA9

IgG4-related disease

Hiroki Takahashi

First Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan

IgG4-related disease is a distinct clinical entity, whose characteristic features are following; Serum IgG4 is prominently elevated, IgG4-positive plasma cells infiltrate in involved tissues, various mass-forming lesions with fibrosis develop in a timely and spatial manner and the response to corticosteroids is prompt and good. IgG4-related diseases mainly target two organs. One is the pancreas (autoimmune pancreatitis; AIP), and the other comprises the lacrimal and salivary glands, the clinical phenotype is Mikulicz's disease (MD). IgG4-related disease should be differentiated from granulomatous diseases, malignant lymphoma and cancers in daily practice. The specific elevation of serum IgG4 concentration in AIP was originally reported in 2001 (Hamano et al) in terms of differentiation from pancreatic cancer. Although MD was reported as lacrimal and salivary glands disease ahead of proposal of Sjögren's syndrome (SS), MD and SS were pathologically identical and no reports about MD appeared in the western countries since the 1950s. However we noticed obvious differences in clinical features between MD and SS. In addition, Yamamoto reported the elevation of serum IgG4 and abundant infiltration with IgG4-positive plasma cells in MD in 2004. Those findings suggested that MD and AIP have a common pathogenesis and constituted a new clinical entity, so called "IgG4-related disease". Involvement of the lung, kidney, lymph nodes, pituitary gland and aorta are also reported as a complication. Although common pathogenesis might exist under those involvements, the etiology of IgG4-related diseases remains to be elucidated. IgG4-related disease is an important condition that is differentiated from various disorders. In this presentation, clinical characteristics and pathogenesis with respect to IgG4-related disease will discuss it in the context of its historical background.

RA10

Current Concept of Total Hip Arthroplasty in Rheumatoid Arthritis

Saiji Kondo¹, Yoshikatsu Kuroki¹, Atsushi Kusaba¹, Noriyuki Henmi², Akihiko Maeda², Kiyohiro Nagase³

¹Institute of Joint Replacement and Rheumatology, Ebina General Hospital, ²Department of Orthopaedic Surgery, Showa University

Northern Yokohama Hospital, ³Department of Orthopaedic Surgery, Showa University Fujigaoka Hospital

(Introduction): We have reviewed the results of Total Hip Arthroplasty (THA) performed in patients with rheumatoid arthritis (RA) at Showa University Fujigaoka Hospital (Fujigaoka) and Institute of Joint Replacement and Rheumatology, Ebina General Hospital (Ebina).

(Materials & Methods): 33 hip joints (22 patients) with RA were treated with THA and evaluated in Fujigaoka. 18 joints in 14 patients who were able for follow-up of more than 10 years (60%) have been examined. The average patient age was 45 years. 11 female patients (13 joints) and 3 male patients (5 joints) were included. Cemented cup was used in 9 joints, non-cemented cup in 8 joints, and bipolar hip replacement in 1 joint. Cemented stem was implanted in 10 joints and non-cemented stem in 8 joints. 66 joints with RA in 55 patients were treated at Ebina by the end of 2010. 27 joints in 25 patients (68%) who were able for follow-up of more than 5 years were evaluated. The average age of 24 women (26 joints) and 1 man (1 joint) was 56 years. On the acetabular side 25 joints were implanted with non cemented cup and 2 joints using a cemented cup in combination with a Mueller ring. All patients were treated without cemented stem. **(Results):** Outcome at the Fujigaoka: Our findings based on JOA score have shown an improvement of average score from 30 points preoperatively to 74 points at one year postoperative and 72 points at 5 years postoperative, and finally 71 points at the last follow-up. Revision was performed in 9 joints (47%): stem loosening in 7 joints, both cup and stem loosening in 1 joint, and stem fracture in 1 joint. The survival rate at 10 years was 78%. Outcome at Ebina: JOA score has shown an improvement of 42 points preoperative to 83 points at one year postoperatively, 81 points at 5 years postoperative and the final follow-up. Both cup and stem fixation was stable. Revision surgery was performed in two joints (7%) because of delayed infection. Survival rate at 5 years follow up was 92%.

RA11

Improvement of sleeping posture on RA with adjusting of pillow for easy rollover

Shuori Yamada

16 Gou Seikeigeka

Incidence of neck pain and problem of sleeping is so high over 70% on Rheumatoid patients. The cause of sleeping problem is due to upper and sub axial cervical disorders. For resolving the sleeping disorders, sleeping posture is so important. However, there has been no clinically proven adjusting mechanism for a pillow based on EBM on a global mass scale.

We developed SSS method (Set-up for Spinal Sleep Method) and have been treating more than 13,000 adjustments on pillows since 2003. This method is based on a principle that a rollover is possible with the least energy by using the best pillow to suit in supine and side sleeping positions.

For the Rheumatoid patients, nearly 70% of patients with RA having cervical spine pathology either upper sub-luxation or a sub axial lesion of cervical spine complain of disorder of sleep due to the related symptom. Pillows used by 43 patients with RA (average: 59.7 yrs) were adjusted based on the SSS method and evaluated with PS, VAS, and Face Scale. 93% of the patients found it easy to make a roll-over after an average follow-up period of 13.6 weeks and the symptom was improved enough to get quality sleep. Satisfaction was highly improved (69%) with the rate of improvement by PS 43.5%, particularly that by ADL 52.6%. There was no correlation

between improvement of the symptom by a height of pillow and ADI. It is considered that comfortableness of cervical spine by using the most suitable pillow during sleep might help with hold flare from spinal cord, nerve root, intervertebral articulations and others in comparatively a short period of time. It was also suggested that an alignment of cervical spine should be checked on patients who have completed more than two-year follow-up. The pillows should be accordingly readjusted to suit the alignment. Even the patients with RA instinctively know a difference of height as much as 3-5mm and have ability to choose the most suitable height against the cervical spine.

RA12

Importance of cohort study in rheumatoid arthritis

Eiichi Tanaka

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

The management of rheumatoid arthritis (RA) has been dramatically altered with the introduction of biologics. There was a significant change in the goal of treatment, from short-term to long-term improvement in QOL 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 and exclusion criteria, thus, the patients subjected 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. Ten years have passed since IORRA study was launched in Institute of Rheumatology, Tokyo Women's Medical University. By accumulating information from more than 5,000 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 such as NinJa and REAL in Japan, indicating that importance of cohort study in clinical research in rheumatology has become greater and greater.

In this seminar, the importance of cohort study in rheumatology will be discussed mainly based on IORRA cohort.

RA13

Reconstructive Surgery for Rheumatoid Cervical Spine

Kuniyoshi Abumi

Department of Spinal Reconstruction, Hokkaido University Graduate School of Medicine

Reconstruction surgery for rheumatoid cervical spine had changed by introduction of Magerl screw, lateral mass screw and pedicle screw in 1990's. Stability of atlantoaxial transarticular screw by Magerl is sufficient; however, risk for the vertebral artery cannot be completely excluded. Recently, Goel procedure of combined use of C1 lateral mass screw and C2 pedicle screw has been popularized. Regardless of screw anchoring procedures, we have to consid-

er the high ratio of abnormal condition of the vertebral artery in the craniocervical junction. Screws inserted into the pedicle, lateral and facet screw can be selected for the anchor of occipitocervical reconstruction.

The strongest cervical anchor of pedicle screw provides indirect decompressive effect of the spinal cord at the craniocervical junction obviating the necessity of direct decompression by transoral and mandible splitting approaches. The lateral mass in the cases with rheumatoid arthritis requiring subaxial fixation is usually destructed severely, and the pedicle only can be reliable fixation anchor for the subaxial rheumatoid cervical spine.

Reconstruction surgery of rheumatoid cervical spine has usually problems caused by bony fragility and specific morphological condition and difficulty by their poor general condition. Past reports demonstrated that neurological recovery by surgical intervention for patients with severe myelopathy was worse than for patients with mild myelopathy. Timing of surgery for the patients with rheumatoid cervical spine must be quite important.

RA14

Diagnosis and therapy for fibromyalgia in Japan

Hiroshi Oka

Institute of medical science, St Marianna university school of medicine

We proved the prevalence of fibromyalgia (FM) was 1.7%(2 million patients) by population based study in Japan. But Mastumoto reported the cognition rate of FM was only 50.7% among Japanese general physicians in 2009, therefore only limited medical doctors can practice FM patients actually. For Japanese rheumatologist, we had better to participate in clinical practice of FM actively. In this study, we attempted to compare the criteria of FM between ACR (American College of Rheumatology) 1990 and 2010, and I will introduce the strategy for FM treatment in Japan. The criteria of ACR 1990 consists of three main points which are more than three months duration, widespread pain, and more than 11 tenderness points out of 18 points. On the other hand, the ACR 2010 criteria has various clinical symptoms and severity without tenderness points. We proposed the cut off point was 13 points after screening of FM and non-FM patients. We have two method of FM therapy, which are medication and non-medication. Cognition behavior therapy is effective as non-medication. Anticonvulsants are very effective, especially myotonia type of FM. Actually I practice combination therapy trigger point injection and anticonvulsant. Clonazepam is also effective for patients with painful muscle cramping. We should pay attention to side effects such as dizziness and somnolence during anticonvulsant therapy. On the other hand, I practice combination therapy anticonvulsant and antidepressant without myotonia. SNRI such as milnacipran or duloxetine are effective, but these medications have side effect such as gastrointestinal tract problem frequently in Japanese patients. Mirtazapine will have rapid efficacy and less frequency of gastrointestinal tract problem. Tricyclic antidepressants are very effective for pain relief, but have several serious side effects. However we had very difficult cases after various combination anticonvulsants and antidepressants. We attempt Tramadol for these difficult cases.

Workshop

W1-1

HAQ short-term improvement in patients administered tocilizumab in our hospital

Keio Ayabe, Takumi Wakisaka, Muneo Aoyagi, Hiromi Kameda, Keiko Sonobe, Sachiko Itoi

Keiyu Orthopedic Hospital, Gunma, Japan

Objective: HAQ improvement was investigated in rheumatoid arthritis (RA) patients administered tocilizumab (TCZ) from March to October 2010 and observed for at least 24 weeks. **Subjects and Method:** 8 RA patients included 1 in stage I, 1 in stage II, 4 in stage III and 2 in stage IV; and 2 in Class 1, 3 in Class 2 and 4 in Class 3. Mean age was 64.7 and disease duration was 7 years. 4 patients switched from other biological agents. **Results:** HAQ improved from 1.8 (0.6–2.5) before TCZ administration to 1.4 (0–1.9) at 12 weeks and 1.3 (0–1.9) at 24 weeks of administration. In addition to HAQ, overall improvements were also seen in DAS28-ESR and MMP-3 and the subjects showed no particular side effects. **Conclusion:** TCZ was found to be a useful drug for short-term improvement of HAQ in RA patients.

W1-2

Evaluation of the injection interval of Tocilizumab after in RA patients

Kaori Yokota¹, Taio Naniwa², Kaneshige Sasaki²

¹Tajimi Hospital, Tajimi, Japan, ²Nagoya City University School of Medical Sciences Department of Medical Oncology and Immunology

Objective: To report on the RA patients who extended the injection interval of Tocilizumab (TCZ) after a clinical remission. **Methods:** 36 patients were treated with TCZ, and background and the clinical course on the patients who were able to have the injection interval extended. **Results:** The injection intervals of 13 patients were extended up to a maximum every eight weeks. The concomitant PSL dosage was significantly low in these patients. Three patients returned every four weeks, and had a significantly longer disease duration and low MMP-3 before TCZ treatment. **Conclusion:** Even if the TCZ treatment the injection interval is extended after a clinical remission, it can be maintained. However, it was thought that attention was necessary for the disease duration.

W1-3

Efficacy of tocilizumab as the first biologics for rheumatoid arthritis patients

Masao Sato¹, Masao Takemura², Ryuki Shinohe³, Katsuji Shimizu¹

¹Department of Orthopaedic Surgery, Gifu University School of Medicine, Gifu, Japan, ²Department of Informative Laboratory Medicine, Gifu University School of Medicine, Gifu, Japan, ³Department of Orthopaedic Surgery, Nishimino Welfare Hospital, Gifu, Japan

OBJECTIVES: The aim of this study is to evaluate the efficacy of tocilizumab (TCZ) as the first biologics for patients with rheumatoid arthritis (RA). **METHODS:** The study population comprised 41 RA patients (8 men, 33 women). The mean age of the patients was 59 years (range 22–76 years). The patients were administered TCZ (8 mg/kg) every 4 weeks and evaluated by DAS 28. **RESULTS:** The disease activity score (DAS) 28 at the baseline and at the evaluated endpoint were 6.87 and 2.49, respectively. The DAS 28 decreased significantly from baseline to at evaluated endpoint ($p < 0.0001$). With or without the usage of MTX, clinical symptoms and DAS 28

improved significantly during TCZ therapy. **CONCLUSION:** TCZ has shown high efficacy in RA as the first biologics.

W1-4

A retrospective study of tocilizumab therapy in rheumatoid arthritis

Hiroshi Tanaka, Mamoru Kanazawa, Toshifumi Kawakami, Kenji Kido, Makoto Kubo, Yasuhiro Tamimoto, Takeshi Tokito, Atsunori Tokushige, Kimio Nibu, Noriyuki Miyazaki, Hajime Miyazato, Kenji Yamamoto, Manabu Yamamoto, Toshiko Watada, Shinji Fukuta, Toshihiko Taguchi

Yamaguchi IL-6 Meeting

Objective: To study the efficacy/safety of tocilizumab (TCZ) in rheumatoid arthritis patients. **Subjects and methods:** The subjects were 46 patients who could be observed for at least 48 weeks, who had a mean age of 61.0 years, a mean duration of illness of 10.1 years, and a DAS28-ESR of 5.1 ± 1.4 , and 63% of whom had been treated with TNF inhibitors in the past. **Results:** After 48 weeks, the proportion of patients exhibiting remission was 58.7%. Of the 21 patients (45.7%) who exhibited remission at 12 weeks, 90.5% were still in remission after 48 weeks. The proportion of patients continuing treatment at 48 weeks was 82.6%. Four serious adverse events (in four patients) were seen. **Conclusions:** The results suggested that TCZ therapy allows patients to stay in remission over the long term.

W1-5

Influence of age in RA patients treated with Tocilizumab from TBC Registry

Nobuyuki Asai¹, Atsushi Kaneko², Hisato Ishikawa³, Seiji Tsuboi⁴, Yuichiro Yabe⁵, Kiwamu Saito², Tomone Shioura⁴, Tomonori Kobayakawa⁶, Toshihisa Kojima⁷, Naoki Ishiguro⁷

¹Nakatsugawa Municipal General Hospital, Nakatsugawa, Japan, ²Nagoya Medical Center, Nagoya, Japan, ³Nagano Red Cross Hospital, Nagano, Japan, ⁴Shizuoka Kousei Hospital, Shizuoka, Japan, ⁵Tokyo Kosei Nenkin Hospital, Tokyo, Japan, ⁶Toyohashi Municipal Hospital, Toyohashi, Japan, ⁷Nagoya University, Nagoya, Japan

Objective: The influence of the age on the effectiveness of TCZ is investigated by using the TBC registry. **Methods:** 123 patients treated with TCZ were divided into two groups (L and H) in the median age. Effectiveness was evaluated as DAS28-ESR every six months. **Results:** H group was significantly the disease duration was long, CLASS progressed, and rate of concomitant MTX was low in baseline characteristics. In DAS measurement, L group was 5.9, 2.9, and 2.8, and H group was 5.7, 3.4, and 3.2 at baseline, 6 months and 12 months, and a significant difference was seen between groups at six months. In the remission rate, L group was 44.7% and 42.9%, and H group was 31.7% and 43.3% at 6 months and 12 months. **Conclusion:** It has been understood to require time by the remission in H group.

W1-6

Minimum two years results of Tocilizumab for Patients with Rheumatoid Arthritis

Yasuharu Nakashima¹, Masakazu Kondo¹, Takashi Ishinishi¹, Takeshi Otsuka¹, Koji Kuroda¹, Hiroshi Jojima¹, Eisuke Shono¹, Eiichi Suematsu¹, Tomomi Tsuru¹, Hitoshi Nakashima¹, Ryuji Nagamine¹, Hiroshi Harada¹, Takahiko Horiuchi¹, Hisaaki Miyahara¹, Ken Wada¹, Yukihide Iwamoto²

We retrospectively observed the clinical efficacy of tocilizumab (TCZ) in 77 patients with RA at 13 hospitals, without any restrictions on disease duration or stage, treatment history, etc. Disease activity was evaluated every 4 weeks for minimum 2 years using DAS28. Remission and treatment response were categorised using EULAR definitions. We also analysed the impact of previous treatment with other biologics and of concomitant methotrexate (MTX) on the efficacy of TCZ. At 2 years, DAS28 had improved to 2.4 and the EULAR remission rate was 66.1%. The biologic-naïve group had a significantly better DAS28 (1.9 versus 2.6) and a significantly higher remission rate (81% versus 60%) than the biologic-exposed group. Concomitant MTX did not show the significant effects through the periods. We conclude that TCZ significantly alleviated the symptoms in a wide range of patients with RA in normal clinical practice.

W2-1

A treatment for a patient CRP rose 4 weeks after the first Tocilizumab infusion

Naohiko Gunji, Takashi Kanno

Ohta Nishinouchi Hospital, Department of Rheumatology, Fukushima, Japan

Background : Time required for tocilizumab (TCZ) to show effect varies among rheumatoid arthritis (RA) cases. Methods/results : A 62 y.o. male had stage I class 2 RA for 1 y (disease onset Jan09) with no other medical history. Adalimumab was started in Nov09 but was ineffective and replaced with TCZ in Jan10. CRP (mg/dL) and DAS28-ESR4 (DAS28) were 7.2 and 8.7, which rose to 13.5 and 8.7 after 4 wk of TCZ. Blood TCZ levels were inadequate and the interval was adjusted to 3 wk. CRP was negative and DAS28 was 4.5 after 10 wk. He remitted after 14 wk (negative CRP; DAS28: 1.2). No adverse events occurred. Conclusion : In highly active TCZ-treated RA cases with high CRP 4 wk after initiating therapy, disease control and early remission occur by adjusting the dosage interval to 3 wk.

W2-2

Prediction of the efficacy of tocilizumab (TCZ) for RA by DNA array analysis

Shunsuke Furuta¹, Mieko Yamagata¹, Isao Matsuura¹, Daisuke Kashiwakuma¹, Itsuo Iwamoto¹, Shoji Yoshida¹, Yoshie Suzuki², Kei Ikeda², Shin-Ichiro Kagami², Hiroshi Nakajima²

¹Research Center for Allergy and Clinical Immunology, Asahi General Hospital, Chiba, Japan, ²Department of Allergy and Clinical Immunology, Chiba University

Purpose: We studied whether the efficacy of TCZ for RA was predictable by analyzing gene expression in PBMC. Methods: We analyzed the gene expression in PBMC of 19 RA patients by using DNA array before TCZ therapy. We classified them as “poor response” (n=3), “good response” (n=10) and “rapidly effective” (n=5) after therapy and extracted the genes for predicting the efficacy. Results: 19 patients were 4 men, 17 RF-positive, 13 treated with MTX, 14 treated with PSL and 10 having a history of anti-TNF therapy. Average DAS28 score was 5.24. Comparing 3 groups, we got 1126 candidate genes that could separate “poor response” and “rapidly effective” by cluster analysis. Conclusion: We can predict the

efficacy of TCZ for RA by analyzing gene expression in PBMC before therapy by using DNA array.

W2-3

Effect of tocilizumab (TCZ) on serum lipid in patients with rheumatoid arthritis

Kentaro Hanami, Saito Kazuyoshi, Masao Nawata, Naoki Yunoue, Ippei Miyagawa, Yoshiya Tanaka

The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

54 patients (pts) on TCZ and 20 pts with MTX as control group were analyzed at 0, 24 wks with DAS28 and biological markers including HMW-AN. DAS28 of the 54 pts reduced after 24 wks of TCZ. Although TC, HDL-C, LDL-C and remnant like particles increased by TCZ, atherogenic index did not affected and remained in the normal range. Those changes were also observed in MTX group. In addition HMW-AN significantly increased. Changes of HMW-AN were not related to DAS28 at baseline, changes of DAS28 at 24 wks, the corticosteroid dose, with or without concomitant MTX and prior use of biologics. This change was higher in pts switching to TCZ than another TNF inhibitors from infliximab. This results was suggesting action of TCZ for lipid metabolism could be independent on inflammation in synovitis.

W2-4

The validity of activity evaluation in rheumatoid arthritis with tocilizumab

Satoshi Nakazaki¹, Takashi Murayama¹, Shinichi Kato²

¹Department of Rheumatology, Johoku Hospital, ²Department of Rheumatology, Kamiaraya Clinic

We investigated the validity of activity evaluation method in RA patients with tocilizumab (TCZ). By reduced rate of ESR, DAS28(ESR) and CDAI, 65 RA patients with TCZ and 43 RA patients with adalimumab (ADA) were analyzed. ESR, DAS28 and CDAI in the TCZ and the ADA was 53:48, 5.01:4.90, 20.6:19.7 at starting points, 12:42, 3.22:3.75, 12.2:10.2 at 3 months, 13:32, 2.77:3.59, 8.8:9.9 at 6 months, 12:34, 2.48:3.54, 6.9:8.8 at 9 months, 12:34, 2.81:3.49, 8.6:9.0 at 12 months, respectively. At any point, the reduced rate of ESR had decreased significantly more than one of CDAI in TCZ compared ADA. DAS28 vs. CDAI was similar results at 3 months and 6 months. When comparing TCZ with other drug about efficacy, evaluation methods without ESR were recommended.

W2-5

PTX-3 as a good marker of clinical response in RA patients treated by Biologics

Yukitaka Ueki, Kaoru Terada, Nozomi Iwanaga
center for Rheumatic diseases, Sasebo Chuo Hospital

Inhibition of IL-6 signaling in responses of inflammation and infection may also prevent the elevation of CRP. Previously, we have reported that PTX-3 is useful marker at the determination of efficacy of tocilizumab and side effect manifestation. PTX-3 and the other inflammatory markers were measured during the period of several biologics treatment in 40 active RA patients. PTX-3 levels were correlated with disease activity score 28. In patients stopped without the effects of several Biologics, PTX-3 levels were maintained as the high levels. The response of PTX-3 is more sensitive than that of

CRP to the pharyngitis and bronchitis during TCZ therapy. PTX-3 is useful marker at the determination of efficacy of biologics.

W2-6

SNP algorithms for prediction of efficacy and adverse events of tocilizumab (TCZ)

Tsukasa Matsubara¹, Satoru Koyano², Keiko Funahashi², Takafumi Hagiwara¹, Takako Miura¹, Kosuke Okuda¹, Akira Sagawa³, Takeo Sakurai⁴, Hiroaki Matsuno⁵, Tomomaro Izumihara⁶, Eisuke Shono⁷, Ko Katayama⁸, Toyomitsu Tsuchida⁹, Mitsuyoshi Iwahashi¹⁰, Tomomi Tsuru¹¹, Motohiro Oribe¹²

¹Matsubara Mayflower Hospital, ²Research Institute of Joint Diseases, ³Sagawa Akira Rheumatology Clinic, ⁴Inoue Hospital, ⁵Matsuno Clinic for Rheumatic Diseases, ⁶Izumihara Rheumatic and Medical Clinic, ⁷Shono Rheumatology Clinic, ⁸Katayama Orthopedic Rheumatology Clinic, ⁹Tsuchida Clinic, ¹⁰Higashi-hiroshima Memorial Hospital, ¹¹PS Clinic, ¹²Oribe Rheumatism and Internal Medicine Clinic

Purpose: We established SNP algorithms for prediction of responder (R) or non-responder (NR), and adverse events in TCZ-treated patients. **Patients and Methods:** 199 RA patients treated with TCZ were included in this study. Efficacy was assessed by Clinical Disease Activity Index within 24-30 weeks after the initial treatment. We scored the relationship between each SNP and efficacy or adverse events, and estimated total score of 10 SNPs. **Results:** 86.4% of the R group scored ≥ -3 point, and 81.9% of the NR group scored ≤ -4 points in TCZ-responsiveness in one algorithm. Similarly, 86.3-90.1% of adverse events +/- in TCZ-treated group could be determined by the algorithm. **Conclusion:** The SNP algorithm could be useful for prediction of efficacy and adverse events before treatment with TCZ.

W3-1

Abnormal ultrasound findings of atlantoaxial joints in RA remission state.

Kensuke Kume, Kanzo Amano, Susumu Yamada

Department of Rheumatology, Hiroshima Clinic, Hiroshima, Japan

Background and purpose) Remission in patients with rheumatoid arthritis is a realistic goal, but In ultrasound findings of hand or wrist joints, there are abnormal findings in even remission state. In this study, we evaluate the atlantoaxial joints in RA patients with remission state.

Methods) We selected RA remission patients that DAS28-E<2.6 were lasted more than 3 months. We enrolled 32 patients, and search the patients by ultrasound.

Results) BM in 11 cases, PD in 6 cases showed abnormal findings.

Conclusions) We found a high percentage abnormality of atlantoaxial joints by ultrasound, even in remission with rheumatoid arthritis.

W3-2

Two cases of the paresis by the upper spinal deformity in RA

Koichiro Satoh, Toshio Kobayashi

Southern TOHOKU Fukushima Hospital

Case 1: 54 years old woman. After a fall, her left limbs did not move slowly. Head CT did not show the abnormality in her brain. X-ray showed C2/3 bone union after the C3 dislocation. Decompression and posterior fusion with instrument was done. After rehabilitation, she could walk herself again. Case 2: 55 years old woman. The numbness of both hands appeared and reinforced it slowly. She could not stand up herself. X-ray showed the serious lordosis of cer-

vical spine. Decompression and posterior fusion with instrument was done. After rehabilitation, her motor function was recovered slowly. She could stand herself now. These two cases taught us the importance of the X-ray examination of c-spine regularly and vertebral changes excluded atlanto-axial dislocation were occur in patients with RA.

W3-3

Ultrasonography and CT Angiography Demonstrate Positional VA Occlusion in RA

Hiroyuki Yoshitomi, Masashi Neo, Hiromu Ito, Mitsuru Takemoto, Takashi Nakamura

Department of Orthopaedic Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan

An 83-year-old man with RA complained of severe vertigo when he leaned head in the left-anterior direction. CT angiography revealed that the left VA was pinched between the posterior rim of the transverse foramen of C1 and the transverse process of C2. Doppler ultrasonography demonstrated positional VA occlusion and a severe reduction in blood flow at the inducible position. Because the space between the transverse foramina of left C1 and C2 was reduced with the destruction of the left C1/C2 lateral masses, slight rotation and anterior shift of C1 led to the occlusion of the VA. After posterior O-C2 fusion at the reduced position, the VA occlusion and vertigo disappeared. Doppler ultrasonography and CT angiography allow valuable measurements in the diagnosis of positional VA occlusion.

W3-4

Cerebral vascular disorder after posterior cervical fusion in RA patients.

Yasuo Saruhashi, Kanji Mori, Katsuhisa Kikuchi, Taku Kawasaki, Yoshitaka Matsusue

Department of Orthopedic Surgery, Shiga University of Medical Science

We performed posterior cervical fusion in 43 RA patients (14 males, 29 females; mean 62.2 years; RA duration 15 years). Two developed cerebral vascular disorders postoperatively. Case 1: A 68y.o. woman with RA mutilans and atlantoaxial subluxation (AAS) had progressive gait disorder, and underwent atlantoaxial fixation. After 3 days she developed a headache, hemianopsia, and right hemiplegia. MRI showed a left posterior cerebral infarction. Case 2: A 61y.o. woman with RA mutilans and AAS underwent atlantoaxial posterior fusion for sudden quadriplegia. After 6 weeks, vomiting and vertigo developed. MRI showed a right cerebellar infarction. Both cases likely resulted from embolism, as each had a stenosis of the vertebral artery caused by a blood vessel disorders of RA.

W3-5

Clinical result of lumbar spine operation for the lumbar RA lesion

Junya Mibe¹, Kengo Yamamoto², Yasutaka Watanabe¹, Ryouhei Kouno¹, Seiichirou Egawa¹

¹Department of Orthopedic Surgery, Tokyo Metropolitan Ohtsuka Hospital, Tokyo, Japan, ²Department of Orthopedic Surgery, Tokyo Medical University

We examined the RA lumbar spine operation. We performed lumbar spine operation for sixteen RA patients, they developed lower extremities neuropathy. The average age was 64.5 years, the

mean follow-up period was 4 years and 9 months. The operative methods were PLIF: 7 examples, pedicle screw (PS) + PLF: 4 examples, PLF: 1 example, fenestration: 4 examples. In image finding, all patients were destroyed facet joint, and had listhesis or scoliosis except one patients. Clinical feature was cauda equina syndrome: 5 patients, radiculopathy 11 patients. All patients were improved after operation, but 5 patients (all examples use instrument) developed radiculopathy by contiguity intervertebral disorders. Lumbar spine in RA patients was destroyed anterior and posterior column synovitis and enthesitis.

W4-1

Anatomic data on the cervical spine : a study of rheumatoid arthritis patients

Kosaku Higashino, Daisuke Hamada, Shunji Nakano, Shunichi Toki, Natsuo Yasui

Department of Orthopaedics, School of Medicine, University of Tokushima, Tokushima, Japan

The effect of rheumatoid arthritis (RA) on the cervical spine has not been clarified. One hundred and twenty nine female patients (90 RA and 39 non-RA) underwent radiographs and CT scanning of the cervical spine. The diameter of the pedicle width, the lateral mass thickness, The high-riding vertebral artery (HVA) were measured. The diameter of the transverse foramen (d1) and that of the spinal canal (d2) were measured, and d1/d2 calculated. The pedicle widths and lateral mass thicknesses in the RA patients were significantly less than those in the non-RA. The areas of the transverse foramina in the RA were significantly greater than that in the non-RA. The ratio of d1/d2 was not significantly different. HVA was 33.9% in the RA and 7.7% , this difference was significant.

W4-2

Clinical results and associated factors of upper cervical operation for RA

Hidetoshi Tanaka, Kengo Yamamoto, Taiichi Kosaka

Department of Orthopedic Surgery, Tokyo Medical University, Tokyo, Japan

(Purpose) We investigated the clinical results and associated factors of operation for RA-related superior cervical lesions. (Subjects and Methods) The operative cases were 22, follow-up period was 9 years. The conservative cases were 15, follow-up period was over 3 years. (Results) In 8 of 14 patients in the operative group, SAS occurred after surgery. However, only 2 cases required reoperation, the other patients were well-controlled for RA. The conservative cases were 1 or 2 grade in Renawat's neural deficit class, and each CRP was within almost 2. (Discussion) The conservative cases (not required operation) and the operative cases without SAS after operation, were well-controlled for RA. Significant improvement of therapy for RA has ability of protects for progress of cervical lesions.

W4-3

The analysis of bone strength and fracture risk of lumbar spine in RA patients

Toshiyuki Dokai¹, Hiroshi Hagino², Yuji Kishimoto¹, Hideki Nagashima¹, Toru Okano¹, Ryota Teshima¹

¹Department of Orthopedic Surgery, Faculty of Medicine, Tottori University, Tottori, Japan, ²School of Health Science, Faculty of Medicine, Tottori University, Tottori, Japan

The purpose of this study was to analyze the bone strength and fracture risk in lumbar spine, and to evaluate the differences between RA and postmenopausal osteoporosis (PO). Participants were all females, and consisted of 34 with RA and 11 with PO. The BMD in lumbar spine was 0.833 g/cm² and 0.701 g/cm², the mean fracture load of L2, which was measured by CT-based finite element methods was 4399 N and 3647 N, the FRAX value was 17.2% and 15.6%, respectively (RA and PO). There were significant differences in age and BMD between the two groups. The fracture load was correlated positively with BMD, and negatively with age and the FRAX value. We concluded that the bone quality played an important role in the bone strength with RA, rather than BMD.

W4-4

Investigation for the fracture risk and the osteoporosis therapy using the FRAX[®]

Shohei Watanabe, Hiroshi Imai, Naohiko Mashima, Hiromasa Miura

Department of Bone and Joint Surgery, Ehime University Graduate School of Medicine

We investigated the relationship between the fracture risk rate and the treatment for osteoporosis using the FRAX[®]. Two hundred thirty two patients, 110 osteoporosis patients and 122 non-osteoporosis patients were examined. The 10-year probability of the osteoporotic fracture was evaluated using the FRAX[®]. Those of hip fracture of the osteoporosis and non-osteoporosis group were 14.2 and 5.4, respectively. The one of a major osteoporotic fracture of the two groups were 27.0 and 13.1, respectively. The values of 15% and 7% were calculated as the points to be recommended the therapy for osteoporosis as the major osteoporotic fracture and the hip fracture, respectively. The FRAX[®] may be useful for not only the probability of osteoporotic fractures, but the index for the osteoporosis therapy.

W4-5

Biologic therapy and suppression of RA cervical spine lesions

Takeshi Matsumoto¹, Masaki Nakamura¹, Yasuhiko Kita², Michio Fujiwara²

¹Department of Orthopaedic Surgery, Yokohama Rosai Hospital, Yokohama, Japan, ²Department of Rheumatic diseases, Yokohama Rosai Hospital, Yokohama, Japan

We retrospectively evaluated cervical spine lesions of 20 rheumatoid arthritis patients treated with biologics (IFX 10 cases, ETN 4 cases). 10 patients treated with MTX were control group. The mean age at the end point was 55.3/65.3 (Bio/ Cont) years, the mean duration of illness was 16.2/14.1 years. The average follow-up was 38.1/35.6 months. From plain lateral radiographs of the cervical spine over time, rheumatoid cervical spine lesions were investigated about atlanto-axial lesions, subaxial lesions and axial shortening. Notable efficacy by biologic therapy may suppress the progression of RA cervical spine lesions. Axial shortening is a convenient parameter about the progression of RA cervical spine lesions.

W4-6

Risk factor of progression of cervical lesions with RA receiving IFX treatment

Yasuhide Kanayama¹, Toshihisa Kojima², Yuji Hirano³, Hideki Takagi¹, Hiroki Tsuchiya¹, Masatoshi Hayashi², Koji Funahashi², Daizo Kato², Hiroyuki Matsubara², Yukiyoishi Oishi³, Hisashi Iwata⁴, Naoki Ishiguro²

¹Department of Orthopedic Surgery, Nagoya kyoritsu Hospital, Nagoya, Japan, ²Department of Orthopedic Surgery & Rheumatology, Nagoya University Graduate School of Medicine, Nagoya, Japan, ³Department of Rheumatology, Toyohashi Municipal Hospital, Aichi, Japan, ⁴Rheumatology & Joint Replacement Center, Nagoya kyoritsu Hospital, Nagoya, Japan

Objective : To determine the risk factor of radiographic progression of cervical lesions with RA receiving IFX treatment. **Methods :** We used IFX for treating 103 RA patients for at least 1 year. Patients were extracted from multicenter study group for the treatment of RA using biologics database (TBC). **Results :** The number who showed progression in at least one of radiographic cervical lesion parameters (ADI, SAC, Ranawat value) for 1 year was 33 (32%). When we performed logistic regression to determine the risk of progression of cervical lesions, and TSS from baseline to Week 54 was statistically significant in the multivariate logistic analysis (HR 1.90 ; 95%CI 1.25-2.88 ; p=0.003). **Conclusion :** The progression of hand joint destruction was high risk of progression of cervical lesions.

W5-1

Clinical results of surgical cases for extensor mechanism disruption after total knee arthroplasty

Koichi Nakagawa¹, Yasuchika Aoki¹, Arata Nakajima¹, Takashi Nakamura², Masato Sonobe¹, Shintaro Tsuge¹, Masahiko Suzuki³, Tae Hyun Lee⁵, Hajime Yamanaka⁴, Manabu Fujino¹, Yoshifumi Shibata¹, Yu Sasaki¹, Toru Suguro², Teruo Furufu¹

¹Department of Orthopaedic Surgery, Toho University Sakura Medical Center, ²Department of Orthopaedic Surgery, Toho University School of Medicine, ³Department of Orthopaedic Surgery, Chiba University Graduate School of Medicine, ⁴Department of Orthopaedic Surgery, Shimoshizu National Hospital, ⁵Department of Orthopaedic Surgery, Chiba Rehabilitation Center

Extensor mechanism disruption after total knee arthroplasty (TKA) is a complication which could cause crucial dysfunction of the affected knee. Among 2050 cases underwent TKA at Toho University Medical Center and Chiba University Hospital from 2000 through 2009, extensor mechanism disruption happened in 14 cases. Surgical treatments were performed in 6 cases (3 OA cases and 3 RA cases) which had complete disruption of knee extensor mechanism. Tension band wiring for patella fracture cases and ligament reconstruction using autologous tendon or artificial ligament for tendon rupture cases were effective. However, 3 cases needed multiple operations showing poor clinical results. Surgical treatment plan should be made considering insufficiency of bone and soft tissue especially in RA cases.

W5-2

Clinical results of FINE[®] total knee arthroplasty in patients with RA

Kimio Masuda¹, Takuo Juji¹, Mitsuyasu Iwasawa¹, Hiroshi Takamura¹, Ryushi Marutani², Toshihito Mori¹

¹Department of Orthopaedic Surgery, National Hospital Organization Sagami Hospital, Kanagawa, Japan, ²Department of Reha-

bilitation, National Hospital Organization Sagami Hospital, Kanagawa, Japan

To analyze the clinical results of FINE[®] TKA system in patients with RA, we investigated 90 TKA (from January 2009 through September 2010). The knee function before and after TKA was evaluated by using the Japanese Orthopaedic Association (JOA) evaluation chart of knee joint functions (JOA score). The mean range of motion (ROM) before TKA was 12.0-110.7 degree and the mean JOA score before TKA was 45.0 point. After TKA, the ROM was 1.7-112.0 degree and the JOA score reached 90.2 point at final follow-up. In short-term data, FINE[®] TKA was successfully performed and improved the function of affected knees in RA, especially better flexion angle compared with Scorpio[®] TKA.

W5-3

Midterm results of the HA coating cementless TKA for RA Patients

Kensuke Koyama, Michitomo Sakuma, Yoshihiro Takayama, Hirotaka Haro

Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi

Objective: To investigate the midterm clinical results of hydroxyapatite coating cementless TKA for RA patients. **Methods:** Thirty one patients (37 knee) were followed over five years or more after operation. The mean age was 64.3 years. **Results:** The mean flexion and extension angle improved from 100.1 and -18.6 to 103.5 and -2.3. The mean JOA RA score improved from 36.3 to 82.1 at five years after operation. The position of implants were 95.6 degree (alpha angle), 89.8 degree (beta angle). No radiolucent line was appeared around the implants. **Conclusion:** Although cement TKA is often used for RA patients, midterm results of the HA coated cementless TKA were favorable.

W5-4

The soft tissue balance in flexion and extension after TKA in RA patients

Tadashi Tsukeoka, Tae Hyun Lee

Chiba Rehabilitation Center

The purpose of this study was to evaluate the soft tissue balance changes in flexion and extension position in rheumatoid arthritis just after TKA and at the time of discharge using Tellos SE arthrometer fluoroscopically and to compare with the results in osteoarthritis patients. We measured coronal lateral and medial ligamentous laxity in flexion and extension in 47 total knee arthroplasties. The preoperative diagnosis was osteoarthritis in 33 knees and rheumatoid arthritis in 14 knees. In osteoarthritis patients, lateral laxities in flexion and extension decreased and medial laxities in flexion and extension increased at the time of discharge (p<0.05). On the other hand, there were no statistically significant changes in both flexion and extension in rheumatoid arthritis patients.

W5-5

Revision of total knee arthroplasty for rheumatoid arthritis patients

Kunihiro Hosaka, Shu Saito, Takao Ishii, Sei Mori, Takanobu Sumino, Keinosuke Ryu, Junnosuke Ryu

29 cases 35 knees with rheumatoid arthritis were enforced the revision TKAs in our department. Female is 27 cases, and man is 2 cases. The average age in revision is 60.0 years. The causes of revision were 11 infections, 10 loosening, 6 polyethylene wears, 2 instabilities, 2 metal backed patella wears, and 1 of hemarthrosis, dislocation of polyethylene insert, and severe pain, respectively. The average period until revision was 7.6 years from primary TKA. The methods of revision were 14 of revisions of all components, 9 of isolated polyethylene insert exchange, 4 of irrigation and polyethylene insert exchange for infection, 3 of arthrodesis, 2 of polyethylene insert exchange and patella exchange, 1 of amputation, and 1 of revision of patella component. The re-revision cases were 4 cases.

W5-6

Long-term clinical results of cementless TKA in rheumatoid arthritis

Takashi Nakamura, Yoshiyasu Miyazaki, Hideyuki Aoki, Ayako Kubota, Toru Suguro, Kazuaki Tsuchiya

Department of Orthopaedic Surgery, Toho University, Tokyo, Japan

(Objective) We investigated the long-term clinical results of cementless total knee arthroplasty (TKA) in rheumatoid arthritis (RA) patients.

(Material and Methods) The subject of the study was 47 knees of 57 RA patients treated by cementless TKA over a 10 years period. The mean follow-up periods was 13 years. Clinical evaluation was based on the Japanese Orthopaedic Association RA knee score (JOA score), and we also assessed the range of motion, radiographic results and complications.

(Results) The mean JOA score improved from 40.6 to 72.8. No revisions of TKA were required because of loosening or sinking.

(Conclusion) We have obtained good clinical results with TKA in RA more than 10 years postoperatively.

W6-1

Comparison between joint-preserving procedure and arthrodesis of the 1st MTPj

Ryota Hara, Yasuhito Tanaka, Yasunori Kobata, Akira Taniguchi, Norikazu Matsumoto

Department of Orthopaedic Surgery, Nara Medical University

Twenty-eight patients (43 feet) who had treated operatively for the forefoot deformity caused by RA were followed. The patients treated with joint-preserving procedure of the 1st MTP joint were assigned to group A (15 patients 22 feet), and the patients treated with arthrodesis were assigned to group B (13 patients 21 feet). The post-operative score of Japanese Society for Surgery of the Foot RA foot ankle scale in group A was significantly high compared with group B. There was no significant difference in the hallux valgus angle between two groups. Our results indicate that joint-preserving procedure provides better function maintaining an ideal alignment of the 1st MTP joint. The joint-preserving procedure was useful treatment for the patients with RA who were controlled favorably.

W6-2

Clinical outcome of surgical intervention on forefoot deformity in RA patients

Kaneyuki Tsuchimochi¹, Yoshiya Arishima¹, Yoshitaka Minamikawa², Nobuhiko Sunahara¹, Yasuhiro Tsuneyoshi³, Setsuro Komiya³

¹Japanese red cross kagoshima hospital, ²Tokyo Hand Surgery & Sports Medicine Institute, ³Kagoshima Rheumatoid Research Group

Purpose: Osteotomy or arthrodesis is commonly used for the treatment of RA forefoot deformity. We have been performed the first MTP joint arthrodesis or osteotomy in addition to the 2-5 MTP joint resection for such cases. Recently arthroplasty using swanson implant for the first MTP joint is included for the surgical treatment. Subject: We included 10 cases of 18 feet which has been passed at least one year after operation. M1M2 angle and hallux valgus angle were measured for the cases. The clinical outcome were compared with the first MTP joint arthrodesis or osteotomy. Result: Arthroplasty using Swanson implant for the first MTP joint in RA patient is considered as an useful surgical treatment for some cases.

W6-3

Clinical results of toe arthroplasty for rheumatoid forefoot deformity

Toshiharu Okuda

Okuda Orthopedic Clinic

The results of toe arthroplasty for forefoot deformities in rheumatoid arthritis (RA) patients were investigated. 39 feet in 26 patients (3 male, 23 female) were evaluated. Their average age at surgery was 59.5 years old, the average of follow up time after surgery was 4.9 years. Swanson silicon implant arthroplasty of MTP in the great toe was performed on 17 joints, MTP arthrodesis of the great toe was performed on 12 joints. Resection arthroplasty of metatarsal neck of the lateral toes was performed through a dorsal approach. There was no MTP dislocation and no implant breakage, but infection was seen in one case. All patients could walk without pain at the time of review, and most of them were satisfied with toe arthroplasty.

W6-4

Surgery of MTP joint arthroplasty for forefoot deformity in rheumatoid arthritis

Noboru Igarashi, Masayuki Sekiguchi, Ayako Kubota, Hideko Torihata, Hirofumi Kawakami, Toru Suguro, Kazuaki Tsuchiya
Department of Orthopaedic Surgery, Toho University Omori Medical Center, Tokyo, Japan

We are using the Swanson implant for RA patients with grommet for the first 1MTP joint on Larsen grade 4 over the forefoot deformity, and doing Lelievre surgery for 2-5 for the first toes. We examined the usefulness of this operation evaluating with X-ray images and 3D-CT images. The subjects performed in our hospital since 2002 RA patients with 44 feet 69 cases. HV angle, M1M2 angle, M1M5 angle, α angle were measured before and after surgery. HV angle, M1M2 angle, M1M5 angles significantly improved after surgery. Showed no significant change in angle α , placement of grommets were kept. In 3D-CT showed a reduction of the dislocation and flexor tendon alignment improvement. For patients with severe progressive joint damage, this surgery seems to be a useful method.

W6-5

The efficacy of forefoot arthroplasty for standing balance in patients with RA.

Motohiro Suzuki¹, Eiji Torikai¹, Yukihiro Matsuyama¹, Tetsuya Ichikawa², Tetsuyuki Nagafusa³, Shigeyuki Miyamoto⁴, Kenji Somura⁵

¹Dept. of Orthop. Surg., Hamamatsu Univ. School of Med., Shizuoka, Japan, ²Dept. of Orthop. Surg., Narita Memorial Hospital, Aichi, Japan, ³Dept. of Orthop. Surg., Morimachi General Hospital, Shizuoka, Japan, ⁴Dept. of Orthop. Surg., Fujinomiya General Hospital, Shizuoka, Japan, ⁵Dept. of Orthop. Surg., Fujieda General Hospital, Shizuoka, Japan

[purpose] The purpose of this study is to evaluate the efficacy of forefoot arthroplasty for standing balance in RA.

[subjects and methods] A forefoot arthroplasty utilizing a shortening oblique osteotomy on lesser toes was performed on 10 patients. A standing balance was measured by GRAVICORDER® (anima) at before and after surgery.

[results] The deviation of center of balance with rest position at before surgery had a tendency to be located at the back side. That was improved in 8 patients after surgery. The deviation of balance to the front side was greater at after surgery than at before surgery.

[conclusion] A forefoot arthroplasty utilizing a restoration of MTP joints of lesser toes is useful for the improvement of standing balance in patients with RA.

W6-6

Joint preservation surgery for correction the great toe deformity with RA

Koichiro Takahi¹, Hajime Owaki², Takeshi Fuji², Kazuhiko Imoto¹

¹Department of Orthopaedic Surgery, Toneyama National Hospital, ²Department of Orthopaedic Surgery, Osaka Koseinenkin Hospital

Materials and Methods: We had performed joint preservation surgery for correction the great toe deformity in 11 RA feet. The surgical procedure that was used included soft-tissue releases and off-set osteotomy of the first metatarsal. All cases were followed-up at least 1 year.

Results: AOFAS score was significantly improved from 37 to 80 points. HVA and IMA were significantly decreased from 47.9 to 2.3 and 12 to 2.2 degrees each other.

Conclusion: Our results show that joint preservatin surgery of RA foot had achieved good clinical and radiographical results. In the treatment of RA, the strategy of medication is changing dynamically, so the surgical procedure for RA feet needs to be reexamined.

W7-1

Infection occurred under the masking of inflammation by tocilizumab treatment

Yoshinori Masui¹, Junwa Kunimatsu¹, Satoshi Kamei¹, Sumie Moriyama¹, Reo Yoshikawa¹, Masafumi Kobayashi², Yuko Takahashi², Akio Mimori², Hiroshi Kaneko³

¹Department of Internal Medicine, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan, ²Division of Rheumatic Diseases, Department of Internal Medicine, National Center for Global Health and Medicine, Tokyo, Japan, ³Department of Rheumatology, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan

Tocilizumab (TCZ) is effective biologics resulting in clinical remission for rheumatoid arthritis, but early detection of the infectious

disease is difficult because TCZ masks the inflammation value. We experimented 3 cases of the infectious disease that occurred during TCZ treatment. Case 1: 77 F suffered from bacterial peritonitis after 12th administration. Case 2: 74 F suffered from acute appendicitis after 3rd administration. Case 3: 70 F suffered from leg cellulitis after 11th administration. Those findings were recovered by appropriate treatment. According to the backward investigation, they had some risk factors of infectious disease in the PMS report. We should do detailed examination for the patients except for laboratory data during TCZ treatment.

W7-2

Three infection cases using tocilizumab after arthroplasty

Ryo Date¹, Atsunori Tokushige¹, Takashi Imagama¹, Toshihiko Taguchi¹, Hiroshi Tanaka²

¹Department of orthopedics, Yamaguchi University, ²Yamaguchi prefectural medical center

We report 3 infection cases using tocilizumab (TCZ) after arthroplasty. All cases were female, average 67.3 ages, switched from adalimumab (ADM) to TCZ.

Each operations were total knee arthroplasty, total knee arthroplasty, bipolar head replacement (BPH), all cases were taken out after infection. It was taken average 12 weeks until infections were overcame. The average period switching from ADM to TCZ were 3-4 weeks.

Though we could diagnose 2 cases easily, for elavating CRP, the other one was infected after 6weeks swiching tocilizumab, we had difficulty to diagnose infection because not elavating CRP.

It is important to consider interval weeks from ADM to TCZ for prevending infection. It is necessary to note the infection when switching drugs especially.

W7-3

Duration of antimicrobial prophylaxis in patients with rheumatoid arthritis.

Kengo Harigane¹, Yuichi Mochida¹, Katsushi Ishii¹, Naoto Mitsugi², Naoya Taki², Yasushi Akamatsu², Tomoyuki Saito³

¹Center for Rheumatic Diseases, Yokohama City University Medical Center, Yokohama, Japan, ²Department of Orthopaedic Surgery, Yokohama City University Medical Center, Yokohama, Japan, ³Department of Orthopaedic Surgery, Yokohama City University School of Medicine, Yokohama, Japan

Objective: The aim of current study was to examine the association between the incidence of surgical site infection (SSI) and the duration of antimicrobial prophylaxis (AMP) in patients with rheumatoid arthritis (RA). **Methods:** The clinical records of 508 patients with RA who underwent orthopedic surgery from 2004 to 2010 were retrospectively reviewed. The incidences of SSI in short duration group (discontinue within 36 hours after surgery) were compared to those in longer duration group. **Results:** The incidence of SSI was 1.5% in short duration group and 2.3% in longer duration group. The incidence rates were not different between two groups. **Conclusion:** Based on our results, short-duration AMP was recommended in patients with RA.

W7-4

Bone and soft tissue infections in rheumatoid patients receiving the biologics

Yukio Esaki¹, Masanobu Ohishi², Masakazu Kondo³, Goh Hirata¹, Nobutaka Kaibara¹, Fuyuki Tominaga¹, Hisaaki Miyahara¹

¹Department of Orthopaedic Surgery, Kyushu Medical Center, National Hospital Organization, Fukuoka, Japan, ²Department of Orthopaedic Surgery, Kyushu University, ³Kondo Clinic for Rheumatism and Orthopaedics

We investigated the bone and soft tissue infections in rheumatoid arthritis patients receiving the biologic therapy. In our department, we experienced one case with the infection in 24 cases receiving IFX, 2 in 50 cases receiving ETN, one in 16 cases receiving ADA, and none in 26 cases receiving TCZ. 8 patients with the infections were treated, 2 with infectious corns on the sole of the foot, 2 with surgical site infections, 2 with phlegmon, one with infectious bursitis of the elbow, and one with infectious arthritis and osteomyelitis of the foot. The infectious corns and the bursitis were cured in short period, however, long-term treatment were needed to cure the plegmon, infectious arthritis, and osteomyelitis. The main origins of the infections seemed to be in oral or foot infection.

W7-5

Infection occurred in limb during biologic agent therapy in rheumatoid arthritis

Hajime Yamanaka, Kenichiro Goto

Department of Orthopaedic Surgery, National Hospital Organization Shimoshizu Hospital

【Objective】To evaluate the clinical feature of infection occurred in limb during biological agent therapy in patient with rheumatoid arthritis. **【Materials and Results】**Thirteen limbs, ten RA patients, who were treated with biological agents, were required hospitalization due to infections occurred in limbs. Two limbs were using Remicade, eight were Embrel, one was Humira, and two were Actemura. Phlegmones occurred in 7 limbs, late infections after total knee arthroplasty 2 limbs, early infections after operation 3 limb, and septic arthritis 1 limb. **【Discussion】**It must be careful that the infection in limb of RA patients who are treated using biological agents occurred suddenly, particularly to the patients that take corticosteroid, have complication and joint arthroplasty.

W7-6

Pyrogenic spondylitis in patients with rheumatic diseases

Tadashi Nakamura¹, Syu-ichi Higashi¹, Kunihiro Tomoda¹, Michishi Tsukano¹, Mitsuru Sakaguchi²

¹Center for Arthritis and Rheumatology, Kumamoto, Japan, ²Kumamoto Orthopaedic Hospital, Kumamoto, Japan

Seven patients with pyrogenic spondylitis, 5 with rheumatoid arthritis, 1 with Crohn's disease, and 1 without an underlying disease were enrolled. When diagnosed, they showed high inflammatory activities with elevated levels of CRP: 9.0 ± 5.8 (mg/dl), complained backaches according to injured vertebral levels, and were judged by MRI imaging. Except one without underlying disease, they were all treated with prednisolone of 11.0 ± 4.2 (mg/day), and immunosuppressants (4 patients) including methotrexate even with etanercept (3 patients). In rheumatic diseases, patients who are taken agents which have immunosuppressive effect and in high disease activities tend to be at the risk of pyrogenic spondylitis. Prompt diagnosis by MRI and early treatment with antibiotics will improve the outcome.

W8-1

The usefulness of CD64 on neutrophils in the perioperative phase in RA patients

Naoki Kondo¹, Katsumitsu Arai², Junichi Fujisawa¹, Takahiro Netsu¹, Toshihiro Matsui³, Akiko Komiya³, Shigeto Tohma³, Naoto Endo³, Jinju Nishino⁴

¹Division of Orthopaedic Surgery, Niigata University, Niigata, Japan, ²Division of Orthopaedic Surgery, Niigata Prefectural Chuo Hospital, ³Department of Rheumatology, Sagami National Hospital, National Hospital Organization, Kanagawa, Japan, ⁴Nishino Clinic, Orthopaedics and Rheumatology

To examine the clinical significance of CD64 on neutrophils in RA patients in the perioperative stage, 4 RA patients (two primary TKA; Case1 & 2), 1 revision TKA; Case3, and 1 removal of implant after deep infection after revision TEA; Case4) were subjected to CD64 on neutrophils in the perioperative stage (preoperative, 1, 3, 7, and 14 days after operation). Each outcome and variation of CD64 were analyzed. Neither perioperative infection (Case1 to 3) nor recurrent infection (Case4) was detected. The average of CD64 was 1484 (preoperative), 1491 (day1), 1203 (day3), 1214 (day7), and 1213 (day14) (molecules/cell), respectively. Each value was under 2000 (cut off value). These data suggest that CD64 is useful for detecting perioperative infection and suppression of infection in RA patients.

W8-2

Eosinophil CD64: possible usefulness in distinguishing drug fever from infection

Narutaka Katoh¹, Jinju Nishino², Keita Nishimura¹, Takashi Matsushita¹

¹Department of Orthopaedic Surgery, Teikyo University School of Medicine, Tokyo, Japan, ²Nishino Clinic Orthopedics and Rheumatology

Antibiotics are essential in the treatment of infection, but long period administration may lead to drug fever. No method exists for early differentiation of these. The new infection marker neutrophil CD64, which rises in both drug fever and infection is not available for differentiation between the two. We compared cytometric measurements of neutrophil CD64 and eosinophil CD64 in twelve patients who presented body temperatures of over 38 degrees C. Seven cases were infection and five cases were drug fever (4 females and 8 males: 35-69 years old; median age: 55 years old). Neutrophil CD64 was elevated in both categories, but eosinophil CD64 was elevated only in the drug fever cases. Conclusion: Eosinophil CD64 can possibly be used as a new marker for drug fever.

W8-3

Measurement of monocyte CD64 expression in RA with bacterial and viral infection

Akiko Komiya¹, Toshihiro Matsui², Kanako Iwata², Shinichi Nogi², Hirokazu Takaoka², Yoshiyuki Arinuma², Atsushi Hashimoto², Kota Shimada², Tatsuoh Ikenaka², Hisanori Nakayama², Hiroshi Furukawa¹, Shigeto Tohma¹

¹Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagami National Hospital, Kanagawa, Japan, ²Department of Rheumatology, National Hospital Organization Sagami National Hospital, Kanagawa, Japan

[Aim and Methods] Quantitative measurement of CD64 expression on neutrophils can be used as a infection marker in Rheumatoid

arthritis (RA) patients. We measured the expression level of CD64 per monocyte quantitatively by flow cytometry in RA patients with infection and compared in each pathogens.[Results] There was no statistical difference between the mean values of monocyte CD64 in patients with bacterial infection (40924.7 molecules/cell) and viral infection (40191.0). On the other hand, the escalation rate compared to monocyte CD64 without infection was 187.8% (bacterial) and 234.8% (viral). [Conclusion] The escalation rate of monocyte CD64 tended to be higher in patients with viral infection than bacterial infection in RA patients.

W8-4

Elevated neutrophil CD64 in a case of rheumatoid arthritis with tuberculosis

Shinichi Nogi, Kanako Iwata, Hidekazu Futami, Hirokazu Takaoka, Yoshiyuki Arinuma, Atsushi Hashimoto, Kota Shimada, Hisanori Nakayama, Toshihiro Matsui, Akiko Komiya, Shigeto Tohma
Sagamihara National Hospital, National Hospital Organization

A 74-year-old woman with rheumatoid arthritis received etanercept after ineffective adalimumab together with isoniazid preventive therapy. Etanercept was discontinued owing to infectious arthritis of knee followed by pyelonephritis. Antibiotics ameliorated her symptoms in addition to normalizing white blood cell count and serum CRP, whereas neutrophil CD64 expression level gradually elevated. CT scan revealed diffuse micronodules in the lungs and an abscess around the lumbar vertebrae. *Mycobacterium tuberculosis* was detected through CT-guided percutaneous drainage of the abscess. She was diagnosed as miliary tuberculosis and tuberculous spondylitis, which were improved by antituberculous. Improvement of CT image was accompanied by reduction in neutrophil CD64 expression level.

W8-5

Usefulness of Aspergillus antigen test for systemic rheumatic disease patients

Shuichiro Nakabo, Kosaku Murakami, Chikashi Terao, Naoichiro Yukawa, Hajime Yoshifuji, Daisuke Kawabata, Takaki Nojima, Koichiro Ohmura, Takao Fujii, Tsuneyo Mimori
Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan.

Objective: To evaluate the usefulness of Aspergillus antigen test (AAT) for rheumatic disease patients.

Study design: Retrospective chart review

Method: We checked the medical records of patients who were admitted to our hospital from April 2009 to March 2010, and picked up 30 patients whose AAT titer was above 0.5. Diagnostic criteria of aspergillosis followed the criteria of European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group.

Result: The number of lymphocyte was significantly lower and the maximum AAT titer was significantly higher in the patients who diagnosed as aspergillosis.

Discussion: AAT titer may be useful for diagnosis of aspergillosis in rheumatic diseases. However, to determine the cut-off value, more data are needed.

W9-1

Morbidity and mortality in patients with antiphospholipid syndrome

Yuichiro Fujieda, Tatsuya Atsumi, Yuka Shimizu, Yuka Kono, Yusaku Kanetsuka, Takashi Kurita, Toshio Odani, Kotaro Otomo, Masaru Kato, Shinji Fukaya, Olga Amengual, Shinsuke Yasuda, Tetsuya Horita, Takao Koike

Department of Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Japan

[Aim] To clarify the morbidity and mortality in patients with antiphospholipid syndrome (APS).[Patients and Methods] This study comprised 113 patients with APS (female 94, age 44(11-83)). We analyzed retrospectively mortality rate, recurrence of thrombotic events and bleeding episodes during the follow-up period. [Results] The mean follow up period was 8.5 years (2-22). Eleven (10%) patients died and ten-year mortality rate was 93%. Thrombotic events recurred in 31 (27%). A total of 8 (7%) had serious bleeding events. In Kaplan-Meier analysis, patients with Diabetes Mellitus (DM) had tended to affect the recurrent thrombosis, bleeding and mortality ($p=0.04$).[Conclusion] Patients with APS develop recurrent thrombosis and serious bleeding with high mortality despite current treatment.

W9-2

The involvement of CD36 in the pathogenesis of antiphospholipid syndrome

Masaru Kato, Tatsuya Atsumi, Kenji Oku, Yuichiro Fujieda, Kotaro Otomo, Olga Amengual, Tetsuya Horita, Shinsuke Yasuda, Takao Koike

Department of Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Purpose. To examine possible involvement of CD36 in the pathogenesis of antiphospholipid syndrome (APS). Methods. Firstly, rs3765187, a gene polymorphism linked to CD36 deficiency, was investigated by TaqMan PCR genotyping in 108 APS patients and 422 healthy subjects. Then, involvement of CD36 in antiphospholipid antibody-induced tissue factor (TF) expression was tested by real-time PCR using CD36-null mice or anti-CD36. Results. Minor allele of rs3765187 was less frequent in APS patients compared to healthy subjects (2.8%(3/108) vs. 10.2%(43/422), $p=0.024$). TF expression was suppressed on macrophages from CD36-null mice compared to wild type and was dose-dependently inhibited by anti-CD36 in human mononuclear cells. Conclusion. Impaired CD36 function may be protective for developing APS.

W9-3

AGTRL1 and PRKCH SNPs in antiphospholipid syndrome

Tetsuya Horita, Hisako Nakagawa, Toshio Odani, Yuichiro Fujieda, Kotaro Otomo, Masaru Kato, Shinsuke Yasuda, Tatsuya Atsumi, Takao Koike

Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Angiotensin receptor-like1 (AGTRL1) and Protein kinase C ϵ (PRKCH) genes were reported to be associated with cerebral infarction. We examined the association of the functional SNP in an Sp1-binding site of AGTRL1 (rs9943582, G/A) and the nonsynonymous SNP (rs223050, G/A, Val372Ile) in PRKCH with antiphospholipid syndrome (APS). DNA samples were obtained from 111 APS patients and 428 controls. AGTRL1 was genotyped using TaqMan

SNP genotyping assay and PRKCH was genotyped using direct sequencing. Both AGTRL1 G allele and PRKCH A allele frequencies were significantly increased in patients with APS (OR=1.43, 95%CI:1.03-2.31 and OR=1.89, 95%CI :1.17-3.05, respectively). AGTRL1 and PRKCH are associated with APS. Our results suggest that these 2 SNPs are additional genetic risk factors for APS.

W9-4

Clinical features of pregnant patients with antiphospholipid syndrome

Yuko Matsuki¹, Kentaro Matsuoka², Koshi Yamaguchi¹, Atsuko Murashima¹

¹Division of Rheumatology, Department of Women's Health, National Center for Child Health and Development, Tokyo, Japan, ²Department of Pathology, National Center for Child Health and Development, Tokyo, Japan

Objective: To investigate clinical features and placental pathology of pregnant patients with antiphospholipid syndrome (APS). **Methods:** Clinical records were reviewed for pregnant patients with APS, and we studied 16 patients who met the Sapporo Criteria. **Results:** All patients were treated with heparin and low dose aspirin. They were divided into two groups: the mild group was well controlled with the above treatment, and the severe group required further treatment. Severe cases tended to be lupus anticoagulant positive or have multiple types of antiphospholipid antibodies (aPLs). Not all cases showed thrombosis in the placenta. **Conclusions:** When APS patients desire pregnancy, it is important to determine the type and titer of aPLs, and the pregnancy and delivery must be carefully managed.

W9-5

Why does APS associate frequently with SLE?

Misato Nishimura, Tetsuo Kubota
Tokyo Medical and Dental University Graduate School of Health Care Sciences

[Objective] To further elucidate the mechanisms of thrombophilic diathesis of APS and develop a novel therapeutic strategy, we intended to establish an in vivo model. **[Methods]** IgG MoAbs were obtained from (NZW x BXSb)F1 mice, and their specificity and biological activity were examined by ELISA and flow cytometry. **[Results]** Obviously, a MoAb WB-6 reacted with CL-β2GPI complex. It showed weak reactivity with CL alone, and did not react with β2GPI alone. In vivo injection of WB-6 to normal BALB/c mice induced expression of tissue factor on circulating monocytes and prolongation of APTT. Furthermore, WB-6 was revealed to be cross-reactive with dsDNA. **[Conclusion]** Some CL-dependent anti-β2GPI antibodies react with dsDNA, suggesting that the common pathogenic mechanism underlies APS and SLE.

W9-6

Clinical aspects of antiphospholipid syndrome undergoing hemodialysis in 9 cases

Shigeru Morioka, Reiko Sunami
Okayama central Hokancho Hospital

Purpose We investigate the clinical aspects of APS in hemodialysis patients. **Methods** We examined the clinical factor as APS diagnosis ACL antibody (ACLIgG), ACLbGPIAb, LA Treatment prognosis result age 55~94yo, male 5, female 4, diagnosis all primary APS, examine deta

ACLIgG elevated 8/9 ACLbGPI elevated 1/9, LA positive 1/9, symptom of thromboembolism cerebral infarction 4 patients, abortion 1 pt, pulmonary embolism 1 patient, ASO symptom 3 patients, shunt insufficiency 2, myocardial infarction 1. Treatment anticoagulant therapy 4 patients, antiplatelet therapy 8 patients, both therapy 3 patients. Prognosis 7/9 death sudden death 2, cerebral hemorrhage 1 patient, cerebral infarction 1 patient, infection 2 patients, aneurysm rupture 1 patient.

Conclusion For HD patients APS is important factor in diagnosis and prognosis.

W10-1

Trend of the clinical practice for fibromyalgia among Japanese rheumatologist

Yoshifumi Matsumoto¹, Hiroshi Oka², Kusuki Nishioka³

¹Fujita Health University Nanakuri Sanatorium, ²Institute of Medical Science, St. Marianna Medical University, ³Institute of Medical Science, Tokyo Medical University

Fibromyalgia (FM) have become well recognized rheumatism in Japan. The population-based survey showed that the prevalence rate of FM was 1.7% in Japan. The second survey for Japanese rheumatologists was conducted to clarify the numbers of FM and RA patients were treated for last year. Although 55% of RA patients were treated by rheumatologists, only 0.6% of FM patients were treated by them. The 37% of Japanese rheumatologists never treated FM patients.

W10-2

Therapeutic evaluation of fibromyalgia (FM) in our department

Makoto Sueishi¹, Takao Sugiyama¹, Toyohiko Sugimoto¹, Masaaki Furukawa¹, Yukiko Hiramatsu¹

¹Department of Rheumatology, Shimoshizu National Hospital, Yotsukaido, Japan, ²Department of Psychiatry, Dokkyo University School of Medicine, Mibu, Japan

We report the clinical evaluation of treatments for FM patients. Included in this study were 55 patients (female 54 male 1). The details of treatments were as follows: Gabapentin 46 cases, Pregabalin 33 cases, Electroconvulsive therapy 2 cases, Melsmon^R injection 11 cases, Fentanyl patch 6 cases. Clinical response ratio was 48% (22 cases) in Gabapentin, 64% (21 cases) in Pregabalin, all cases in Electroconvulsive therapy, 45% (5 cases) in Melsmon^R injection, all cases in Fentanyl patch. The reasons of discontinuation were as follows: drowsiness and/or dizziness 14 cases in Gabapentin and 12 cases in Pregabalin, mild defect of memory in 1 case of Electroconvulsive therapy, no clinical response 2 cases in Gabapentin, 1 case in Pregabalin and 5 cases in Melsmon^R injection.

W10-3

Clinical significance of the shoulder joint ROM for the fibromyalgia

Masahiro Iijima
Kouenji-minami Clinic of Integrative Medicine, Tokyo, Japan

Purpose: The aim of this study is to discuss the clinical significance of the shoulder joint ROM measurement for the patients with fibromyalgia syndrome (FMS). **Background:** For the assessment for FMS, several methods have established, but they are not enough for the joint function of the patients. **Methods:** The bilateral shoulder joint ROM of 20 FMS (2 male, 18 female) patients were measured on the outpatient primary care setting. Flexion, extension and abduc-

tion range of the bilateral shoulder joints of each patient were recorded. Results: 16 FM (1 male, 15 female) patients revealed shoulder ROM dysfunction. Discussion: Most FMS patients may suffer from shoulder joint dysfunction which aggravate their QOL level. Conclusion: Check on the shoulder joint ROM are clinically important for the patients with FMS.

W10-4

Frequency of Sacroiliitis (SI) in Patients with Inflammatory Bowel Disease (IBD)

Yohei Ito¹, Junichiro Nakamura¹, Naoto Mitsugi¹, Tomoyuki Saito²
¹Yokohama City University Medical Center, Yokohama, Japan, ²Department of Orthopaedic Surgery, Yokohama City University, Yokohama, Japan

[Objective] IBD sometimes overlapped with spondyloarthritis. This study aimed to examine SI frequency in IBD patients and a relationship between SI and patient background. [Methods] 150 patients were reviewed. X-ray findings of the sacroiliac joint were analyzed by age, sex, Crohn's disease/ulcerative colitis, and IBD duration. SI was classified by modified New York criteria. [Results] X-ray showed SI in 43 patients (28.7%). SI was correlated with age and IBD duration. [Discussion] SI frequency may increase with IBD duration and age, as IBD-related arthritis chronically progresses. The SI frequency is reportedly 2.0-45.7% in English literature, but there have been no such studies in Japan. Further study is required in a larger population to understand clinical symptoms of SI.

W10-5

The course after discontinuation of adalimumab for ankylosing spondylitis

Kurusu Tada¹, Eri Hayashi¹, Naoto Tamura¹, Shigeto Kobayashi², Hisashi Inoue³, Yoshinari Takasaki¹
¹Rheumatology and Internal Medicine, Juntendo University School of Medicine, ²Internal Medicine, Juntendo Koshigaya hospital, ³Orthopaedics, Juntendo University School of medicine

As a new treatment for ankylosing spondylitis adalimumab became available in 2010 in Japan. The excellent effect of adalimumab has been reported in EU and U.S. But many patients relapse when they stop adalimumab and they required re-treatment. Here we show two patients with ankylosing spondylitis, who were high disease activity even after conventional treatment, administered adalimumab. They have rapidly improved disease activity by adalimumab and were able to stop NSAID and steroid. A case now is scheduled to stop by the will of his future administration, we report the progress of disease activity after discontinuation.

W11-1

Golimumab (GLM), A Human Anti-TNF α Monoclonal Antibody Administered Subcutaneously Every Four Weeks as Monotherapy in Patients with Active Rheumatoid Arthritis Despite DMARD Therapy: 52-Week Results of Clinical and Radiographic Assessments

Tsutomu Takeuchi¹, Masayoshi Harigai², Yoshiya Tanaka³, Hisashi Yamanaka⁴, Naoki Ishiguro⁵, Kazuhiko Yamamoto⁶, Nobuyuki Miyasaka⁷, Takao Koike⁸, Golimumab - Japan Clinical Study Group
¹Division of Rheumatology, Department of Internal Medicine, School of Medicine, Keio University, ²Department of Pharmacovigilance, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, ³The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental

Hearth, ⁴Institute of Rheumatology, Rheumatology, Tokyo Women's Medical University, ⁵Department of Orthopaedic Surgery, Nagoya University, Graduate School & Faculty of Medicine, ⁶Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, ⁷Department of Medicine & Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, ⁸Department of Medicine II, Hokkaido University Graduate School of Medicine

Objective: To assess the efficacy and safety of GLM as a monotherapy in Japanese pts with active RA despite DMARD therapy. **Methods:** Pts were administered Placebo (P), GLM 50 mg or GLM 100 mg SC q4wks. The primary endpoint was ACR20 at wk 14. **Results:** 308 pts received treatment. At wk 14, GLM 50 mg (50.5%) and GLM 100mg (58.5%) were significantly better than P (19.0%) in ACR20. At wk 24, GLM 100 mg significantly inhibited radiographic progression (Total Sharp Score) compared with P. Both GLM were well-tolerated through wk 16. **Conclusion:** Both GLM improved signs, symptoms and physical function. GLM 100 mg inhibited progression of structural damage. Through wk 16, GLM was similar to other anti-TNF agents with safety profile. The results through wk 52 will be presented on the day.

W11-2

Golimumab (GLM), a Human Anti-TNF α Monoclonal Antibody Administered Subcutaneously Every Four Weeks in Patients with Active Rheumatoid Arthritis Despite Methotrexate Therapy: 52-Week Results of Clinical and Radiographic Assessments

Yoshiya Tanaka¹, Masayoshi Harigai², Tsutomu Takeuchi³, Hisashi Yamanaka⁴, Naoki Ishiguro⁵, Kazuhiko Yamamoto⁶, Nobuyuki Miyasaka⁷, Takao Koike⁸, Golimumab - Japan Clinical Study Group
¹The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, ²Department of Pharmacovigilance, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, ³Division of Rheumatology, Department of Internal Medicine, School of Medicine, Keio University, ⁴Institute of Rheumatology, Rheumatology, Tokyo Women's Medical University, ⁵Department of Orthopaedic Surgery, Nagoya University, Graduate School & Faculty of Medicine, ⁶Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, ⁷Department of Medicine & Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, ⁸Department of Medicine II, Hokkaido University Graduate School of Medicine

Objective: To assess the efficacy and safety of GLM in Japanese pts with active RA despite MTX therapy. **Methods:** Pts were administered Placebo (P), GLM 50 mg or GLM 100 mg SC q4wks. All pts received MTX 6-8 mg orally/wk. The primary endpoint was ACR20 at wk 14. **Results:** 261 pts received treatment. At wk 14, GLM 50 mg+MTX (72.1%) and GLM 100 mg+MTX (74.7%) were significantly better than P+MTX (27.3%) in ACR20. At wk 24, both GLM+MTX doses significantly inhibited radiographic progression (Total Sharp Score) compared with P+MTX. Both GLM+MTX were well-tolerated through wk 24. **Conclusions:** Both GLM+MTX improved signs, symptoms, physical function and inhibited progression of structural damage. Through wk 24, Both GLM+MTX were similar to other anti-TNF agents with safety profile. The results through wk 52 will be presented on the day.

W11-3

Dose-Response Study of Ocrelizumab for RA with inadequate response to MTX

Yoshiya Tanaka¹, Masayoshi Harigai²

¹First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, ²Department of Pharmacovigilance, Tokyo Medical and Dental University, Tokyo, Japan

[Objective] To assess the efficacy and safety of ocrelizumab (OCR) at different doses in MTX-IR RA patients for 24 weeks. [Methods] OCR 50mg, 200mg or 500mg and placebo (PBO) were administered intravenously on Day1 and 15 to 151 active RA patients in combination with MTX. Among them, 70.3% were biologics-naïve. [Results] At week 24, ACR20 response was achieved in 54.1%, 55.6%, and 47.2% of patients in OCR 50, 200, and 500mg arms, respectively, and 25.0% in PBO arm. The incidence of adverse events in OCR arms was 73.7%, and that of PBO arm was 59.5%. Seven cases of serious infections occurred in OCR arms and 0 in PBO arm. [Conclusion] OCR therapy significantly improved signs and symptoms. Serious infections including opportunistic infections only occurred in OCR arms.

W11-4

LY2127399 in Rheumatoid Arthritis (RA)

Chin H Lee¹, Mark C Genovese², Pierre-Yves Berclaz¹, Julie H Satterwhite¹, Damon Disch¹, Melissa Veenhuizen¹, Olivier Benichou¹

¹Eli Lilly and Company, Indianapolis, USA, ²Stanford University, Palo Alto, USA

LY2127399 (LY) is a monoclonal antibody binding both membrane-bound and soluble BAFF. In this study 156 subjects with RA on stable doses of methotrexate were randomized by a Bayesian-adaptive design to receive placebo (PBO), 1, 3, 10, 30, 60 or 120mg of LY in 6 monthly subcutaneous injections. At week 24 there was a significant dose response for ACR20 and ACR50 (primary analysis; $p < .1$) and a significant difference in ACR20 between 120 mg and PBO (71% vs 44%, $p < .05$). In LY arms total B cells transiently increased within 1 week then decreased below baseline by week 24. There were similar numbers of TEAEs (61% LY and 61% PBO) and SAEs (10% LY and 11.1% PBO) and more infections (31% vs. 19%) and serious infections (2.5% vs 0) in LY subjects. LY has clinical efficacy and was well tolerated.

W11-5

Rheumatoid arthritis complicated by malignant lymphoma introduced rituximab

Erika Matsubara, Tokutaro Tsuda

Department of Rheumatology, JR Tokyo General Hospital, Tokyo, Japan

Case is 73 year-old female diagnosed RA in 1993. She had suffered from malignant lymphoma since Oct. 2004, and 6 courses of R-CHOP were finished, and complete remission was achieved. In Feb. 2004, prednisolone(15mg/d), methotrexate(4mg/w) and actarit(300mg/d) were commenced because of a flare up of polyarthralgia. Although infliximab was added since Apr. 2008, lymphoma relapsed in the next month. 2 courses of R-cMOPP introduced in Jul 2008 resulted in remissions of lymphoma and RA. However RA relapsed again in May 2010. In spite of orally administered salazopyridine and articular injections of corticosteroid, remission could not be achieved. In Oct. 2010, we commenced rituximab therapy

(500mg/body, twice). CRP was lowered 2 weeks after, and rheumatoid factor decreased 4 weeks after.

W12-1

Studies on lupus psychosis using IFN α transgenic mice

Eriko Honda¹, Shunichi Shiozawa^{1,2,3}

¹Department of Biophysics, Graduate School of Health Science, Kobe University, Kobe, Japan, ²Department of Medicine, Graduate School of Medicine, Kobe University, Kobe, Japan, ³The Center for Rheumatic Disease, Kobe University Hospital, Kobe, Japan

OBJECTIVE; We have shown that IFN α transgenic mice(IFN α Tg) induces production of anti dsDNA antibody and renal diseases akin to human SLE. IFN α is also highly expressed in the brain and cerebrospinal fluids of patients with lupus psychosis. We here studied the contribution of IFN α to neuropsychiatric disease.

METHODS; Open field test (OFT), which reflects spontaneity and activity, Forced Swimming Test (FST) and Tail Suspension Test (TST), which express depression and anxiety-like behavior were performed in IFN α Tg 30weeks after induction of IFN α .

RESULTS; Locomotion score of OFT was significantly declined in IFN α Tg compared with normal mice ($P < 0.005$), which shows IFN α Tg had a lower exploratory activity.

CONCLUSION; Lupus psychosis is caused by IFN α .

W12-2

Clinical Manifestations in Serum Anti-NR2A Antibody-Associated SLE

Takahisa Gono, Yasushi Kawaguchi, Hirotaka Kaneko, Masanori Hanaoka, Yasuhiro Katsumata, Kae Takagi, Sayumi Baba, Yuko Okamoto, Sayuri Kataoka, Hisashi Yamanaka

Institute of Rheumatology, Tokyo women's medical university, Tokyo, Japan

Objective. To evaluate the relationship between anti-NR2A antibody and organ involvement in SLE. **Methods.** Serum anti-NR2A antibody was measured by ELISA, using the new peptide. Clinical characteristics were compared between 27 anti-NR2A antibody-positive (P group) patients and 80 antibody-negative patients. **Results.** The frequency of neuropsychiatric SLE (NP SLE) was significantly higher ($P = 0.0002$) in the P group, although the frequencies of serositis and nephritis were not significant. Significant inverse correlations were found between anti-NR2A antibody and leukocyte count and hemoglobin. NP SLE was the most significant independent variable ($P = 0.0008$) associated with anti-NR2A antibody positivity. **Conclusion.** Anti-NR2A antibody is associated with NP SLE and may involve cytopenia.

W12-3

Increased levels of plasma pentraxin3 as a diagnostic marker for lupus psychosis

Yuki Shimada, Yu Asanuma, Fumihiko Miyoshi, Takuma Wada, Muneo Ota, Mayuko Sakamoto, Akinori Yamamoto, Yasufumi Shindo, Kazuhiro Yokota, Kyoichi Nakajima, Hiroshi Kajiyama, Kojiro Sato, Yuji Akiyama, Toshihide Mimura

Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University

Lupus psychosis is often observed among the psychiatric symptoms in SLE. A wide range of the symptoms and few diagnostic tests make lupus psychosis difficult to be diagnosed promptly. Pentraxin3 (PTX3) is produced by a variety of cells in response to the

inflammatory stimuli. We have examined the hypothesis if PTX3 reflects activities in SLE and if it is a useful diagnostic marker for lupus psychosis. Plasma PTX3 were measured in 58 patients with SLE and 53 healthy controls by ELISA. PTX3 levels were significantly higher in patients with SLE than those of controls, and were extremely high in patients with lupus psychosis. Additionally the factor analysis demonstrated the close relation between PTX3 and lupus psychosis. PTX3 may be a novel and useful marker for diagnosing the condition.

W12-4

Post-steroid neuropsychiatric manifestations in systemic lupus erythematosus

Yuka Shimizu, Tatsuya Atsumi, Michihito Kohn, Yusaku Kanetsuka, Takashi Kurita, Toshio Odani, Yuichiro Fujieda, Masaru Kato, Kotaro Otomo, Shinji Fukaya, Tetsuya Horita, Shinsuke Yasuda, Takao Koike

Department of Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Objective: To clarify the characteristics of post-steroid neuropsychiatric manifestations (PSNP) in patients with systemic lupus erythematosus (SLE) and other autoimmune diseases. **Patients and Methods:** This study comprised 74 patients with SLE, 99 patients with other autoimmune diseases who were treated with high-dose corticosteroids (Prednisolone ≥ 40 mg/day). The prevalence and characteristics of PSNP were retrospectively reviewed. **Results:** The prevalence of PSNP was higher in SLE (23%, 17/74) than that in other diseases (1%, 1/99) (OR 29.23, 95%CI [3.79-225.47]). In most of lupus patients with PSNP, one or more of impaired laboratorial findings were confirmed. **Conclusion:** PSNP was almost specific in patients with SLE, thus could be classified one of the features of NPSLE.

W12-5

Comparative study of patients with NPSLE

Eisuke Ogawa, Sumiaki Tanaka, Ryosuke Hara, Takeo Kudo, Toshihiro Tono, Noriko Tono, Satoko Tejima, Tatsuhiko Wada, Junichi Tanaka, Kenta Hoshi, Tatsuo Nagai, Akira Ishikawa, Shunsei Hirohata

Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Sagami-hara, Japan

Involvement of the nervous system by systemic lupus erythematosus (SLE) includes a wide variety of neurologic and psychiatric. From 2005 to 2010, 25 patients with Neuropsychiatric manifestations of systemic lupus erythematosus (NP-SLE) admitted in Kitasato University Hospital. We make a comparative review of their clinical features. The most common of the NP-syndrome were Neurologic syndromes (22 patients), Diffuse psychiatric syndromes (7 patients), and Peripheral nervous system disorder (3 patients). The most common of the serological features were anti-DNA antibody (95.8%), anti-SS-A antibody (77.5%), anti-Sm antibody (69.9%), and anti-Ribosomal-P antibody (60%). And the cases presented Diffuse psychiatric syndromes accepted the tendency with the immunity abnormality.

W12-6

Investigation of NP-SLE presented psychiatric symptoms as a first manifestation

Sumie Moriyama¹, Reo Yoshikawa¹, Satoshi Kamei¹, Yoshinori Masui¹, Junwa Kunitatsu¹, Yuko Takahashi², Hiroyuki Yakashita², Akio Mimori², Hiroshi Kaneko³

¹Department of Internal Medicine, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan, ²Division of Rheumatic Diseases, Department of Internal Medicine, National Center for Global Health and Medicine, Tokyo, Japan, ³Department of Rheumatology, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan

This study was aimed at investigating the characteristics and prognosis of neuropsychiatric (NP)-SLE patients whose onset was psychiatric symptoms. The patients were 8 females with NP-SLE ranging in age from 29 to 63 years old. Their psychological symptom covered from seizure, depression and schizophrenic reaction. Most patients were treated as mentally ill at first. The median time to the diagnosis of SLE was 1 month from the first visit. The data of this retrospective study suggests the delay of first consultation may develop an irreversible brain damage. Family background may also affect the prognosis. Early cooperation of psychiatrists, neurologists and rheumatologists is required for effective treatment of NP-SLE patients.

W13-1

Autoantibody predicts outcomes of interstitial lung disease in dermatomyositis

Masataka Kuwana¹, Shinji Sato²

¹Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, ²Division of Rheumatology, Department of Internal Medicine, Tokai University School of Medicine, Isehara, Japan

Interstitial lung disease (ILD) is a leading cause of mortality in dermatomyositis (DM), including clinically amyopathic DM (CADM). To evaluate whether autoantibody status predicts outcomes of ILD, 70 patients diagnosed as having DM and ILD were evaluated for autoantibodies by immunoprecipitation. Anti-aminoacyl tRNA synthetase (ARS) and anti-CADM-140 were detected in 40 and 16, respectively. Cumulative survival rates were significantly worse in anti-CADM-140+ than in anti-ARS+ ($P < 0.05$). All deaths in anti-CADM-140+ occurred within 7 months after onset, whereas survival rates in anti-ARS+ were gradually reduced and comparable with those in anti-CADM-140+ at 10 years after onset. In summary, autoantibody detection is useful in predicting variable outcomes of ILD in DM patients.

W13-2

Clinical Manifestation and Prognostic Factor in Anti-MDA5 Antibody-associated DM

Takahisa Gono¹, Yasushi Kawaguchi¹, Takashi Satoh², Masataka Kuwana², Yasuhiro Katsumata¹, Kae Takagi¹, Ikuko Masuda¹, Hisae Ichida¹, Akiko Tochimoto¹, Sayumi Baba¹, Masanori Hanaoka¹, Yuko Okamoto¹, Yuko Ota¹, Sayuri Kataoka¹, Hisashi Yamanaka¹

¹Institute of Rheumatology, Tokyo women's medical university, Tokyo, Japan, ²Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

Purpose: To evaluate the clinical manifestation and prognostic factors of anti-MDA5 antibody-associated DM. **Methods:** Clinical

manifestations in 14 DM patients with anti-MDA5 antibody (MDA5 patients) were compared to those in 10 DM patients with anti-aminoacyl-tRNA synthetase antibody (ARS patients). **Results:** The frequencies of C-ADM and rapidly progressive interstitial pneumonia (RP-IP), the liver enzyme and ferritin values were significantly higher in the MDA5 patients. The most significant prognostic factor was ferritin. The cumulative survival rate was significantly lower ($P < 0.0001$) in the subset with ferritin ≥ 1600 ng/mL than the other subset in the MDA5 patients. **Conclusion:** Both serum ferritin and anti-MDA5 antibody are powerful indicators for the diagnosis of RP-IP with DM.

W13-3

Clinical factors to predict refractory disease in PM and DM associated with ILD

Yoshifumi Tada¹, Kentaro To², Eiichi Suematsu³, Akira Ueda⁴, Shuji Nagano⁵, Takuya Sawabe⁶, Hiroaki Nishizaka⁷, Hiroshi Tsukamoto², Rie Suematsu¹, Hisako Inoue¹, Syuichi Koarada¹, Akihide Ohta¹, Takahiko Horiuchi², Kohei Nagasawa¹

¹Department of Rheumatology, Faculty of Medicine, Saga University, ²Department of Medicine and Biosystemic Science, Graduate School of Medical Sciences, Kyushu University, ³Department of Internal Medicine and Rheumatology, National Hospital Organization Kyushu Medical Center, ⁴Department of Internal Medicine, Miyazaki Prefectural Miyazaki hospital, ⁵Department of Rheumatology, Oita Red Cross Hospital, ⁶Department of Rheumatology, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, ⁷Department of Internal Medicine, Kitakyushu Municipal Medical Center

Interstitial lung disease (ILD) is a serious complication in patients with PM and DM. To predict poor prognostic and refractory patients, we reviewed medical records of idiopathic PM/DM patients associated with ILD. Patients were categorized into three groups; fatal cases (11 patients), refractory cases (8 patients) and responsive cases (42 patients), and the clinical factors were analyzed by Cox proportional Hazards model. By a multivariate analysis, PaO₂/FiO₂ < 400 OR Chest X-ray score > 2 and LDH/CK > 1 were significant risk factors. The presence of one or more factor predicts fatal or refractory disease with 95% sensitivity and 55% specificity. The evaluation of these clinical factors may help to predict poor prognosis and refractory disease.

W13-4

The prognostic value of anti MDA 5 antibody in dermatomyositis

Tomohiro Koga¹, Keita Fujikawa³, Naoki Iwamoto¹, Akitomo Okada¹, Shin-ya Kawashiri¹, Satoshi Yamasaki¹, Hideki Nakamura¹, Tomoki Origuchi¹, Masataka Kuwana², Hiroshi Mukae⁵, Katsumi Eguchi⁴, Atsushi Kawakami¹

¹Unit of Translational Medicine Department of Immunology and Rheumatology Nagasaki University Graduate School of Biomedical Sciences, ²Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine., ³Isahaya Health Insurance General Hospital, ⁴Sasebo City General Hospital, ⁵Department of Respiratory Disease, School of Medicine, University of Occupational and Environmental Health

Objective: To determine the prognostic value of anti-MDA5 antibody (Ab) in dermatomyositis (DM). **Methods:** We examined the difference toward clinical features and distribution of myositis-specific autoantibodies in 88 DM patients in the presence or absent of anti-MDA5 Ab determined by ELISA. **Results:** Anti-MDA5 Ab was detected in 17 patients. Anti-CADM140kDa Ab determined by

immunoprecipitation was also found in 16 out of 17 patients positive with anti-MDA5 Ab. The anti-MDA5 Ab-positive patients frequently showed amyopathic dermatomyositis (CADM) and rapidly progressive ILD (RPILD). The survival rate at 6 months from the diagnosis was significantly low in the anti-MDA5 Ab-positive patients. **Conclusion:** Anti-MDA5 Ab was useful for identifying CADM and/or RPILD among patients with DM.

W13-5

Clinical features of Anti-aminoacyl tRNA synthetase antibody positive 12 cases

Tsukasa Ishiwata, Takahiro Nunokawa, Naofumi Chinen, Yoshiki Nagai, Katsuaki Shiroto, Naoto Yokogawa, Kota Shimada, Shoji Sugii, Shinichi Inada

Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center

We examined clinical features of Anti-aminoacyl tRNA synthetase (ARS) antibody positive cases detected in inflammatory muscle diseases, polymyositis and dermatomyositis. We experienced 12 anti-ARS antibody positive cases. Seven cases had anti-jo-1 antibody, three had anti-EJ antibody, one had anti-KS antibody, one had anti-PL-7 antibody. In anti-ARS antibody positive cases, about 80% had interstitial lung disease and more than half had mechanic's hand. Moreover, in anti-jo-1 antibody positive cases, about 60% had joint deformity of hands. Some anti-ARS antibody positive cases required immunosuppressive therapy.

Anti-ARS antibody positive cases were accompanied by more interstitial lung disease than negative, and had characteristic skin findings.

W13-6

Clinical & immunogenetic features of Japanese patients with anti-PL-12 antibody

Michito Hirakata¹, Yuko Kaneko², Tetsuya Takada², Noriyuki Seta², Tsutomu Takeuchi²

¹Medical Education Center, Keio University School of Medicine, Tokyo, Japan, ²Department of Internal Medicine, Keio University School of Medicine

PURRPOSE: To elucidate the clinical and immunogenetic features of patients with anti-PL-12 (AlaRS) autoantibodies. **METHODS:** Autoantibodies in sera from 15,000 patients with connective tissue disease were examined by immunoprecipitation. The HLA-class II alleles were identified using genomic DNA. **RESULTS:** Anti-PL-12 antibodies were identified in the sera of 8 patients (idiopathic ILD:6, scleroderma:2). No patients had muscle weakness, but chronic ILD was observed in all patients. Five of 8 (63%) patients had DRB1*1501-DQA1*0102-DQB1*0602, compared to 9% of healthy controls ($P < 0.01$, OR=17.5). **CONCLUSIONS:** These results indicate that anti-PL-12 autoantibodies have a stronger association with ILD than with myositis, and may be associated with the immunogenetic background.

W14-1

Antisynthetase syndrome as a cause of deforming arthritis

Takahiro Nunokawa, Mutsuhito Ui, Satoshi Watanuki, Naofumi Chinen, Yoshiki Nagai, Katsuaki Shiroto, Naoto Yokogawa, Kota Shimada, Shoji Sugii, Shinichi Inada

Background : The antisynthetase syndrome is associated with anti-aminoacyl-tRNA antibodies and typically presents with inflammatory myopathy and ILD. In addition, this syndrome rarely shows polyarthritis. **Method :** We evaluated joint manifestations in 14 patients (Jo-1: 8, EJ: 4, KS: 1, PL-7: 1). **Results :** Five patients had DIP involvement and two patients had RA-like hand deformities. Two patients had bone edema and erosions of carpal bones in MRI. One patient had prominent periarticular calcinosis. All patients with deforming arthritis had anti-Jo-1-antibody.

Conclusion : Antisynthetase syndrome can present with deforming arthritis mimicking RA.

W14-2

2 cases of polymyositis complicated with myocarditis

Junya Yamamoto, Atsushi Noguchi, Riki Satoh, Satoru Kunisaki, Satoshi Jodo, Atsushi Fujisaku
Tomakomai City Hospital, Tomakomai, Japan

We present 2 cases of polymyositis (PM) complicated with myocarditis. The first case exhibited muscle weakness, diffuse skin sclerosis, generalized edema, and elevated muscle enzymes. Cardiac US and MRI were consistent with myocarditis. Both endomyocardial and limb muscle biopsy showed cellular infiltration. The second case developed muscle weakness, tachycardia, and elevated muscle enzymes. ECG showed various arrhythmias. Both patients were diagnosed as PM with myocarditis and treated with steroid plus cyclophosphamide and MTX, respectively. Although PM with myocarditis is well known, patients suffered from clinical congestive heart failure or overt severe arrhythmias are relatively rare. We discuss the pathophysiology and differential diagnosis of myocarditis in patients with PM.

W14-3

Five cases of polymyositis or dermatomyositis preceded by rheumatoid arthritis

Takao Nagashima, Masahiro Iwamoto, Seiji Minota
Jichi Medical University, Division of Rheumatology and Clinical Immunology

Among 62 patients hospitalized for polymyositis (PM) or dermatomyositis (DM) in our institution during 2005-2010, 5 (8.1%) were found to have preceding rheumatoid arthritis (RA): man 1, women 4; PM 2, DM 3 (amyopathic DM 1); age at the diagnosis of PM/DM, 43-73 years old (median 49); duration between the diagnoses of RA and myositis, 4 months-23 years (median 1.5 years); anti-Jo-1 antibody positivity in 3/5; RF positivity in 4/5; and anti-CCP antibody positivity in all patients. The Steinbrocker stage was I in 2; II in 2; and IV in 1. All patients had interstitial pneumonia. The figure of 8.1% is not rare and we should bear this overlap in mind when treating patients with RA.

W14-4

Malignancy-associated dermatomyositis/polymyositis. A single center analysis.

Shinya Tamechika, Taio Naniwa, Shinji Maeda, Maiko Watanabe, Kaneshige Sasaki, Shiho Iwagaitsu, Yoshihito Hayami

AIM: To identify the association between dermatomyositis (DM), polymyositis (PM) and malignancy. **METHODS:** 115 DM/PM cases were retrospectively analyzed. **RESULTS:** Mean age at the onset of DM/PM was 51.1 years, and that with malignancies was 60 years which was significantly higher than that without. 89 were female and, mean follow-up duration was 77 months. Malignancy was detected in 23 cases (20%) after 34 (-30 to 140) months, and in 11 of them within 2 years from the onset of DM/PM. The common sites of malignancies were digestive tract (7 cases), followed by breast in 4, and lung cancer in 3. About 50% of patients with active DM/PM and concomitant malignancies had refractory DM/PM despite immunosuppressive therapy that was resolved after receiving therapy for malignancies.

W14-5

STAT-4 gene polymorphisms in Japanese patients with polymyositis/dermatomyositis

Tomoko Sugiura, Yasushi Kawaguchi, Takefumi Furuya, Yasuhiro Katsumata, Takahisa Gono, Manabu Kawamoto, Masako Hara, Hisashi Yamanaka
Institute of Rheumatology, Tokyo Women's Medical University School of Medicine

The aim of the present study was to investigate the involvement of the STAT-4 gene polymorphisms in the susceptibility of polymyositis/dermatomyositis (PM/DM) in Japanese. We genotyped single nucleotide polymorphisms at rs7574865, rs10168266, rs1183934 and rs3821236 of the STAT-4 gene in 138 patients with PM, 115 patients with DM and 615 control individuals. In the DM patients, the frequency of A allele at rs3821236 was significantly higher than that in the control individuals (0.53 versus 0.41, $p=0.001$, odds ratio=1.62, 95% confidence interval=1.22-2.14). In the PM patients, the A allele frequency was not different from control individuals. The involvement of rs3821236 of the STAT-4 gene in the susceptibility of Japanese DM patients was shown.

W14-6

Analysis of circulating Th17, TGF- β and IL-21 in dermatomyositis / polymyositis

Yasuhiro Shimojima, Masayuki Matsuda, Ko-ichi Tazawa, Shu-ichi Ikeda

Department of Neurology and Rheumatology, Shinshu University School of Medicine

We investigated circulating CD4+IL-17+ lymphocytes (Th17), serum TGF- β and IL-21 in dermatomyositis (DM) and polymyositis (PM). Fifteen patients with DM and 10 with PM were studied. Th17 in both DM and PM showed significant decreases compared with controls ($p<0.0001$, $p<0.05$, respectively), and significantly increased after clinical remission ($p<0.05$). A significant decrease of naïve Th17 (CD4+CD45RA+IL-17+) was only shown in DM ($p<0.05$). Serum levels of TGF- β was significantly increased in both diseases ($p<0.05$), but showed no apparent correlation with Th17. IL-21 was undetectable in all samples. Circulating Th17 may be usable as a clinical marker in diagnosis and treatment of DM and PM, but it remains unconfirmed whether Th17 is correlated with serum levels of TGF- β and IL-21.

W15-1

The role as a health information manager for RA treatment: creation of database

Wataru Yamamoto¹, Kazuhiko Ezawa², Ryutaro Yamanaka², Misuzu Yamashita², Koji Takasugi², Masamitsu Natsumeda², Kayo Ezawa², Yoshihisa Nasu³

¹Department of Health Information Manage, Kurashiki Kosai Hospital, Kurashiki, Japan, ²Department of Internal Medicine, Kurashiki Kosai Hospital, Kurashiki, Japan, ³Department of Orthopaedic Surgery, Kurashiki Kosai Hospital, Kurashiki, Japan

Objective: To contribute a favorable outcome of RA patients by compiling the information of their clinical evaluation and therapeutic process in a database. **Methods:** We assembled a database which we could unify multilaterally intended for about 320 RA patients taking biologic medications in our hospital. **Results:** Our database system helped a doctor get hold of patients' clinical course and control their disease activity tightly. It also supported steady implementation of periodic examination. In addition, it was made available for lots of reports in recent academic conferences. **Conclusion:** Further building of database system is necessary to furnish our patients with sufficient information about their therapeutic process in real time and to support patient-centered therapy in the future.

W15-2

The regional multi-professional research society for rheumatology in Hyogo

Masanori Taketomi¹, Goh Tsuji², Satoshi Kashiwagi³, Shimpei Kasagi⁴, Kinue Matsuo^{5,6}, Yasushi Miura⁶

¹Department of Orthopedic Surgery, Shinko Hospital, Kobe, Japan, ²Department for Rheumatic Diseases, Shinko Hospital, Kobe, Japan, ³Department of Orthopedic Surgery and Rheumatology, Amagasaki medical coop Hospital, Amagasaki, Japan, ⁴Department of Clinical Immunology, Kobe University Graduate School of Medicine, Kobe, Japan, ⁵Department of Rehabilitation, Konan Kakogawa Hospital, Kakogawa, Japan, ⁶Department of Rehabilitation Science, Kobe University Graduate School of Health Sciences, Kobe, Japan

OBJECTIVE: Biologic agents have brought the new era for the treatment of RA. Concurrently lots of new issues have also arisen.

METHODS: To resolve the issues, we established a regional multi-professional research society for rheumatology in Hyogo Prefecture in February 2010 and held the 1st meeting in May to promote skills and mutual understanding.

RESULTS: 206 medical workers of 12 different professions participated and 11 subjects were presented, Patient education, rehabilitation, and patient cares were the most desired topics. 87% of the participants were interested in multi-professional working for patients with rheumatic diseases.

CONCLUSION: The research society of rheumatology based on the region and the multi-professional working will be useful to promote better cares.

W15-3

The Incidence of Cancer among Japanese RA patients on 2003-2009 using iR-net.

Noriyuki Chiba¹, Shigeto Tohma²

¹Morioka National Hospital, Morioka, Japan, ²Sagamihara National Hospital, Sagamihara, Japan

In a prospective cohort study using iR-net, 36330 patients on 2003- 2009 with RA were enrolled from 25 national hospital. A total

of 207 cases of cancer were observed. Standardized Incidence Ratio (SIR) of all cancers revealed no significant difference compared with general population. SIR of colon cancer (0.33) and gastric cancer (0.64) in female was lower as expected, and SIR of malignant lymphoma (3.03) and bladder cancer (3.82) in female was higher as expected. Increased risk of malignant lymphoma in RA patients has been reported by many investigators. We expect to continue this cohort study for long time period and contribute to the epidemiology about the cancer risk of Japanese patients with RA.

W15-4

Cross-sectional Survey of 1194 RA Patient Examined by the Akita Orthopedic Group

Seiya Miyamoto¹, Yoichi Kataoka², Masaaki Ogino³, Hiromi Morita⁴, Kunitaka Yan⁵, Wataru Watanabe⁶, Nobuhiro Ishizawa⁷, Kazuhiro Shoji⁸, Takeshi Kashiwagura⁹, Tsutomu Sakuraba⁹, Moto Kobayashi¹, Yoichi Shimada¹⁰

¹Nakadori General Hospital, Akita, Japan, ²Joto Orthopedic Clinic, Akita, Japan, ³Koto General Hospital, Akita, Japan, ⁴Morita Orthopedic Clinic, Akita, Japan, ⁵Yan Orthopedic Clinic, Akita, Japan, ⁶Honjo daiichi Hospital, Akita, Japan, ⁷Fujiwara Memorial Hospital, Akita, Japan, ⁸Shoji Orthopedic Clinic, Akita, Japan, ⁹Akita City Hospital, Akita, Japan, ¹⁰Dept. of Orthopedic Surgery Akita University Graduate School of Medicine, Akita, Japan

【Purpose】AORA was established in July 2010 to construct a network of medical treatment for RA in Akita prefecture, consisting mainly of 20 orthopedists examining patients with RA. Herein, we report the data collected from RA patients.

【Method】A cross-sectional survey was performed on RA patients consulting their 20 physicians.

【Results】The number of RA patients was 1194, their mean age was 64 years. According to Steinbrocker's classification, 26% of the patients were in stage I, 23% in stage II, 23% in stage III, and 28% in stage IV; and 33% were in class I, 49% in class II, 13% in class III, and 5% in class IV. Out of the patients, 21% were treated with biological products.

【Conclusion】We plan to share the data of RA treatment and reflect them in our future treatment.

W15-5

Correlations of RAPID3 with disease activity scores in IORRA cohort

Yohei Seto, Eisuke Inoue, Naoki Sugimoto, Daisuke Hoshi, Kumi Shidara, Eri Sato, Mariko Kitahama, Toru Yamada, Eiichi Tanaka, Ayako Nakajima, Atsuo Taniguchi, Shigeki Momohara, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University

Background and Purpose: Importance to assess patient reported outcomes (PROs) has been determined recently. We analyzed correlations of RAPID3, DAS28 and CDAI in patients with RA enrolled in IORRA cohort. **Methods:** Correlations were analyzed between each score and also between the changes of each score during six months in patients who consecutively participated in IORRA study held in October, 2009 and April, 2010. **Result:** In 4932 patients included, RAPID3 vs DAS28 and RAPID3 vs CDAI were both well correlated (Spearman's rank-order correlation $\rho=0.66$ and 0.78 , respectively), whereas correlations of the changes of each score were $\rho=0.59$ and 0.66 in RAPID3 vs DAS28 and in RAPID3 vs CDAI.

Conclusion: RAPID3 was determined as an important score to assess disease status in patients with RA.

W15-6

Orthopedic surgery for RA in NinJa report 2009

Koichiro Saisho^{1,2}, Shigeto Tohma^{2,3}, Etsuo Chosa⁴, Hiroaki Hamada⁴

¹Department of Orthopedics/Rheumatology, National Hospital Organization Miyakonojo Hospital, Miyakonojo, Japan, ²iR-net, ³Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagamihara National Hospital, Sagamihara, Japan,

⁴Department of Orthopedics, Miyazaki University School of Medicine, Miyazaki, Japan

Aim Analyzer/report RA-related orthopedic surgeries performed in '09 using NinJa. **Method** RA-related surgeries examined in 7085 patients registered in '09 (F5817, M1268) & compared with '03 to '08. **Results/Discussion** Of 7085 patients in '09, 294 patients/347 events (4.2%/4.9%) underwent RA surgeries. The number of RA surgery cases in '03, '04, '05, '06, '07, and '08 was 8.5%, 7.3%, 7.2%, 7.1%, 6.4%, and 4.7% respectively: a decrease. In '09, RA surgeries to total patient number ratios were (per type) 2.9% (artificial joint), 0.3% (synovectomy), 0.9% (arthroplasty), 0.3% (arthrodesis) and etc.. Medication: 55%, and 18% of patients received total MTXs, & total biologicals, respectively: an increase. The number of surgery cases was influenced by an increase in the development of new drugs to decrease.

W16-1

Remission rate of early RA by tight control and residual physical disability

Toshihide Shuto

Dept Rheumatology, Orthopaedics, Chiyoda Hospital, Miyazaki, Japan

Patients with recent-onset RA with a disease duration of 2 years or less (average 9.9 months) were included in this study. Principally, patients started sulphasalazine. For patients failing on their medication, followed by sequential treatment steps; methotrexate plus sulphasalazine, then methotrexate plus anti-TNF therapy. Further if needed, switching to the other biologics or to tacrolimus was chosen. The percentage of patients in clinical remission (defined as DAS28-ESR < 2.6) and functional ability measured by the HAQ were assessed. Clinical remission was achieved by 70% at 1 year. Two patients achieved DAS < 2.6 on the initial treatment (sulphasalazine monotherapy), six on the sulphasalazine plus methotrexate. Six patients were treated with anti-TNF agents. Sixteen patients had HAQ score of 0.0.

W16-2

The evaluation of function in RA patients with clinical and structural remission

Hiroshi Harada, Takaaki Morooka, Masaaki Morooka
Morooka Orthopaedic Hospital

Some RA patients in clinical and structural remission are unable to attain functional remission, and some in complete remission remain in disorder of ADL.

We study, in 34 RA patients keeping clinical remission more than 6 months, correlation between HAQ in final exam and period from onset to clinical remission, mTSS, erosion score, and JSN score.

As a result, functional remission was achieved in some cases required more than 5 years to clinical remission or showed mTSS

more than 100, while HAQ-DI of 0 required all factors of clinical remission within 2.3 years, mTSS ≤ 60, erosion score ≤ 52, and JSN score ≤ 4.

It is suggested that critical factors contributing to the remission without ADL disorder are clinical and structural remission before progress of joint damage especially joint space narrowing.

W16-3

Therapy for patients in clinical remission (CR) after discontinuing biologics

Takafumi Hagiwara¹, Tomoko Nakamura², Yasuhiro Saegusa³, Kaoru Atsui⁴, Keisuke Hashimoto⁵, Hideyuki Okamoto⁶, Yasunori Shimaoka⁷, Yutaka Furumitsu⁸, Hajime Owaki⁹, Tsukasa Matsubara¹

¹Matsubara Mayflower Hospital, Rheumatology, Kato, Japan, ²Hyoogo Prefectural Rehabilitation Hospital at Nishi-Harima, Rheumatology, Kobe, Japan, ³Konan Hospital, orthopedics, Kobe, Japan, ⁴Medical corporation Atui Orthopaedics Rheumatology Clinic, Kobe, Japan, ⁵Medical corporation Atui Orthopaedics Rheumatology Clinic, Kobe, Japan, ⁶Okamoto Clinic, Himeji, Japan, ⁷Yukioka Hospital, Orthopaedics Surgery, Osaka, Japan, ⁸Ohno Memorial Hospital, Rheumatology, Osaka, Japan, ⁹Osaka Koseinenkin Hospital, Orthopaedic Surgery, Osaka, Japan

(Purpose) The use of biologics rapidly improves the prognosis of RA. However, there are issues concerning their use; increased risk of infections or higher medical costs. We examined maintenance therapy strategies to be used once biologics are discontinued.

(Method) Retrospectively, we examined disease activity of RA patients registered at several facilities after they had, regardless of reason, discontinued biologics.

(Result) 24.4% of patients maintained CR with DMARDs treatment. 36.6% showed low disease activity 1 year after discontinuing biologics. For those achieving CR during biologics treatment, CR was 45.5%. **(Conclusion)** It's important to achieve CR during the treatment period with biologics in order to maintain CR after discontinuance and replace it with regular DMARDs therapy.

W16-4

Evaluation of the new ACR/EULAR definition for remission using the REAL database

Hayato Yamazaki^{1,2}, Ryoko Sakai^{1,2}, Kaori Watanabe^{1,2}, Michi Tanaka^{1,2}, Toshihiro Nanki^{1,2}, Ryuji Koike^{1,2,3}, Nobuyuki Miyasaka², Masahiro Harigai^{1,2}

¹Department of Pharmacovigilance, Tokyo Medical and Dental University Graduate School of Medicine, Tokyo, Japan, ²Department of Rheumatology, Tokyo Medical and Dental University Graduate School of Medicine, Tokyo, Japan, ³Faculty of Medicine Clinical Research Center, Tokyo Medical and Dental University Hospital, Tokyo, Japan

Objective: To compare rates of remission in patients with rheumatoid arthritis (RA) recruited to the REAL database using DAS28-CRP and the new ACR/EULAR definition for remission (SJC ≤ 1, TJC ≤ 1, VAS ≤ 1/10, CRP ≤ 1 mg/dl). **Method:** We identified 854 patients with RA who started biologics at their registration to the REAL and calculated rate of remission overtime. Baseline mean DAS28-CRP of these patients was 4.2 ± 1.2. **Results:** Numbers of patients who achieved remission at month 6 (n=811) and month 12 (n=687) using DAS28-CRP were 354 (43.6%) and 343 (49.9%), respectively. However, these numbers were only 101 (12.5%) and 119

(17.3%) using the new definition for remission. Conclusions: We have to treat patients with RA more tightly to achieve this new goal.

W16-5

Continuation of biologics-free in the rheumatoid patients in clinical remission.

Kazuko Shiozawa¹, Yasushi Tanaka¹, Ryosuke Yoshihara¹, Miki Murata¹, Takashi Yamane¹, Chihiro Tanaka^{1,2}, Noriaki You¹, Shigeaki Imura¹, Natsuko Nakagawa¹, Kohzoh Kohyama¹, Yasuhiro Terashima¹, Shigeru Matsuda¹, Kiminobu Yokoyama¹, Koji Tateishi¹, Shunichi Shiozawa²

¹Kohnan Kakogawa Hospital, Rheumatic Disease Center, ²Kobe University School of Medicine, Rheumatic Disease Center

The 22 patients with rheumatoid arthritis (RA) who achieved DAS28/CRP < 2.3 and biologics-free were followed. Among 15 of 327 (4.6%) patients with infliximab, 3 of 365 (0.8%) patients with etanercept, 1 of 82 (1.2%) patients with tocilizumab and 3 of 139 (2.2%) patients with adalimumab, 16 (73%) patients maintained biologics-free for 21.9 ± 15.9 months. Six other patients resumed the same or another biologics after 12.1 ± 7.2 months. Age of onset of the patients was 51.0 ± 14.3, disease duration and DAS28/CRP at the time of the start of biologics were 13.0 ± 11.3 and 4.1 ± 1.2, respectively. Biologics were stopped because of adverse events such as pneumonia n = 13, and the proposal from patients n = 9.

W16-6

Remission of RA cases in our department using ACR/EULAR Definition of Remission

Aihiro Yamamoto, Masataka Kohno, Amane Nakabayashi, Takashi Kida, Hidetake Nagahara, Wataru Fujii, Ken Murakami, Kaoru Nakamura, Takahiro Seno, Hidetaka Ishino, Yutaka Kawahito
Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

A severer remission is requested by the advance of recent treatment to rheumatoid arthritis (RA). It is thought that the remission criteria such as Disease Activity Score (DAS) 28 of European League Against Rheumatism (EULAR) is insufficient in general practice. We revalued 82 cases of RA that have administered biologics by ACR-EULAR Definition of Remission which was newly shown in American College of Rheumatology (ACR) in 2010. The remission cases were 13 examples (16%) by the new definition among 40 cases (49%) that had been diagnosed as remission by DAS28-CRP. Moreover, the remission cases was 13 examples (16%) and 12 examples (15%), respectively diagnosed by SDAI and CDAI. We examine the utility and the problem of the new definition of remission from our results.

W17-1

Induction of type B synoviocyte-like cells from bone marrow plasmacytoid DC

Shunsei Hirohata¹, Tetsuya Tomita², Hideki Yoshikawa²

¹Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, ²Department of Orthopedic Surgery, Osaka University Medical School

We examined the capacities of bone marrow (BM) plasmacytoid dendritic cells (pDC) to differentiate into type B synoviocyte-like cells. CD34+ cells and pDC purified from BM, obtained from 24 RA patients and 19 OA patients during joint operations via aspiration from the iliac crest, were cultured with various cytokines for

2-4 weeks. RA BM pDC as well as OA BM pDC comparably differentiated into fibroblast-like cells (FLC), producing MMP-1, especially in the presence of TNF- α . Depletion of BDCA4+ pDC from RA BM CD34+ cells significantly diminished their capacities to differentiate into FLC, which were restored by addition of BDCA4+ cells. These results indicate that pDC are one of the progenitors of type B synoviocytes, suggesting that BM pDC might be involved in the pathogenesis of RA.

W17-2

Electronmicroscopic analysis of characteristic inflammation in RA synovium

Akihisa Kamataki¹, Kenya Murakami^{1,2}, Takashi Sawai¹

¹Department of Pathology, Iwate Medical University School of Medicine, Morioka, Japan, ²Department of Orthopaedic Surgery, Iwate Medical University School of Medicine, Morioka, Japan

Inflammation in synovium of rheumatoid arthritis (RA) shows nonspecific and chronic characters. However, responsible cells for this characteristic inflammation are not clear. In this study, electronmicroscopic analysis of RA synovium was performed using non-specific granulation tissue as control. In RA synovium, nurse-like cells (NLC) were observed everywhere. Nursed round cells were considered as plasma cells. In granulation tissue, NLC was not observed. Immunoelectron microscopy showed that the shape of CD14+ cells was various from round to spindle and some CD14+ cells contained NLC. Detailed analysis showed cell fusion of NLC and round cell in part. These results suggest that the interaction and direct transport between NLC and round cells may cause characteristic RA inflammation.

W17-3

A pro-inflammatory role for ABIN1 in a subtype of RA-FLS

Hideya Igarashi¹, Jun Hashimoto³, Tetsuya Tomita², Hideki Yoshikawa², Katsuhiko Ishihara¹

¹Department of Immunology and Molecular Genetics, ²Department of Orthopaedic Surgery, Osaka University Medical School, ³NHO Osaka Minami Medical Center

By the microarray analysis between the transformed fibroblast-like synoviocytes (FLS) derived from RA (RA-FLS) and OA, we found that ABIN1 as a useful marker to classify the RA-FLS to a distinct subtype. Namely, we could divide the non-transformed primary FLS cell lines into two categories, one group (6 cases defined as responder) showed the inducible transcription of *TNFA*, *IL-1 β* and *IL-6* with the increase of *ABIN1*, *ABIN3*, and *A20* upon stimulation with TNF α whereas another group (5 cases defined as non-responder) did not. In addition, enhanced NF- κ B activation by TNF α in the responder was confirmed by western blotting probed with anti-phospho I κ B α , and EMSA. ABIN1, which is involving in inhibitory pathway for NF- κ B activation, seems to play a role for the augment of inflammation in RA-FLS.

W17-4

Analysis of Chemerin/ChemR23 in synovitis of rheumatoid arthritis

Makoto Kaburaki¹, Hirahito Endo¹, Toshiko Shibata², Hidehiro Yamada², Natsuko Kusunoki¹, Shinichi Kawai¹

¹Toho University Ohmori Medical Center Department of Rheumatology, ²St Marianna University School of medicine Department of Rheumatology

To evaluate the role of chemerin in inflammatory arthritis, we measured the levels of chemerin in synovial fluids and its receptor chemR23 expression of synovial tissues obtained from patients with RA and OA. **Methods.** Level of chemerin in sera and synovial fluids from RA and OA measured by a specific ELISA. Real-time PCR. In situ hybridization and histochemistry were performed to detect mRNA for chemerin, chemR23 in synovial tissues from RA and OA. **Results.** Chemerin showed significantly higher levels in RA synovial fluid than OA. Expression of Chemerin were stronger in RA synovium than OA synovium. ChemR23 mRNA also expressed in macrophages of RA synovium. **Conclusion.** These data indicated that Chemerin/Chem23 may be a new therapeutic target for inflammatory synovitis of patients with RA

W17-5

Semi-quantitative evaluation of survivin expression to distinguish RA from OA.

Sho Mokuda¹, Tatsuhiko Miyazaki², Masato Nose², Kiyoshi Takasugi¹

¹Department of Internal Medicine, Center for Rheumatic Diseases, Dohgo Spa Hospital, Matsuyama, Ehime, Japan., ²Department of Pathogenomics, Ehime University Graduate School of Medicine, Ehime, Japan.

Survivin is a member of the inhibitor of apoptosis (IAP) family. RA cases with a high serum level of survivin tend to develop bone erosion. We analyzed synovial tissue specimens from 8 cases of OA, 9 cases of active RA and 8 cases of inactive RA using double immunohistochemistry for survivin, and CD55 or CD68. The density of signals for survivin was analysed by a morphometry program, and were into four groups: (-), (\pm), (+), (++) , then the IHC index was evaluated. The mean survivin IHC index of synovial fibroblasts was 57.50 ± 16.03 in OA, 528.7 ± 69.49 in active RA and 171.9 ± 51.92 in inactive RA respectively. Synovial macrophages revealed similar results. These findings suggest the immunohistochemical analysis of survivin expression might therefore be a useful tool to distinguish RA from OA.

W17-6

Attenuation of T cell receptor signaling causes autoimmune disease

Shinji Maeda¹, Satoshi Tanaka¹, Shuji Akizuki¹, Motomu Hashimoto¹, Shimon Sakaguchi¹

¹Department of Experimental Pathology, Institute for Frontier medical Sciences, Kyoto University, Kyoto, Japan, ²Department of Medical Oncology and Immunology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

We have gradationally expressed the zeta-associated protein-70 (ZAP-70) in normal mice by tetracycline-inducible genetic control, and examined whether TCR signal alteration is able to cause autoimmune disease. We show that developing T cells expressing lower amounts of ZAP-70 are less sensitive to thymic negative selection than those expressing normal levels of ZAP-70, which results in thymic production of pathogenic self-reactive T cells and occurrence of autoimmune disease, such as autoimmune arthritis. This indicates that genetic anomalies or variations attenuating TCR-proximal sig-

naling enhance the production of pathogenic autoimmune T cells and make the host succumb or susceptible to autoimmune disease.

W18-1

Pathogenic role of lysophosphatidic acid on rheumatoid arthritis

Yoshishige Miyabe, Shin Fukuda, Kayoko Kaneko, Nobuyuki Miyasaka, Toshihiro Nanki

Department of Medicine and Rheumatology, Tokyo Medical and Dental University, Tokyo, Japan

Lysophosphatidic acid (LPA) is a bioactive lipid, which is generated by autotaxin (ATX). In this study, we analyzed expression of ATX and LPA receptors (LPAR1-5) in rheumatoid arthritis (RA), and examined the pathogenic role in RA. ATX and LPAR1-5 were expressed in the RA synovium. Stimulation with LPA upregulated expression of IL-6, MCP-1, and MMP-3 by fibroblast-like synoviocytes (FLS) from RA. Treatment with BrP-LPA (antagonist for ATX and LPAR) reduced clinical arthritis score and bone destruction of murine collagen-induced arthritis. These results indicate that LPA plays an important role for activation of FLS in the RA synovium, and LPA could be a new target for RA therapy. This study is collaborated with Masayuki Miyasaka (Laboratory of Immunodynamics, Osaka University).

W18-2

Angiopoietin-like protein 2 contributes to pathogenesis of rheumatoid arthritis

Tatsuya Okada, Hiroto Tsukano, Hiroshi Mizuta

Department of Orthopaedic and Neuro-Musculoskeletal Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

Infiltration of inflammatory cells and vascular inflammation play a fundamental role in pathogenesis of rheumatoid arthritis (RA). More recently, it has been reported that angiopoietin-like protein 2 (Angptl2) activates an inflammatory cascade in endothelial cells and induces chemotaxis of monocytes/macrophages, resulting in initiation and propagation of inflammation. Angptl2 mRNA and protein are abundantly expressed in hyperplastic rheumatoid synovium of RA patients. Angptl2 concentration in joints of RA patients was also significantly increased in comparison with patients with osteoarthritis. Notably, Angptl2 promoted increased chemotactic activities of monocytes from synovial fluid of RA patients. Therefore, Angptl2 acts as an important inflammatory mediator in RA pathogenesis.

W18-3

Osteoclast formation and S100A4 calcium binding protein

Hidehiko Sugino¹, Hooi-Ming Lee¹, Chieko Aoki², Masashi Wada², Miho Murakami², Takaji Matsutani², Takahiro Ochi³, Norihiro Nishimoto^{1,2}

¹Graduate School of Frontier Biosciences, Osaka University, Suita, Japan, ²Laboratory of Immune Regulation, Wakayama Medical University, Wakayama, Japan, ³Osaka Police Hospital, Osaka, Japan

Object: S100 protein family is composed of at least 20 members in vertebrates. Elevated levels of S100A4, A8, A9 and A12 have been reported in RA. We investigated a role of S100 proteins in osteoclast formation. **Method:** Pre-osteoclasts were cultured with M-CSF and sRANKL in vivo. S100A4 siRNA was transfected into pre-osteoclasts. Suppression of S100A4 was confirmed by RT-PCR. Osteoclast was identified histologically as well as by TRAP staining

at day 5. **Result:** S100A4 was consistently and highly expressed throughout the osteoclast differentiation compared to the other S100 families. Suppression of S100A4 by siRNA in pre-osteoclasts inhibited the differentiation into mature osteoclasts. **Conclusion:** The intracellular S100A4 has a critical role for the osteoclast formation.

W18-4

Regenerating gene (REG)1 α Promotes Pannus Progression in Rheumatoid Arthritis

Kazuhisa Nozawa¹, Maki Fujishiro², Ayako Yamaguchi², Mikiko Kawasaki², Keigo Ikeda², Yoshinari Takasaki¹, Iwao Sekigawa²

¹Department of Rheumatology, Juntendo University School of Medicine, Tokyo, Japan, ²Institute for Environment and Gender Specific Medicine, Juntendo University Graduate School of Medicine, Chiba, Japan

Introduction: A proteome analysis revealed that regenerating gene (REG) 1 α appears to be related to the pathogenesis of RA. Therefore, the present study was conducted to examine the mechanism of REG 1 α in RA pathogenesis. **Methods:** REG 1 α serum concentration and the effects of REG 1 α on apoptosis and proliferation of synovial fibroblasts were evaluated. **Results:** The serum concentrations of REG 1 α in RA patients were higher than in normal controls. TNF- α upregulated REG 1 α production from the synovial fibroblasts MH7A cell line. Exogenous REG 1 α protein inhibited MH7A apoptosis and promoted the cell proliferation of MH7A cells. **Conclusion:** The present study suggested that aberrant REG 1 α production has a central role in the increased cell growth of synovial fibroblasts resulting in pannus formation.

W18-5

The Sp1 contributes to the gliostatin production in rheumatoid synoviocytes.

Kenji Ikuta¹, Yuko Nagaya¹, Takanobu Otsuka¹, Mineyoshi Aoyama², Kiyofumi Asai²

¹The Department of Orthopaedic Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan, ²The Department of Molecular Neurobiology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Gliostatin (GLS) is known to have angiogenic and arthritogenic activities. GLS has been reported to be considerably related with the pathology of RA. Mithramycin is a DNA-binding transcription inhibitor specific for GC-rich sequences, which prevents the binding of Sp1 to its cognate DNA. We investigated the effect of mithramycin on the production of GLS in RA fibroblast-like synoviocytes (FLSs). The expression levels of GLS mRNA and protein are shown to be significantly increased following tumor necrosis factor (TNF) α treatment alone, and are inhibited by mithramycin in RA FLSs in a dose dependent manner. This study suggests that the Sp1 transcription factor might contribute to the GLS production induced by TNF α in RA FLSs.

W18-6

Histological changes of synovium after etanercept treatment for RA

Miwa Uzuki^{1,3}, Ayako Kubota², Takashi Sawai³, Takashi Nakamura², Yoshiyasu Miyazaki², Toru Suguro²

¹Department of Pathology, School of Medicine, Faculty of Medicine, Toho University, ²Department of Orthopedics, School of Medicine, Faculty of Medicine, Toho University, ³Department of Pathology,

Division of Leading Pathophysiology, Iwate Medical University, School of Medicine

Purpose: We examined histological changes of synovium after biologics treatment for rheumatoid arthritis (RA).

Methods: The paraffin embedded synovium were obtained from 52 RA patients. We examined histological and immunohistochemical changes before and after treatment.

Results: In responder, the number of synovial lining cells, high endothelial venules and inflammatory cells decreased. In addition, the number of positive cells of MMP-3, TNF α , CD68 and CD34 decreased, too. On the other hand, synovial inflammation worsened in non-responder and immunohistochemical findings showed opposite results to responder.

Discussion: Biologics may stop the vicious circle in responder by decreasing the number of TNF α positive cells.

Summary: In responder, biologics suppress the synovial inflammation.

W19-1

MRI Findings in 4 Cases of Rheumatoid Arthritis that Achieved Clinical Remission with Etanercept Treatment

Kae Kikuchi¹, Nobuo Matsui¹, Yasuhiro Kubota², Osamu Ogikubo¹, Saori Nagao¹

¹Department Orthopaedic Surgery, Nagoya city Rehabilitation and Sports Center, ²Kubota Orthopedic and Rheumatology Clinic, Toyota, Japan

<Objective> We analyzed MRI findings of the hands in 4 patients with rheumatoid arthritis(RA) who achieved clinical remission in response to etanercept (ETN) treatment. <Methods> We performed MRI on the hands of the patients before and after ETN treatment. Each case was scored using the RAMRIS system. The mean of before ETN treatment, MRI scores for synovitis, erosion and bone edema were 12.3, 22.5 and 15, with a total score of 48.5. After the ETN treatment, the mean of MRI scores for synovitis, erosion and bone edema were 3.75, 15.5 and 5.75, with a total score of 25. <Conclusion> All cases showed a decrease in a total MRI score after ETN treatment. Although a significant improvement was noted in the MRI synovitis score of all cases, synovitis and bone edema were still observed with the exception of bone edema in case 4. MRI might be useful in determining the therapeutic efficacy of RA treatment.

W19-2

Etanercept promotes bone formation via suppression of Dickkopf-1 expression

Atsushi Tanida¹, Yuji Kishimoto¹, Toru Okano¹, Hiroshi Hagino², Ryota Teshima¹

¹Department of Orthopedic Surgery, Faculty of Medicine, Tottori University, Tottori, Japan, ²School of Health Science, Tottori University, Faculty of Medicine

To examine the effects of etanercept (ETN) on bone formation, we investigated the gene expression of cytokines relevant to osteoblast differentiation, and histological evaluation of bone repair in rats with collagen-induced arthritis (CIA).

CIA rats were divided into ETN administration group (E group) and placebo group (P group). Total RNA was extracted from destruction bone tissue and analyzed using real-time PCR for relative quantities of DKK-1, Wnt m-RNA expression. Histological findings in hard tissue specimens were taken from the distal femur then compared

between the groups.
DKK-1 mRNA expression decreased and Wnt mRNA expression, Osteoid, and labeling surface on surface of pannus increased significantly with E group.
ETN promotes bone formation via suppression of DKK-1 expression.

W19-3

Changes in cytokines and bone metabolism markers in RA cases on etanercept (ETN)

Akiko Suda¹, Shohei Nagaoka¹, Kenji Ohmura¹, Shigeto Tohma³, Hiroshi Furukawa³, Yoshiaki Ishigatsubo²

¹Department of Rheumatology, Yokohama Minamikyosai Hospital, Yokohama, Japan, ²Department of Internal Medicine and clinical Immunology, Yokohama City University, Kanagawa, Japan, ³Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami Hospital, National Hospital Organization, Kanagawa, Japan

Objective We examined changes in cytokines & bone metabolism markers in RA out-pts newly treated with ETN. **Methods** 19 pts starting ETN at our hospital Nov/05 - Jan/07 w/ consent incl. 2 men (mean age 62.0 yo; mean RA duration 8.7 yrs); cytokines & bone metabolism markers (IL-2, IL-4, IL-6, IL-8, TNF α , TRACP-5b, NTx) were measured at baseline, Weeks 4 & 24 to explore correlation with disease activity (DA). **Results** Mean DAS28-ESR scores at each timepoint were 6.74, 4.99 & 3.80. Increases in TNF α (baseline vs. Week 24: 2.3 vs. 96.9) & TRACP-5b (13.7 vs. 22.9) and decrease in IL-6 (37.4 vs. 9.73) were significant. No other cytokines changed significantly. **Discussion** DA significantly decreased after ETN treatment. Although most cytokines had no correlation with DA, IL-6 decreased & TNF α increased.

W19-4

The Efficacy in the Prevention of Bone and Joint damage treated with Etanercept

Hiroyuki Miyake
Ichinomiya Municipal Hospital, aichi

Objective The efficacy in the prevention of bone and joint damage on DAS28ESR during week 12 of ETN was evaluated. **Methods** Administration to subjects who were administered ETN until Week 52, and the subjects were 16 patients on carrying out evaluation of bone and joint damage in X-rays (vdH total Sharp score (TSS)). The difference between TSS prior to administration and 52 weeks in 8 subjects of DAS28ESR ≤ 3.2 in week 12 (low group) was compared with that in 8 subjects of DAS28ESR > 3.2 in week 12 (moderate group). **Results** Progress was inhibited, with the average change of TSS at low/moderate group is 0.7/6.3. **Conclusion** The possibility that DAS28ESR at week 12 of ETN can be used to predict the inhibition of bone and joint damage after 1 year of administration was suggested.

W19-5

Effect of etanercept on weight-bearing joints in patients with RA

Masato Sonobe¹, Ayako Kubota¹, Kazuaki Tsuchiya¹, Koichi Nakagawa², Yasuchika Aoki², Arata Nakajima², Yoshifumi Shibata¹, Shintaro Tsuge¹, Teruo Furufu², Toru Suguro¹

¹Department of Orthopaedic Surgery Toho University of Medicine,

²Department of Orthopaedic Surgery Toho University of Medicine

The aim of the present study was to assess the effect of etanercept on weight-bearing joints in patients with RA. We investigated the changes in radiological findings in 316 weight-bearing joints (77 hip joints, 67 knee joints, 86 ankle joints, 86 subtalar joints). Structural damage to the weight-bearing joints was assessed using the Larsen scoring method. The progression of joint damage was mostly inhibited in weight-bearing joints as well as in small joints, while damaged weight-bearing joints of Larsen grades 3 and 4 at baseline showed progression even in patients with a good response. Early initiation of ETN should be necessary before or at the appearance of minor radiographic changes in the weight-bearing joints.

W19-6

Clinical efficacy of once-weekly etanercept 50mg treatment for RA patients

Masayuki Azukizawa, Haruki Takagi, Kazutaka Takatsuka, Hiroko Morise

Department of Orthopaedic Surgery, Fukui Red Cross Hospital, Fukui, Japan

Purpose: We investigated the clinical efficacy of once-weekly 50mg etanercept (ETN) in patients with RA.

Objectives: 12 patients with RA received treatment of 50mg ETN once a week in our institution. The mean age was 66.0 years old, and the majority were women (11 patients). One patient had received prior treatment with adalimumab, another had never received any biological DMARDs administration, and the other 10 patients had continued twice-weekly 25mg ETN injection (Group T). The clinical response was measured by changes in DAS28-ESR and MMP-3.

Results: One patient of Group T had discontinued in 4 weeks because of RA flare-up. The other 11 patients received once-weekly 50mg ETN without adverse events.

Conclusion: We suggested once-weekly 50mg ETN treatment was effective and safe.

W20-1

Osteoblastogenesis of mesenchymal stem cells is accelerated under inflammation

Koshiro Sonomoto¹, Kunihiro Yamaoka¹, Koichi Oshita¹, Shunsuke Fukuyo¹, Yosuke Okada¹, Kazuyoshi Saito¹, Yoshiya Tanaka¹, Makoto Satake²

¹The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, School of Medicine, Kitakyushu, Japan, ²Integrative Technology Research Institute, Teijin Limited, Tokyo, Japan

Because of the known pluripotency and immunosuppressive effect of mesenchymal stem cells (MSCs), they possess the potential as a new tool to treat rheumatoid arthritis (RA). To investigate the potential of MSCs to differentiate into osteoblasts under active inflammation *in vitro*, human MSCs (hMSCs) was cultured with inflammatory cytokines. Among the tested cytokines, IL-1 β prominently enhanced mineralization through activation of Wnt5a/Ror2 pathway. To evaluate the effect *in vivo*, hMSCs was transplanted to rat collagen induced arthritis (CIA). Both control rat and CIA rat showed mineralization at the site. As a result, hMSCs are possible to differentiate into osteoblasts under inflammatory condition both *in*

vitro and *in vivo* suggesting their usefulness for RA treatment aiming joint repair.

W20-2

Atherogenic effect of TNF- α and IL-6 on foam cell formation in THP-1 macrophages

Misato Hashizume, Masashi Shiina, Hiroto Yoshida, Miho Suzuki, Masahiko Mihara

Product Research Department, Chugai Pharmaceutical Co., Ltd., Gotemba, Japan

The risk of cardiovascular disease is increased in patients with rheumatoid arthritis (RA). In recent times, it has been identified that TNF- α and IL-6 play the key role in RA pathogenesis. However, the role of these cytokines in atherogenesis is not elucidated. TNF- α and IL-6 augmented oxidized LDL (oxLDL) uptake into THP-1 macrophages. Next, the effect of these cytokines on the expression of the scavenger receptors, SR-A and LOX-1 was examined. IL-6 induced SR-A expression and TNF- α induced both SR-A and LOX-1 mRNA. Interestingly, IL-6 participated in TNF- α -mediated foam cell formation partially. In conclusion, we firstly demonstrated that TNF- α and IL-6 promoted foam-cell formation. The blockades of TNF- α and IL-6 may have potency to attenuate the cardiovascular risk.

W20-3

Increased CCL13 by Estrogen Promotes Pannus Formation

Ayako Yamaguchi^{1,2}, Kazuhisa Nozawa^{1,2}, Mikiko Kawasaki¹, Maki Fujishiro¹, Yoshinari Takasaki², Iwao Sekigawa^{1,3}

¹Institute for Environment and Gender Specific Medicine, Juntendo University Graduate School of Medicine, Chiba, Japan, ²Department of Rheumatology, School of Medicine, Juntendo University, Tokyo, Japan, ³Department of Internal Medicine and Rheumatology, Juntendo University Urayasu Hospital, Chiba, Japan

We report the role of estrogen in the pathogenesis of rheumatoid arthritis (RA). Co-stimulation with 17 β -estradiol and TNF α increased the MMP-3 expression in human synoviocytes. To investigate how estrogen directly affects the synoviocytes, the changes in their gene expression after 17 β -estradiol stimulation were determined by DNA microarray analysis. CCL13 was shown to be strongly upregulated by 17 β -estradiol stimulation. To confirm the microarray result, the gene expression and the supernatants of CCL13 were evaluated. Furthermore, CCL13 was aberrantly produced in RA compared to osteoarthritis and the prevalence of elevated CCL13 in sera was higher in patients with active RA. 17 β -estradiol stimulation leads to induction of CCL13, it may be associated with initial pannus formation.

W20-4

Suppressive function of regulatory T cell in human is mediated by IL-35

Souichiro Nakano¹, Satoshi Suzuki¹, Takashi Watanabe¹, Shinji Morimoto¹, Hidenori Hase², Yoshinari Takasaki¹

¹Department of Rheumatology and Internal Medicine, Juntendo University School of Medicine, Tokyo, Japan, ²Department of Molecular Immunology, Graduate School, Tokyo Medical and Dental University, Tokyo, Japan

IL-35 is the newest member of the IL-12 family. In mouse, it has been reported that IL-35 is produced by autocrine and suppresses the immune response through the expansion of regulatory T cells

(Treg). Here we demonstrated that human IL-35 is expressed in the naturally occurring Treg isolated from peripheral blood, but not in CD4+CD25- responder T cells (Tres). The treatment with IL-35 enhanced the regulatory function of Treg to suppress the cell growth of Tres stimulated by anti-CD3/CD28. On the other hand, the suppressive function of Treg was significantly reduced by the knockdown of IL-35 with siRNA, suggesting that human IL-35 might be participated in the regulation of T cell activation events through the promotion of Treg function in peripheral immune response.

W20-5

The role of IL-25 receptor expression on eosinophil committed progenitors

Yojiro Arinobu^{1,2}, Shun-ichiro Ota², Atsushi Tanaka², Naoyasu Ueda², Kumiko Noda², Kentaro To², Yasushi Inoue², Hiroaki Niino², Hiroshi Tsukamoto², Takahiko Horiuchi², Koichi Akashi^{1,2}

¹Center for Cellular and Molecular Medicine, Kyushu University Hospital, ²Department of Clinical Immunology, Rheumatology, and Infectious diseases, Kyushu University Hospital

IL-17E, also known as IL-25, is a member of IL-17 family cytokines (IL-17A-F). IL-17A and F evoke inflammation and play critical roles in the exacerbation of autoimmune disorders. In contrast, IL-25 displays anti-inflammatory function through the induction of Th2 cytokines and plays a pivotal role in innate immune cell-mediated allergic inflammation. It has been discussed which type of cells express IL-25 receptor (IL-25R), however, still remains controversial. We here present the newly-identified IL-25R expressing cell population. Interestingly, IL-25R is expressed on eosinophil lineage-committed progenitors (EoPs) stage specifically. We would like to reveal the biological function of this population and clarify the role of IL-25 signaling in allergic inflammation.

W20-6

Possible involvement of JAK pathways in production of IL-6 induced by BAFF

Keiko Yoshimoto¹, Maiko Tanaka¹, Hideko Ogata¹, Masako Kojima¹, Tohru Abe², Tsutomu Takeuchi¹

¹Division of Rheumatology/Clinical Immunology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, ²Division of Rheumatology and Clinical Immunology, Saitama Medical University, Saitama Medical Center, Kawagoe, Japan

We showed that BAFF induced robust production of IL-6 by SS monocytes as compared with normal monocytes. We found that SS monocytes and a human monocyte cell line, THP-1, showed similar response to BAFF in the production of IL-6. In this study, we investigated signaling pathways triggered by BAFF for the production of IL-6 by using THP-1 as a model of SS monocytes. When IFN- γ -gamma-primed THP-1 cells were cultured with BAFF in the presence of JAK3 inhibitor, the production of IL-6 was strongly suppressed in a dose dependent manner. Moreover, we found that the expression of JAK3 was elevated when IFN- γ -gamma-primed THP-1 cells were cultured with BAFF. These data suggest that BAFF plays a role in the induction of IL-6, which is one of major players of inflammatory responses, through JAK pathway.

W21-1

15d-PGJ₂ Reduces the Arthritis and the Formation of Atherosclerotic Lesions

Takahiro Seno¹, Masahide Hamaguchi², Masataka Kohno¹, Hidetaka Ishino¹, Aihiro Yamamoto¹, Kaoru Nakamura¹, Ken Murakami¹,

Wataru Fujii¹, Hidetake Nagahara¹, Takashi Kida¹, Amane Nakabayashi¹, Yutaka Kawahito¹

¹Inflammation and Immunology, Kyoto Prefectural University of Medicine, Kyoto, Japan, ²WPI Immunology Frontier Research Center, Osaka University, Osaka, Japan

Rheumatoid arthritis is a chronic inflammatory disease that has been associated with increased cardiovascular event rates. Atherosclerosis has a key role in cardiovascular events. 15-Deoxy- $\Delta^{12,14}$ Prostaglandin J₂ (15d-PGJ₂) is a ligand of peroxisome proliferator-activated receptor γ (PPAR γ) having diverse effects. 15d-PGJ₂ can also regulate the expression of inflammatory mediators independent of PPAR γ . Intraperitoneal administration of 15d-PGJ₂ ameliorated adjuvant-induced arthritis with suppression of pannus formation and mononuclear cell infiltration. Moreover, administration of 15d-PGJ₂ to apolipoprotein E-deficient mice reduced atherosclerotic lesion formation of aortic root. 15d-PGJ₂ is a beneficial therapeutic agent for rheumatoid arthritis and atherosclerosis.

W21-2

The role of IL-2Ra in clonal expansion of Th17 cell.

Kenjiro Fujimura^{1,2}, Koji Sakuraba^{1,2}, Akiko Oyamada^{1,2}, Yukihide Iwamoto², Yasunobu Yoshikai¹, Hisakata Yamada^{1,2}

¹Division of Host Defense, Medical Institute of Bioregulation, Kyushu University, ²Department of orthopaedic surgery, Kyushu University

IL-2 is important for clonal expansion of antigen-specific T cells. Cyclosporine A and FK506 block IL-2 transcription and are used for the treatment of rheumatoid arthritis (RA). However, it was recently reported that IL-2 suppressed the differentiation of Th17, which was believed to play pathogenic role in RA. Because the role of IL-2 for clonal expansion of Th17 cell remained unclear, we analyzed the development of Th17 cell in IL-2 receptor α (IL-2Ra) deficient mice and ovalbumin specific TCR transgenic mice. We found that in the absence of IL-2Ra, the absolute number of Th17 cells decreased, although less severely than Th1 cells. Thus, clonal expansion of Th17 cell is also promoted by IL-2, which is consistent with the therapeutic effect of IL-2 blocker in RA.

W21-3

Effect of a c-Fos/AP-1 inhibitor T-5224 on the cytokines production in mouse CIA

Yukihiko Aikawa¹, Akira Hashiramoto^{2,3,4}, Shuichi Hirono⁵, Shunichi Shiozawa^{2,3,4}

¹Research Laboratories, Toyama Chemical Co., Ltd., ²Department of Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, ³The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan, ⁴Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan, ⁵Department of Pharmaceutical Sciences, School of Pharmacy, Kitasato University, Tokyo, Japan

Objective: The effect of a c-Fos/AP-1 inhibitor T-5224 on the cytokines production in the arthritic hind paws of mice with type II collagen-induced arthritis was examined.

Methods: DBA/1J mice were immunized with collagen (days 0 and 21). On day 35, the levels of cytokines in the hind paws were measured by Bio-Plex Protein Array System after a single oral administration of T-5224.

Results: Ten cytokines in the arthritic hind paws were significantly higher than those in normal paws. Especially, IL-1 β , IL-6 and KC/

gro α significantly increased. T-5224 significantly decreased these cytokines within several hours after a single administration.

Conclusions: The results suggest that the prompt inhibitory effect of T-5224 on the cytokines production contributes to the antiarthritic action in RA.

W21-4

Histone modification in TCR locus to generate autoantibody-inducing CD4⁺ T cell

Kenichi Uto¹, Ken Tsumiyama¹, Shunichi Shiozawa^{1,2,3}

¹Department of Biophysics, Kobe University Graduate School of Health Science, Kobe, Japan, ²Department of Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, ³The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

Objective: Our 'self-organized criticality theory' explains that the generation of autoantibody-inducing CD4⁺ (aiCD4⁺) T cell *de novo* TCR α revision at periphery is the key for causing of SLE. Here we examined the histone modification in TCR locus to study the mechanism of TCR revision.

Methods: BALB/c mice were immunized 8x with SEB. Histone acetylation and H3K4 trimethylation in TCR locus of splenic CD4⁺ T cell was examined by using ChIP assay.

Results: In CD4⁺ T cell of SEB-immunized and control mice, histone H3 of TCR locus was equally highly acetylated and trimethylated, as well as in thymocyte.

Conclusion: The results suggest that regardless of repeated immunization with antigen, peripheral CD4⁺ T cell is ready for the TCR revision in terms of chromatin structure.

W21-5

A new derivative, 5-I of Roxithromycin ameliorates collagen-induced arthritis.

Satoshi Iwata¹, Tomoki Katayose¹, Yoshiko Kichikawa¹, Hiroshi Kawasaki¹, Osamu Hosono¹, Yoshiyuki Kanai^{1,3}, Hiroto Tanaka¹, Chikao Morimoto¹

¹Institute of Medical Science, The University of Tokyo, Japan, ²Department of Pathology, School of Medicine, Keio University, Japan, ³Sawarabikai

Objective: The macrolide antibiotics have immunomodulatory properties distinct from antibacterial functions. We synthesized 5-I, the new derivative of Roxithromycin with less antimicrobial activity, and studied immunomodulatory effects of 5-I in vitro and in vivo. **Methods & Results:** 5-I specifically inhibited the production of Th1, IL-17, and proinflammatory cytokines by activated T cells, and proinflammatory cytokines by stimulated monocytes. 5-I also inhibited activated T cells migration. Finally, we found that the administration of 5-I to collagen-induced arthritis mice reduced severity of arthritis. The effectiveness was also observed in the case of delayed treatment model. **Conclusion:** Our findings strongly suggest that 5-I may be useful for the therapy of rheumatoid arthritis.

W22-1

Bone fracture risk factors in RA patients on long-term steroid and BIS therapy

Ko Katayama

Katayama Orthopedic Rheumatology Clinic

Objective: RA patients treated with BIS and long-term use of steroids with and without bone fractures were compared, and the risk factors for fractures were examined. **Subjects:** The subjects

were 129 RA patients without fractures and 38 with fractures who took PSL at 2-15 mg/d for more than one year as well BIS for more than 10 months. Results: As risk factors, high age, low BMD, high final urine NTX level, pre-existing fractures, severe RA grade, severe inflammation with increased doses of PSL were observed between two groups. The fracture risk factors were different for patients given alendronate and those given risedronate. Discussion: The severity and continuous activation of RA are connected with increased risk of fractures in addition to the risk factors for primary osteoporosis.

W22-2

Changes in serum RANKL and OPG after glucocorticoid therapy in rheumatic disease

Kaichi Kaneko, Natsuko Kusunoki, Nahoko Tanaka, Tatsuhiro Yamamoto, Makoto Kaburaki, Sei Muraoka, Koutarou Shikano, Yoshie Kusunoki, Hirahito Endo, Shinichi Kawai

Division of Rheumatology, Department of Internal Medicine (Omori), School of Medicine, Faculty of Medicine, Toho University, Tokyo, Japan

<Purpose> To clarify whether serum RANKL and OPG play a role in the pathogenesis of glucocorticoid (GC)-induced osteoporosis in patients with rheumatic diseases. <Methods> Sixty patients (female 39) with rheumatic diseases who received initial therapy with 30-60 mg prednisolone and bisphosphonate were included. Serum RANKL and OPG levels were measured by ELISA at 0, 1, 2, 3 and 4 weeks after GC therapy. <Result> The average serum RANKL increased, while average serum OPG was significantly decreased after GC therapy. <Conclusion> The 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.

W22-3

Combination therapy with bisphosphonates and statin in RA patients

Masakazu Nagashima, Kohichi Wauke, Hiroshi Takahashi, Nobuyuki Suzuki, Yoshiyuki Yamazaki

Department of Rheumatology, Tokyo Metropolitan Bokutoh Hospital

To investigate the effects of combination therapy with bisphosphonates (Bis) and statin on the BMD and bone metabolism of rheumatoid arthritis (RA) patients. Eighty-three RA patients receiving Bis for over 4 years were divided into 2 groups: Bis and Bis+statin (n=46 and 37, respectively). During a 12-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, lumbar spine, and femoral neck were compared by using QDR. No significant difference was observed between the BMD of the 2 groups. However, the serum RANKL levels were significantly decreased at 12 months after the start of statin administration. These results suggest that the combination therapy regulated osteoclast induction via a decrease in RANKL levels.

W22-4

Regulation of osteoclastogenesis by HO-1 and the repressor, Bach1

Maasa Hama, Yohei Kirino, Kaoru Takase, Ryusuke Yoshimi, Atsuhisa Ueda, Mitsuhiro Takeno, Yoshiaki Ishigatsubo

Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

We examined roles of HO-1 and its repressor, Bach1 in osteoclastogenesis by using *Bach1*^{-/-} mice, which constitutively express HO-1. Osteoclast (OC) differentiation from bone marrow macrophages (BMM) was induced by stimulation with M-CSF and RANKL. Transcription of HO-1 was downregulated during the differentiation and HO-1 expression was low even in *Bach1*^{-/-} OCs. TRAP staining and bone resorption assay revealed that the osteoclastogenesis was suppressed in *Bach1*^{-/-} mice, associated with reduced expression of RANK, TRAF6, c-Fos, NFATc1, and Blimp-1. Pretreatment with HO-1 shRNA into *Bach1*^{-/-} BMM canceled the suppression of RANK and increased number of OCs but not affected Blimp-1 activation. In conclusion, Bach1 is involved in osteoclastogenesis via HO-1-dependent and independent manners.

W22-5

Roles of PPAR agonists in osteoblast differentiation regulated by BMP and TNFα

Mariko Takano¹, Fumio Otsuka², Yoshinori Matsumoto¹, Kenichi Inagaki¹, Ken-ei Sada¹, Hirofumi Makino¹

¹Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, ²Okayama University Hospital, Okayama, Japan

Impairment of osteoblast functions is involved in the rheumatic bone damages. We investigated the cellular mechanism by which PPARs interact with osteoblastic differentiation regulated by BMP and TNFα using C2C12 cells. BMP induced the expression of bone differentiation markers, in which PPARα-agonist specifically enhanced BMP-4-induced bone differentiation. Of note, PPARα- /γ-agonists inhibited TNFα suppression of BMP-4-induced bone differentiation by downregulating TNFR expression and its signaling including MAPK and NFκB. Inhibition of JNK and NFκB reversed TNFα suppression of osteoblastic differentiation. PPARα-agonists also enhanced BMP-4-induced Smad1/5/8 activation. The activation of PPARα promotes osteoblastic differentiation by modulating interaction of BMP-R and TNF-R signaling.

W23-1

Economic Effects of Biologics for Rheumatoid Arthritis (1) early induction

Ichiro Yoshii

Yoshii Hospital

Economic effect of biologics for treatment of rheumatoid arthritis has been investigated. Medical cost and income loss was estimated based on the established data. Patient group who have been treated only with DMARD but in high disease activity level (G0), group with biologics who quit biologics after remission (G1), group who continues biologics after remission (G2), group with biologics but more than in middle activity level (G3), and group quits biologics after adverse events (G4) were simulated. Medical cost and income loss of these groups were estimated and compared for each group year by year. Results showed that economic effect of biologics is large if clinical remission is achieved.

W23-2

The cost and the effect of DMARDs, analysis with data from NinJa

Yasuo Suenaga¹, Shigeto Tohma²

¹Department of Rheumatology, Beppu Medical Center, NHO, Oita, Japan, ²Department of Rheumatology, Sagami National Hospital, NHO, Kanagawa, Japan

[Objectives] To know the change of the cost and the effect in DMARDs in 2004-2009. [Method] Data from RA patients registered in the large cohort database (NinJa) in 2004-2009 was analyzed. [Results] Each frequency of usage was DMARDs: 87.2%, methotrexate: 55.3%, biologics: 17.4%. The cost of DMARDs was about 360,000 yen/ year/ patient. They were increasing year by year. (The rate of the number of low activity patients to that of high activity patients) / cost decreased in 2004-2006, but that is almost constant in 2006-2009. We estimated the cost per patient in each medicine. That of methotrexate and infliximab is also increasing. But that of etanercept is decreasing. [Conclusion] The cost of DMARDs is increasing year by year. But the cost per patient in etanercept is decreasing.

W23-3

Analysis of biologics use and medical expenses in patients with RA

Mieko Hasegawa¹, Kiichiro Tsutani², Hisashi Yamanaka³

¹The Japan Rheumatism Friendship Association, Tokyo, Japan, ²Department of Drug Policy and Management, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan, ³Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Purpose: To assess biologics use and economic burden in RA patients.

Methods: We examined the medical cost burden on RA patients with or without biologics using questionnaire survey by the Japan Rheumatism Friendship Association in 2010.

Results: A total of 8,999 patients responded (response rate 59.8%, average 63.8 y.o, duration 20.0 y, female 92.7%). Of 3,125 biologics users (average direct costs 33,325/mo), 1,130 (36.2%) cut down on their household expenses such as clothing, recreation and cosmetic fee to maintain their treatment. Of 5,587 patients who did not use biologics (average direct costs 8,728/mo), 606 (10.8%) could not use biologics for financial reason.

Conclusion: This survey suggested that a heavy economic burden lies on treatment in RA patients regardless of biologics use.

W23-4

Indirect cost and disease burden for RA via JRFA questionnaire survey

Ataru Igarashi¹, Kentaro Kikuta¹, Eiichi Tanaka², Daisuke Hoshi², Hisashi Yamanaka³, Saeko Hasegawa³, Kiichiro Tsutani¹

¹Dept. of Drug Policy & Management, Graduate School of Pharmaceutical Sciences, The University of Tokyo, ²Institute of Rheumatology Tokyo Women's Medical University, ³Japan Rheumatism Friendship Association

Objective: To estimate annual indirect cost (productivity losses) and disease burdens of RA patients in Japan Rheumatism Friendship Association via survey with questionnaire.

Methods: We calculated direct / indirect costs of RA patients, and evaluated their relationships with QOL.

Results: Employment rate are decreased with worsening QOL, both

for full-time and part-time jobber. We estimated annual indirect cost with data from basic survey on wage structure. Annual indirect costs were JPY1,074,000. These costs increased progressively with worsening QOL, from JPY522,000 to 2,068,000.

Conclusions: QOL score has strong influences on both employment rate and working time. The results also suggest that the increase in non-medical cost may be suppressed by proactively controlling RA.

W23-5

The correlation of working status with quality of life in RA patients

Eiichi Tanaka¹, Daisuke Hoshi¹, Ataru Igarashi², Kentaro Kikuta², Kiichiro Tsutani², Hisashi Yamanaka¹, Mieko Hasegawa³

¹Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, ²Department of Drug Policy and Management, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan, ³The Japan Rheumatism Friendship Association, Tokyo, Japan

Purpose: To assess work disability in RA patients.

Methods: We examined the working status of RA patients and correlation of the status with QOL (EQ-5D) using questionnaire survey by the Japan Rheumatism Friendship Association in 2010.

Results: A total of 8,999 patients responded (response rate 59.8%). The percentages of full-time, part-time, and household workers in the high EQ5D group (average 0.83) were 17.8%, 11.1% and 60.0% and those in the low EQ5D group (average 0.37) were 5.2%, 2.6% and 52.6%, respectively, indicating the lower the EQ5D score, the worse the working status. Lower EQ5D had a greater impact on work disability rather than the status of biologics use.

Conclusion: This study supported that maintenance of QOL may contribute to prevent the increase in indirect medical costs.

W23-6

Analysis of work disability in RA patients using a large cohort database, IORRA

Eiichi Tanaka¹, Daisuke Hoshi¹, Ataru Igarashi², Eisuke Inoue¹, Kentaro Kikuta², Ayako Nakajima¹, Shigeki Momohara¹, Atsuo Taniguchi¹, Kiichiro Tsutani², Hisashi Yamanaka¹

¹Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, ²Department of Drug Policy and Management, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan

Purpose: To determine work disability in Japanese RA patients using IORRA.

Methods: We examined the working status of RA patients who enrolled in IORRA in October 2008, and assessed correlation of the status with disease activity and QOL.

Results: Of 5,201 patients, 469 (9.0%) changed their jobs or reduced working hours, and 400 (7.7%) gave up their jobs due to RA. Of 2,097 (40.3%) patients who involved in housework, 839 (40.0%) reduced their housework. These work disability increased with worsening disease activity or QOL.

Conclusion: This study indicated that RA patients have difficulty keeping their working status due to RA. These work disability is considered to be economic burden, and the increase in indirect medical costs may be suppressed by controlling RA disease activity.

W24-1

Can anti-CCP titer to be a predictor of the efficacy of the biological agents?

Ryo Takahashi, Kumiko Otsuka, Michihito Sato, Kuninobu Wakabayashi, Tsuyoshi Odai, Takeo Isozaki, Nobuyuki Yajima, Yusuke Miwa, Masao Negishi, Hirotsugu Ide, Tsuyoshi Kasama
Division of Rheumatology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

OBJECTIVE: We investigated the correlation between the efficiency of biological agents and the titer of anti-CCP in 58 RA patients. Disease activity was assessed by DAS28 (ESR) at week0 and 14. **RESULT:** The titer of anti-CCP was 73.7 ± 112.1 in good response group, 230.3 ± 261.5 in moderate response group, and 1335 ± 1791.5 in no response group. A significant difference was admitted between three groups. The titer of anti-CCP was 85.9 ± 879.1 in the group that had remission at 14 weeks, 396.8 ± 129.2 in those had no remission. A significant difference was admitted between two groups. The result suggests that anti-CCP titer might be one of significant predictors of the efficacy of the biological agents.

W24-2

Repair of bone erosion occur in well-controlled RA irrespective of DMARDs used.

Shigeru Ohno¹, Haruko Ideguchi¹, Kaoru Takase², Takeaki Uehara¹, Yoshiaki Ishigatsubo²

¹Yokohama City University Medical Center, Yokohama, Japan, ²Department of internal medicine and clinical immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

Objective: To examine the frequency and clinical characteristics associated with repair of RA bone erosion. **Methods:** RA patients fulfilling the ACR classification criteria treated for longer than 1 year were included. Radiographs of hands and feet were evaluated in a blinded manner. **Results:** 122 patients treated with non-biologic and 84 with biologic DMARDs were enrolled. Patients in biologic group showed some features: young age, short disease duration and high disease activity. Repair of bone erosions were observed in 10.7% and 8.7% in non-biologic and biologic group, respectively. Decrease of DAS28 and change in TSS was associated with repair of bone erosion. **Conclusion:** Repair of bone erosion occur in well-controlled RA patients irrespective of the DMARDs used.

W24-3

Follow up of three RA patients with anti-CCP antibody positive and CRP negative

Yukiyoshi Oishi, Yuji Hirano, Mamoru Fujita, Kenichi Yamauchi, Tomonori Kobayakawa, Toshiyuki Okura, Taro Inoue
Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan

In the case of anti-CCP antibody positive it's tend to diagnose RA. But when the swollen joint is nothing or one and CRP is negative, we hesitate to start RA treatment. We followed up three patients with anti-CCP antibody positive and CRP negative for about four years without RA treatment. Case 1; 46 y.o. female, onset in July ('04), visited in Sep, stage 1, class 1, CARF +8.7AU/ml, CRP 0.01 mg/dl, CCP +48.3U/ml, TJC 11, SJC 0. Case 2. 51 y.o. female, onset in July ('05), visited in Dec, stage 1, class 1, CARF +16.0 AU/ml, CRP 0.1 mg/dl, CCP +16.2U/ml, TJC 2, SJC 0. Case 3; 47 y.o. female, onset in Dec ('05), visited in Jan ('06), stage 1, class 1, CARF +86.8 AU/ml, CRP 0.01 mg/dl, CCP +100U/ml TJC 1, SJC

1. In these three cases anti-CCP antibody was positive and CRP was negative in 2010.

W24-4

Taqman array analysis of a predictive marker for patients with TCZ therapy

Keisuke Hagihara¹, Atsuyoshi Morishima¹, Yoshihiro Hishitani¹, Mari Kawai¹, Junsuke Arimitsu^{1,2}, Toru Hirano¹, Yoshihito Shima¹, Masashi Narazaki¹, Atsushi Ogata¹, Toshio Tanaka¹

¹Department of Respiratory Medicine, Allergy and Rheumatic Diseases, Osaka University Graduate School of Medicine, ²Department of Kampo medicine, Osaka University Graduate School of Medicine

Predictive markers for biologic agents is still unknown. To investigate predictive markers for tocilizumab (TCZ) therapy, we examined Taqman array analysis using cDNA derived from PBMC of 17 patients (RA15, PMR1, RS3PE1, M/F:3/14, PRD8.1 \pm 4.1mg, before biologics: IFX6, ETN6). After 6 months, TCZ improved DAS-28CRP (4.8 ± 1.1 - 2.6 ± 1.0) and MMP-3 (354.4 ± 259.3 - 185.2 ± 107.4 ng/ml). As compared with 21 healthy volunteers, IL-2R α , IL-7, IL-8, IFN- γ , T-bet, Foxp-3, CTLA-4, STAT-6 significantly differed. Relative expression of TNF- α was changed (1.5 ± 1.9 - 7.3 ± 9.2) after TCZ therapy ($p=0.025$, paired t-test). Regression analysis showed that the serum MMP-3 level (6M after) were correlated with Foxp-3 (before) (correlation coefficients -0.56, $p=0.018$) and CTLA-4 (6M after) (correlation coefficients -0.57, $p=0.016$).

W24-5

Effect of improvement of disease activity on lipid profiles in RA patients.

Yumi Koseki, Atsuo Taniguchi, Eisuke Inoue, Haruko Inoue, Mikiko Shinozaki, Wako Urano, Naomi Ichikawa, Shigeki Momohara, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Some studies including our investigation have shown that high disease activity is associated with adverse lipid profile in RA. Few studies are available regarding the effect of disease activity control on lipid profile. The aim was to evaluate the effect of change in RA disease activity on lipid profiles by longitudinal study. 4372 RA patients who participated in both 2008 and 2009 IORRA studies were included. Serum lipid profiles (TC, HDL-C, LDL-C) and disease activity were measured. During one year, CRP and DAS28 were significantly reduced and HDL-C was significantly elevated. No change in LDL-C was detected. LDL-C/HDL-C (L/H) and the proportion of patients with L/H>2 were significantly decreased. Effective control of disease activity was suggested to reverse the adverse lipid profiles.

W25-1

MRI bone edema is the strongest predictor for radiographic progression in UA

Junko Kita¹, Mami Tamai², Shin-ya Kawashiri¹, Naoki Iwamoto¹, Akitomo Okada¹, Tomohiro Koga¹, Yoshikazu Nakashima¹, Takahisa Suzuki¹, Satoshi Yamasaki¹, Hideki Nakamura¹, Kazuhiko Arima³, Tomoki Origuchi⁴, Kiyoshi Aoyagi⁵, Masataka Uetani⁶, Katsumi Eguchi⁷, Atsushi Kawakami¹

¹First Department of Internal Medicine, Nagasaki University, Nagasaki, JAPAN, ²Center for Health and Community Medicine, Nagasaki University, Nagasaki, JAPAN, ³Department of Medical Gene Technology, Atomic Bomb Disease Institute, Nagasaki University,

Nagasaki, JAPAN, ⁴Department of Rehabilitation Sciences, Nagasaki University, Nagasaki, JAPAN, ⁵Department of Public Health, Nagasaki University, Nagasaki, JAPAN, ⁶Department of Radiology and Radiation Research, Nagasaki University, Nagasaki, JAPAN, ⁷Sasebo City General Hospital, Sasebo, JAPAN

We have tried to find what variables at entry are able to predict the further plain radiographic progression in patients with UA by using early UA cohort at Nagasaki University. Among the patients, we have focused on the 58 out of 129 patients who developed RA at 1 year and all of the follow-up data including serial plain radiography of both hands were completed. After the follow-up of 2 years, eighteen patients were classified as having plain radiographic progression whereas 40 were not. Logistic regression analysis have revealed that MRI-proven bone edema of wrist and finger joints at entry is the first ($p=0.023$, Odds ratio 13.84) and RF is the second ($p=0.049$, Odds ratio 6.65) predictors toward plain radiographic progression.

W25-2

Evaluation of early arthritis by 2010 classification criteria and Nagasaki score

Mami Tamai¹, Shin-ya Kawashiri¹, Naoki Iwamoto¹, Kazuhiko Arima³, Junko Kita¹, Akitomo Okada¹, Tomohiro Koga¹, Yoshikazu Nakashima¹, Takahisa Suzuki¹, Satoshi Yamasaki¹, Hideki Nakamura¹, Tomoki Origuchi⁴, Kiyoshi Aoyagi⁵, Masataka Uetani⁶, Katsumi Eguchi⁷, Atsushi Kawakami¹

¹Center for Health and Community Medicine, Nagasaki University, Nagasaki, JAPAN, ²First Department of Internal Medicine, Nagasaki University, Nagasaki, JAPAN, ³Department of Medical Gene Technology, Atomic Bomb Disease Institute, Nagasaki University, Nagasaki, JAPAN, ⁴Department of Rehabilitation Sciences, Nagasaki University, Nagasaki, JAPAN, ⁵Department of Public Health, Nagasaki University, Nagasaki, JAPAN, ⁶Department of Radiology and Radiation Research, Nagasaki University, Nagasaki, JAPAN, ⁷Sasebo City General Hospital, Sasebo, JAPAN

We have tried to evaluate early UA patients by 2010 RA classification criteria and Nagasaki score. One hundred-ninety nine early UA patients were enrolled. Eight-five patients were newly diagnosed as RA by 2010 criteria and 100 patients by Nagasaki score. After 1 year 103 patients had received DMARDs. Median score of 2010 criteria diagnosed as RA was 7 whereas that who not diagnosed as RA was 4. The outcome as receiving DMARDs at 1 year, a diagnostic performance of 2010 criteria at entry was 60% sensitivity, 77% specificity, 75% PPV, 63% NPV and 68% accuracy, respectively. MRI-proven symmetrical synovitis, bone edema and bone erosion were significantly distributed in the former as compared with the latter. In addition, a good correlation of 2010 RA criteria with Nagasaki score.

W25-3

The relationship between BMI and disease activity in RA -Results from IORRA-

Mariko Kitahama, Ayako Nakajima, Eisuke Inoue, Eiichi Tanaka, Toru Yamada, Eri Sato, Kumi Shidara, Daisuke Hoshi, Shigeki Momohara, Atsuo Taniguchi, Hisashi Yamanaka
Institute of Rheumatology, Tokyo Women's Medical University

Object

To analyze relationship of BMI and disease activity of Japanese RA patients.

Methods

From IORRA cohort April 2010 (N:5575), we divided each male and female RA patients into quartiles. After adjusting age and durations of disease, DAS28, J-HAQ, EQ-5D of the second quartile were compared with other quartiles by linear model.

Results

BMI of each quartile was 14.0-20.8, ~22.9, ~24.9, ~39.3 in male and 12.3-19.1, ~20.8, ~22.8, ~41.2 in female. DAS28 in both genders and J-HAQ in female were better in the 2nd quartile than the 1st. Quality of life indicated by EQ-5D was better in the 2nd and the 3rd quartiles than the 1st and the 4th.

Conclusion

Japanese RA patients with the 2nd quartile BMI was better condition in disease activity and quality of life than those with the lowest BMI.

W25-4

Baseline ADAMTS5 and the prediction of response to TNF inhibitors in RA patients

Kensei Tsuzaka, Yuka Itami, Haruo Abe
Tokyo Dental College Ichikawa General Hospital

We have reported ADAMTS5 as a predicting marker for the efficacy of infliximab (IFX) in RA patients (J Rheumatol 2010). Also we have reported ADAMTS5 as a predicting marker for adalimumab (ADA) in last JCR Meeting. To investigate the possibility of ADAMTS5 as a marker for sorting TNF inhibitors, 100 or 80 RA patients were treated with ADA or IFX. Baseline peripheral blood ADAMTS5 mRNA was quantified using real-time PCR. Baseline low-ADAMTS5 mRNA level ($<1.12 \times 10^{-4}$) could predict good response to IFX (PPV 70.4% and NPV 68.5% for the remission at 14 weeks) while high-ADAMTS5 ($>4.90 \times 10^{-4}$) could predict respectable reaction to ADA (PPV 75.1% and NPV 66.7% for the remission at 12 weeks), suggesting ADAMTS5 could sort the prediction of response to these two TNF inhibitors.

W25-5

Evaluation of 2010 ACR/EULAR classification criteria for rheumatoid arthritis

Hiroshi Kanazawa, Hiromitsu Takemori
Department of Rheumatology, Aomori Prefectural Hospital, Aomori, Japan

Objective: To evaluate the validity of 2010 ACR/EULAR classification criteria for RA. Methods: 207 steroid naïve and DMARD naïve patients with less than one year of joint symptom were registered. We diagnosed and classified into 3 groups (RA, arthritis that was not able to be diagnosed as RA (IA) and no arthritis (NA)). Clinical data was analyzed by new criteria. Results: The criteria point (RA/IA/NA: 74/48/85) was $6.3 \pm 2.1/4.0 \pm 1.2/1.7 \pm 1.5$. In the IA group, 4 patients (SLE, DM, pseudogout, and RS3PE) scored 6 or more, and 13 patients were finally diagnosed as RA (criteria point: 3.9 ± 1.2 , ACPA+: 7). The diagnostic probability of RA was sensitivity 72.4% and specificity 95.0%. Conclusion: The new criteria are useful for diagnosis of early RA by detecting of synovitis and other CTDs.

W25-6

The minimally important difference for J-HAQ in RA patients: from IORRA cohort

Kumi Shidara, Eiichi Tanaka, Eisuke Inoue, Daisuke Hoshi, Naoki Sugimoto, Eri Sato, Yohei Seto, Toru Yamada, Ayako Nakajima, Shigeki Momohara, Atsuo Taniguchi, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's medical University, Tokyo, Japan

Objective: We studied to determine the minimally important difference (MID) in J-HAQ in RA using IORRA cohort. **Methods:** RA patients (N=2,356) who were enrolled in IORRA in both Oct. 2008 and Apr. 2009 and had J-HAQ \geq 0.5 in Oct. 2008 were analyzed. The MID was estimated by examining change in J-HAQ and a 5-point Likert scale for their overall status at Apr. 2009. **Results:** The mean MID in J-HAQ for improved was -0.12. When stratified by baseline DAS28 with remission, low, moderate and high disease activity, the mean MID were -0.03, -0.11, -0.14 and -0.15, respectively. When stratified by pain-VAS, results were same tendency as that by obtained disease activity. **Conclusions:** The MID in J-HAQ for improved was -0.12 in IORRA cohort. The MID varies in concordance to disease activity and pain-VAS.

W26-1

How can we keep our outpatients coming to our hospital without events

Mayumi Kawaguchi¹, Akihiko Mukai²

¹Mimihara general hospital, Osaka, Japan, ²Co-op Osaka Hospital, Osaka, Japan

Introduction; We lost two RA patients from cancer so rapidly. **Purpose;** To find the better way of following outpatients from evaluating the prognosis and events. **Methods;** We evaluated all my outpatients from Apr. 1st 2004 to June 30th 2004. **Result;** Total 511 patients, 475 of them needed keep following. Collagen disease/diabetes/others are 178/168/129 patients. Death 15/14/0. Keep following 118/122/98. Events 48/60/9. orthopedic events 20/13/2. Lethal events of collagen patients are cancer (5), arterial events (5), infection (1), varix rupture (1), drug overdose for suicide (1), and unknown (2). **Conclusions;** More patients die from cancer and arterial events than collagen disease itself. Diabetes patients have more event though lethal one is more in collagen patients. Most patients lose their QOL from Orthopedic events.

W26-2

Poor prognostic factors of elderly-onset RA in Registry of Elderly RA patients

Takahiko Sugihara, Waka Yokoyama, Naoshi Kanda, Tadashi Hosoya

Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan

[Purpose] To evaluate prognostic factors of elderly-onset RA (EORA). [Methods] Efficacy of tight control was evaluated by a prospective observational study. The target of treatment was low disease activity. [Results] MTX was non-effective in 70 %, 50% and 30% of EORA with the average DAS28 during initial 3 months >6.1, = 5.1-6.1, and <5.1, respectively. Kaplan-meier analysis showed that the discontinuation rates of three groups were significantly different. Multivariate analysis showed prognostic factors of bone destruction was the average DAS28 >6.1 and anti-CCP antibody. TNF inhibitors were effective for the refractory EORA. [Conclusion] TNF inhibitors should be considered three months after the initiation of DMARDs in EORA with the average DAS28 > 6.1 during initial 3 months.

W26-3

Features of RA patients who failed to respond biologics: Analysis of YCURD

Kayo Terauchi¹, Yoshiaki Ishigatsubo¹, Mitsuhiro Takeno¹, Atsushi Ihata¹, Shigeru Ohno², Shohei Nagaoka³, Toshihisa Igarashi⁴, Takako Kawai⁵, Akiko Sekiguchi⁶, Yuko Iijima⁷

¹Yokohama City University Graduate School of Medicine, Department of Internal Medicine and Clinical Immunology, ²Yokohama City University Medical Center, ³Yokohama Minami Kyosai Hospital, ⁴Yamato Municipal Hospital, ⁵Yokohama seamen's insurance hospital, ⁶Fujisawa City Hospital, ⁷Yokosuka City Hospital

We studied clinical factors which are responsible for poor response to biologics. Of 325 RA patients who had received one or more biologics, the first line biologics was discontinued or switched to another in 28 patients because of insufficient efficacy (poor responders) and in 18 patients due to adverse events. The poor responders did not show any significant differences in age, disease duration, dosages of PSL and MTX, DAS28(CRP), DAS28(ESR) at the initiation of the first biologics when compared with other patients who had been receiving a single biologics. Thus, it is hard to predict therapeutic efficacy of biologics before the initiation based on pretherapeutic clinical backgrounds, findings, and parameters.

W26-4

Incidence of stroke in patients with RA - Analysis in IORRA

Toru Yamada, Eiichi Tanaka, Eisuke Inoue, Daisuke Hoshi, Kumi Shidara, Naoki Sugimoto, Eri Sato, Yohei Seto, Ayako Nakajima, Atsuo Taniguchi, Shigeki Momohara, Hisashi Yamanaka
Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

OBJECTIVE: To examine the incidence of stroke in Japanese RA patients. **METHODS:** We investigated the incidence of first-ever stroke cases in IORRA cohort from October 2000 to March 2009, and compared to that in Japanese population. **RESULTS:** Among 8,549 patients, age-adjusted incidences of all stroke per 100,000 patient-year was 127.1 (95%CI: 69.0-214.3) in all patients, 104.3 in men and 148.8 in women. Analysis by proportional hazards models revealed that older age, longer duration of RA, hypertension and using of steroid were significant risk factors for incidence of stroke. **CONCLUSION:** Incidence of strokes in Japanese RA patients was confirmed.

W26-5

The causes of death in deceased patients with RA using NinJa 2009

Atsushi Kaneko^{1,4}, Toshihiro Matsui^{2,4}, Shigeto Tohma^{3,4}

¹Department of Orthopaedic surgery and Rheumatology, Nagoya Medical Center, NHO, Nagoya, Japan, ²Department of Rheumatology, Sagami National Hospital, National, ³Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami National Hospital, NHO, Kanagawa, Japan, ⁴iR-net

<**Objectives**> The purpose of the present study is to evaluate the age at death and the cause of death in patients with rheumatoid arthritis (RA) in 2009. <**Methods**> 68 deceased patients with RA were registered 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. <**Results**> The mean age at death was 73.5 years old. The major causes of death of deceased patients

was infection in 19 patients involving in pneumonia in 8 patients, four of them had received anti-TNF therapy. Next was malignancy in 11 patients, cardiovascular disease in 10 patients. < **Discussion** > The major causes of death were still infection involving in pneumonia.

W26-6

The factor for the better survival rate of biologics; Results from TBC registry

Toshihisa Kojima¹, Masatoshi Hayashi¹, Koji Funahashi¹, Daizo Kato¹, Hiroyuki Matsubara¹, Atsushi Kaneko², Takeshi Oguchi³, Hideki Takagi⁴, Yuichiro Yabe⁵, Yuji Hirano⁶, Hisato Ishikawa⁷, Hiroyuki Miyake⁸, Takayoshi Fujibayashi⁹, Takefumi Kato¹⁰, Naoki Ishiguro¹

¹Department of Orthopedic Surgery & Rheumatology, Nagoya Univ. School of Medicine, ²Department of Orthopedic Surgery, Nagoya Medical Center, ³Department of Orthopedic Surgery, Anjo Kosei Hospital, ⁴Department of Orthopedic Surgery, Nagoya Kyoritsu Hospital, ⁵Department of Orthopedic Surgery & Rheumatology, Tokyo Kosei-nenkinn Hospital, ⁶Department of Orthopedic Surgery & Rheumatology, Toyohashi City Hospital, ⁷Department of Orthopedic Surgery, Nagano Red cross Hospital, ⁸Department of Orthopedic Surgery, Ichinomiya City Hospital, ⁹Department of Orthopedic Surgery, Konan Kosei Hospital, ¹⁰Kato Orthopedic Clinic

Objective; To study 1) the changes of treatment with biologics during these seven years and 2) the factor for the better survival rate of treatment with biologics using the 1481 cases from TBC registry.

Methods; We determined the survival rate of the 1st biologics by Kalpan-Meier. Patients' characteristics treated with 1st Bio such as age, disease activity, and disease duration were recorded.

Results and Discussion; In later period, less advanced RA patients with shorter disease duration were treated with biologics. The rate of drug discontinuation with adverse events was less. The better drug survival was attained in the patients with lower disease activity (DAS-CRP < 5.34, VAS < 60mm). Treatment strategy should be changed to the target with these 7 years experiences in Japan.

W27-1

TRAF6 induction via Syk is pivotal in Bcell activation by BCR with CD40 and TLR9

Shigeru Iwata¹, Kunihiro Yamaoka¹, Hiroaki Niino², Kazuhisa Nakano¹, Koichi Akashi², Yoshiya Tanaka¹

¹The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, ²Department of Medicine and Biosystemic Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Syk functions as a key molecule in BCR signaling. Underlying mechanisms of Syk-mediated activation in human B-cell subsets remain elusive. We demonstrated stimulation by BCR, CD40 and TLR9 caused robust proliferation and differentiation in memory B cells, compared with naïve B cells. Syk inhibitor completely abrogated these functions. We sought how Syk regulates CD40 and TLR9 signaling. We found BCR cooperate with CD40 and TLR9 signals to induce expression of TLR9, TRAF6, and NF-κB phosphorylation. Syk inhibitor inhibited them. We postulate Syk-mediated BCR signaling is prerequisite for optimal induction of TLR9 and TRAF6, allowing efficient propagation of CD40 and TLR9 signaling. These results show the potential role of Syk in B-cell-mediated pathological processes in autoimmune disease.

W27-2

T-bet overexpression regulates the development of collagen induced arthritis

Yuya Kondo¹, Zhaojin Yao¹, Masahiro Tahara¹, Satoru Takahashi², Isao Matsumoto¹, Takayuki Sumida¹

¹Division of Clinical Immunology, Doctoral Program of Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan, ²Department of Anatomy and Embryology, Biomolecular and Integrated Medical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba

Objective: To clarify the role of T-bet in CIA.

Methods: 1) Incidence and severity of CIA were assessed in C57BL/6 and T-bet transgenic (T-bet Tg) mice. 2) CII reactive T-bet and RORγt expression and cytokine production were analyzed by ELISA and qPCR. 3) Cytokine production on CD4⁺ T cells cultured in the condition favoring Th-17 differentiation was analyzed by FACS.

Results: 1) CIA was significantly suppressed in T-bet Tg mice. 2) Higher expression of T-bet and lower expression RORγt were observed, and CII specific IL-17 production was significantly suppressed in T-bet Tg mice. 3) Th-17 differentiation was inhibited in both T-bet Tg and T-bet Tg/IFNγ^{-/-} mice.

Conclusion: Suppression of CIA might be due to IFNγ independent inhibition of antigen specific Th-17 differentiation in T-bet Tg mice.

W27-3

Glycolipid antigens RCAI-56 and RCAI-61 ameliorate collagen induced arthritis.

Masanobu Horikoshi, Daisuke Goto, Seiji Segawa, Isao Matsumoto, Takayuki Sumida
University of Tsukuba, Ibaraki, Japan

Objective : RCAI-56 and RCAI-61 are both analogs of alpha-galactosylceramide, which are able to activate invariant NKT cells. We investigated the effects of these glycolipids on collagen-induced arthritis (CIA). **Methods :** Glycolipids were kindly provided by RIKEN research center. 1) DBA/1J mice were administered RCAI-56 or 61 at the same time as induction of CIA. 2) In vitro CII specific cytokines responses were evaluated using splenocytes from mice immunized with CII and each glycolipids. **Results :** 1) RCAI-56 significantly reduced the severity of CIA compared to RCAI-61. 2) CII reactive IL-17 production was reduced in RCAI-56 treated mice but not in RCAI-61 injected mice. **Conclusion :** The different effects on CIA by RCAI-56 and RCAI-61 might be due to the distinct cytokine production.

W27-4

Histone deacetylase inhibitor (HDAi) ameliorates arthritis via dendritic cells

Kenta Misaki¹, Akio Morinobu¹, Jun Saegusa¹, Shimpei Kasagi¹, Shunichi Kumagai²

¹Department of Clinical Pathology and Immunology, Kobe University, Kobe, Japan, ²Center of Rheumatology, Shinko Hospital, Kobe, Japan

Purpose; To elucidate the effects of HDAi on dendritic cells (DC) and on arthritis (AR) in SKG mice. **Methods & Results;** AR was induced in SKG mice by Zymosan A (ZyA) injection. Trichostatin A (TSA), a HDAi, was administered and its effects on AR was evaluated by joint swelling. TSA, when administered both before

and after the onset of AR, prevented SKG mice from AR. TSA reduced IL-17 production by lymph node cells, but not Treg cells by splenic CD4 T cells, TSA treatment also decreased CD80, CD86 expression on splenic DC *in vivo*. *In vitro* TSA markedly suppressed ZYA-induced IL-12, IL-6 production, T cell stimulation and up-regulated indoleamine 2,3-dioxygenase expression by bone marrow derived DC. **Conclusion;** HDAi changes DC to a tolerogenic phenotype and ameliorates arthritis in SKG mice.

W28-1

Cytokine effect involving Ang-1 variant induction by α -U1RNP Ab in MCTD patients

Yuka Kosugi¹, Koichiro Komai¹, Kazuko Shiozawa², Akira Hashiramoto^{1,3,4}, Shunichi Shiozawa^{1,3,4}

¹Dep. of Biophysics, Graduate School of Health Sciences, Kobe Univ., Kobe, Japan, ²Rheumatic Diseases Center, Konan Kakogawa Hosp., Kakogawa, Japan, ³Dep. of Medicine, Graduate School of Medicine, Kobe Univ., Kobe, Japan, ⁴The Center for Rheumatic Diseases, Kobe Univ., Hosp., Kobe, Japan

OBJECTIVE: We found that *Ang-1* splicing variant with nt805GGT insertion (*Ang-1/ins*) was associated with the anti-U1RNP Ab titers in the Japanese patients with MCTD. We also identified that anti-U1C and U1-70K Abs especially induced *Ang-1/ins* mRNA in Human pulmonary artery smooth muscle cells (HPASMC) with IL-6 and TNF- α . Here we studied the effects of IL-6 and TNF- α on *Ang-1/ins* expression in HPASMC.

METHODS: HPASMC were stimulated with IL-6 and/or TNF- α for 24 h. The expression of *Ang-1*, U1A, U1C and U1-70K were evaluated by q-PCR and Western blotting.

RESULTS: U1C mRNA ($P < 0.05$) and protein was increased in the presence of both IL-6 and TNF- α .

CONCLUSION: It is suggested that U1C is upregulated with IL-6 and TNF- α and becomes major antigen of auto Ab that affects the splicing of *Ang-1*.

W28-2

MICA 129Val allele is a novel risk factor in the Japanese patients with MCTD

Hitomi Inoue¹, Koichiro Komai¹, Kohsuke Yoshida¹, Kazuko Shiozawa², Shunichi Shiozawa^{1,3,4}

¹Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan, ²Rheumatic Diseases Center, Konan-Kakogawa Hospital, Kakogawa, Japan, ³Department of Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, ⁴The Center for Rheumatic Disease, Kobe University Hospital, Kobe, Japan

OBJECTIVE: To identify the genetic factor of the Japanese patients with MCTD, we studied the MHC class I polypeptide-related sequence A (*MICA*) polymorphism and the association of *HLA-DRB1*.

METHODS: We genotyped for Val129Met polymorphism (rs1051792), microsatellite polymorphism in the transmembrane (TM) region of *MICA*, and *HLA-DRB1* polymorphism in the Japanese patients with MCTD (n=97) or controls (n=350).

RESULTS: *MICA* 129Val allele was significantly increased in the patients with MCTD as compared with controls (144/172 (83.7%) vs. 501/700 (71.6%); $P = 0.001$; OR=2.0), independently of the *HLA-DRB1* *0901, reported as the risk allele. Distinctive TM polymorphism was not found.

CONCLUSIONS: The *MICA* 129Val allele is a novel risk factor independent of *HLA-DRB1* in the Japanese patients with MCTD.

W28-3

An association study of *IRF7* polymorphisms with systemic lupus erythematosus

Aya Kawasaki¹, Hiroshi Furukawa², Yuya Kondo³, Satoshi Ito^{3,4}, Taichi Hayashi³, Makio Kusaoi⁵, Isao Matsumoto³, Shigeto Tohma², Yoshinari Takasaki⁵, Hiroshi Hashimoto⁶, Takayuki Sumida³, Naoyuki Tsuchiya¹

¹Molecular and Genetic Epidemiology, University of Tsukuba, Tsukuba, Japan, ²Department of Rheumatology, Sagami National Hospital, ³Division of Clinical Immunology, University of Tsukuba, ⁴Department of Rheumatology, Niigata Rheumatic Center, ⁵Department of Internal Medicine and Rheumatology, Juntendo University, ⁶School of Medicine, Juntendo University

Interferon regulatory factor 7 (IRF7) is essential for the induction of type I interferon. Association of rs4963128 located closely to *IRF7* with systemic lupus erythematosus (SLE) has been reported in Caucasians. Here we conducted a case-control study on 303 patients and 310 healthy controls to test whether *IRF7* was associated with SLE in Japanese. 17 SNPs including a nonsynonymous SNP Lys179Glu, 3 indels and 1 repeat polymorphism were detected by resequencing. Lys179Glu was in absolute linkage equilibrium with rs4963128. As compared with Caucasians, risk allele frequency of these SNPs was lower, and significant association was not detected ($P = 0.54$, odds ratio:1.31). None of the other polymorphisms was associated. Thus, evidence for association of *IRF7* was not obtained in this study.

W28-4

Antigen cross-presentation via proteasome/endosome causes lupus kidney disease

Ken Tsumiyama¹, Shunichi Shiozawa^{1,2,3}

¹Department of Biophysics, Kobe University Graduate School of Health Science, Kobe, Japan, ²Department of Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, ³The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

Objective: Antigen cross-presentation is required for the generation of cytotoxic T lymphocyte which induces lupus tissue injuries. Here we show that proteasomal degradation and endosomal trafficking are required for antigen cross-presentation and subsequent lupus-like kidney disease.

Methods: MG132 or primaquine (PQ) was repeatedly co-immunized with OVA to inhibit proteasomal degradation or endosomal trafficking. Proteinuria and IFN γ -producing CD8⁺ T cell in spleen were detected.

Results: Proteinuria were minute in mice treated with MG132 or PQ. Further, treatment of MG132 or PQ inhibited an increase of IFN γ -producing CD8⁺ T cell.

Conclusion: Proteasomal degradation and endosomal trafficking are essential for antigen cross-presentation, hence the generation of lupus tissue injuries.

W28-5

Studies on the association of IFN α and pathogenesis of SLE in NZB/W F1 mice

Yusuke Ueda¹, Eriko Honda¹, Shunichi Shiozawa^{1,2,3}

¹Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan, ²Department of Medicine, Kobe Uni-

versity Graduate School of Medicine, Kobe, Japan, ³The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

OBJECTIVE: We have shown that IFN α induces SLE such as the production of autoantibodies and renal diseases. To study the association of IFN α and pathogenesis of SLE, we investigated autoantibodies and renal lesions in autoimmune prone NZB/W F1 mice expressing IFN α .

METHODS: IFN α had been expressed in NZB/W F1 mice since 4-week-old by using tet-off system. Immune complex and anti-Sm, ssDNA, dsDNA antibodies in sera were measured by using ELISA. Further, renal lesions were assessed by proteinuria and histopathology.

RESULT: IC in sera, Anti-Sm, ssDNA and dsDNA antibodies, and glomerulonephritis were appeared in IFN α -expressing NZB/W F1 mice 12 weeks earlier than NZB/W F1 mice.

CONCLUSION: IFN α is important factor which hastens the onset of SLE.

W28-6

Elevated serum level of circulating syndecan-1 in active SLE

Kentaro Minowa, Hirofumi Amano, Souichiro Nakano, Seichiro Ando, Takashi Watanabe, Yutaka Nakiri, Eri Amano, Yoshiaki Tokano, Shinji Morimoto, Yoshinari Takasaki

Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo, Japan

Syndecan-1 (CD138) is expressed on plasma cells derived from B cells, and is suspected to play a role in SLE. We evaluated the expression of soluble CD138 (sCD138) in patients with active SLE and in those with clinically inactive disease. We also evaluated the expression of cell surface CD138 as well as serum BAFF and APRIL in these patients. The serum sCD138 levels in SLE patients was found to correlate with the proportion of CD20⁺CD38⁺CD138⁺ plasma cells and SLEDAI. There were decrease of sCD138 along with APRIL when SLE was clinically inactive. Our results suggest that sCD138 may be potentially useful as a surrogate marker of disease activity in SLE, and Syndecan-1/APRIL signaling may be considered as a potential target for active lupus patients.

W29-1

Induction therapy of lupus nephritis with combination of MZR and Tacrolimus

Takayuki Hara¹, Hidetoshi Kagawa¹, Tsutomu Hiromasa¹, Ken-ei Sada², Hirofumi Makino²

¹Department of Internal Medicine, Himeji Red Cross Hospital, Himeji, Japan, ²Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan

We tested a combination treatment of mizoribine (MZR) and tacrolimus for the induction therapy of 6 newly diagnosed SLE patients with LN. At baseline, the patients had a mean age of 41.5 years; all 6 patients had positive anti-double-strand DNA antibody titers (DNA), and 3 (50%) were nephrotic. The levels of daily proteinuria were 4.25 g. By month 2, significant improvements in DNA; levels of proteinuria, and C3 were observed. By month 6, five patients (83%) were in complete remission (CR). Patients treated with this regimen achieved CR with a lower cumulative prednisone dosage and a shorter hospital stay than those who received the conventional treatment. Our results suggests that MZR and tacrolimus

treatment may prove to be an optimal remission-inducing regimen in newly diagnosed LN.

W29-2

The efficacy and safety of tacrolimus for lupus nephritis, A prospective study

Toshiyuki Aramaki¹, Munetoshi Nakashima¹, Tomohiro Koga², Shin-ya Kawashiri², Satoshi Yamasaki², Hideki Nakamura², Seiyu Honda³, Hiroaki Ida³, Tomoki Origuchi³, Akaaki Fukuda⁴, Katsumi Eguchi⁶, Atsushi Kawakami²

¹Rheumatology, Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki, Japan, ²Department of Immunology and Rheumatology, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan, ³Division of Respiratory, Neurology, and Rheumatology, Department of Medicine, Kurume University School of Medicine, Kurume-city, Japan, ⁴Kurume University Medical Center, Center for Rheumatic Disease, Kurume-city, Japan, ⁵Nagasaki University Graduate School of Health Sciences, Nagasaki, Japan, ⁶Department of Internal Medicine, Sasebo City General Hospital, Sasebo-city, Japan

We administered 3mg/day of tacrolimus for the patients with persistent lupus nephritis, through receiving 10mg/day and more oral prednisolone. The patients were classified according to the ISN/RPS criteria by the renal biopsy within 1month before. The first treatment was oral prednisolone or one series of methylprednisolone pulse. Therapeutic effects were evaluated according to urinary protein, and the lupus nephritis disease activity index (LNDAI) calculated as previously described and others. The subjects were 9 patients with LN. Proteinurea was decreased from 2.33g/day to 0.43g/day at 6 months. The LNDAI changed from 7.63 to 2.63. The treatment of tacrolimus was effective in inducing and maintaining for lupus nephritis.

W29-3

Efficacy of oral tacrolimus on relapsed lupus nephritis

Shigenori Tamaki^{1,2}, Motokazu Kai², Kunikazu Ogawa³, Hisaji Ohshima⁴, Ikuko Tanaka^{1,5}

¹Nagoya Rheumatology Clinic, ²Department of Rheumatology, National Hospital Organization Mie Chuo Medical Center, Thu, Japan, ³Department of Orthopaedic Surgery, National Hospital Organization Mie Chuo Medical Center, Thu, Japan, ⁴Department of Collagen Disease, National Hospital Organization Tokyo Medical Center, Tokyo, Japan, ⁵Department of Laboratory Medicine, Fujita Health University School of Medicine, Toyoake, Japan

Of 78 SLE cases treated with low dose prednisolone (10mg/day), 8 cases relapsed proteinuria and nephritis. These 8 cases treated with tacrolimus, we investigated the efficacy of tacrolimus additional therapy with low dose steroid therapy. Tacrolimus (3mg/day) was administered 6 months. After the treatment, proteinuria disappeared in 6 cases and serum albumin level increased significantly from 3.1 to 3.7 mg/dL (p=0.007). Serum CH50 increased significantly from 32 to 47 U/mL (p=0.002) and ESR decreased significantly from 45 to 15 mm/hr (p=0.002). Serum Cr level didn't significantly change after the treatment. This study demonstrates that tacrolimus additional therapy can show a significant therapeutic response in cases relapsed lupus nephritis with low dose steroid therapy.

W29-4

Effect of combination therapy of mizoribine and tacrolimus to lupus nephritis

Goh Tsuji¹, Sho Sendo¹, Shunichi Kumagai¹, Hiroki Hayashi²

¹Department of Rheumatic Disease, Shinko Hospital, Hyogo, Japan,

²Department of Nephrology, Fujita Health University Hospital, Aichi, Japan

We report two cases of lupus nephritis treated with mizoribine (MZB) and tacrolimus (Tac). The therapeutic drug monitoring of these drugs were undergone. Case1: A 69 year-old-man was diagnosed as lupus nephritis. He was treated with 30 mg of prednisolone (PSL), 3mg/day of Tac and 600mg/every other day of MZB. His proteinuria was reduced and he achieved remission. Blood concentration of Tac was 6.0ng/ml and that of MZB (C3) was 4.23μg/ml. Case2: A 55 year-old woman, who was suffered from SLE 35 years ago and lupus nephritis 6 years ago. Neither 60mg of PSL, CY, AZA nor MZB had cured her nephritis. She was treated with 30mg/day of PSL, 3mg/day of Tac and 600mg/every other day of MZB. She could achieve remission. Blood concentration of Tac was 6.0ng/ml and MZB (C3) was 7.38μg/ml.

W29-5

The study of urine podocyte-associated markers in 15 SLE cases

Hiroshi Kajiyama, Takuma Wada, Akinori Yamamoto, Yuki Shimada, Yasufumi Shindo, Yoshihiro Yoshida, Kazuhiro Yokota, Yasuto Araki, Haruhiko Akiba, Kyoichi Nakajima, Kojiro Sato, Yu Asanuma, Yuji Akiyama, Toshihide Mimura

Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University

Background) The mechanisms of podocyte injury in lupus nephritis (LN) is not clearly understood.

Methods) Podocyte number in urine sediments (U-pod) was quantified by IIF and whole urine level of podocalyxin was quantified by ELISA and corrected with urine creatinine (U-PCX/U-Cr) in 15 SLE cases. Kidney disease was defined to be presented in 9 cases (KD(+)), and not in 6 cases (KD(-)).

Results) U-pod tended to be higher in KD(+) cases. U-PCX/U-Cr was not significantly different between KD(-) and KD(+). In 2KD(-) cases, U-pod or U-PCX/U-Cr increased when proteinuria worsened, and U-PCX/U-Cr sustained to be abnormally high although U-pod decreased after the treatment in 3KD(+) cases.

Conclusion) U-PCX/U-Cr is potentially more sensitive podocyte injury marker than U-pod in LN.

W29-6

Long-Term Renal Survival in Patients with Lupus Nephritis

Michihito Kohno¹, Tatsuya Atsumi¹, Yuichiro Fujieda¹, Masaru Kato¹, Yuka Shimizu¹, Yusaku Kanetsuka¹, Takashi Kurita¹, Toshio Odani¹, Kotaro Otomo¹, Shinji Fukaya¹, Shinsuke Yasuda¹, Tetsuya Horita¹, Makoto Kondo², Masaya Mukai², Takao Koike¹

¹Department of Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Japan, ²Department of Rheumatology, Sapporo city general hospital, Sapporo, Japan

Objective: To clarify the outcome of renal disease in patients with lupus nephritis (LN).

Methods: The retrospective analysis consisted of 182 patients diagnosed with LN by renal specimen between 1984 and 2009, and followed for 11.3±6.9 years. The end point was defined as death or end-stage renal failure. Six patients presented with WHO class I

LN, 75 with II, 8 with III, 64 with IV, and 29 with V.

Result: Fourteen patients died, and 8 patients are undergoing maintenance dialysis. Kaplan-Meier analysis revealed the 10-year renal survival of 94.0%. Male sex and proteinuria $\geq 3.5\text{g/gCr}$ at renal biopsy were identified as independent risk factors for renal outcome in proportional hazards analysis.

Conclusion: Male sex and proteinuria $\geq 3.5\text{g/gCr}$ could be critical factors in predicting renal outcome.

W30-1

The efficacy of high-dose infliximab therapy in patients with RA

Toshihiko Hidaka¹, Kazuyoshi Kubo¹, Shota Sakaguchi¹, Hiroshi Kuroda¹, Kunihiro Umekita², Akihiko Okayama²

¹Institution of Rheumatology, Zenjinkai Shimin-no-Mori Hospital,

²Internal Medicine, Department of Rheumatology, Infectious diseases and Laboratory medicine, University of Miyazaki

We assessed the efficacy of high-dose infliximab (HD-IFX) in patients with rheumatoid arthritis (RA). Thirty-three of RA patients who dose not achieve low disease activity were administered HD-IFX (6mg/kg or 10mg/kg). Over the 12 months treatment period, we evaluated responses to HD-IFX therapy based on disease activity score (DAS) 28. The mean levels of DAS28 decreased from 4.50 to 3.56 (12-month, $p < 0.001$) compared with pre-increasing IFX dose. Based on the EULAR response criteria, 88% and 34% of patients exhibited better than a moderate and good response to therapy, respectively. No severe adverse reactions were reported. These data indicate that HD-IFX therapy is safe and clinically effective for RA.

W30-2

Therapeutic effect by shortening intervals and/or increased quantity of IFX

Fumiharu Yamashita¹, Takanori Nagaoka¹, Noboru Funakoshi¹, Daisuke Mori¹, Mioko Ohzeki¹, Megumi Itoi², Taku Yamashita³

¹Kyoto Shimogamo Hospital, ²Meiji University of Integrated Medicine, ³Yamashita Clinic

IFX increase in quantity and/or dosing-interval shortening were performed in 21 patients with RA who had insufficient effect. There were 16 cases increased in quantity, three cases with dosing-interval shortening and increased in quantity and two cases of dosing-interval shortening. The curative effect was judged by DAS28/ESR for 21 patients (2 males, 19 females, 51-years-old of average age). (Result) The quantity of IFX was increased from the average of 3.81/kg to 6.17 (4.0-8.6)/kg in 16 cases. Seven cases were improved into the remission and four cases were switched to the other biologics. In three cases increased in quantity and shortening of interval, DAS28 was improved from 6.12 to 3.96. One of short intervals was changed into the remission and the other was switched to the other.

W30-3

High doses of Infliximab with the RA patients in our department.

Yumi Iwasaku, Jo Nishino, Miyuki Nozaki, Daisuke Hirano, Tomonobu Iwadata, Nobuko Tosaka, Satoru Onoda, Kenichi Kato, Shusaku Fukaya, Shunji Yoshida

Division of Rheumatology Department and Infectious Diseases of Internal Medicine Fujita Health University School of Medicine, Aichi, Japan

Purpose: To investigate the backgrounds and the effects on patients with Infliximab (IFX) in high doses. Method: From July 2009

to October 2010, we classified 44 RA patients with IFX into 2 groups; the low doses group (L) and the high doses group (H), and analyzed the backgrounds and efficacy of each group. Results: Among 44 patients, 18 belonged to H group. Before administration, CRP level of the H group (5.3 ± 3.7) has been significantly higher than that of the L group (1.6 ± 1.6) ($P < 0.05$). Among 30 patients who were followed up more than one year, 27 could be continued IFX therapy: 14 out of 16 in L group (88%), and 13 out of 14 in H group (93%). Conclusion: The higher doses of IFX have been given to the active cases, and, in addition, the continuation rates were similar in both group.

W30-4

Efficacy of dose escalation of IFX and switch to second biologics in IFX failure

Ran Matsudaira, Naoto Tamura, Fumio Sekiya, Takashi Watanabe, Yoshinari Takasaki

Department of Internal Medicine and Rheumatology, Juntendo University, School of Medicine

<Objective> To study efficacy of IFX escalation and switch to second biologics (2nd bio) in IFX failure. **<Methods>** Among 152, efficacy in failure was assessed by DAS28/CRP. **<Results>** Among 79 failure (first failure: 26, second failure: 53) treated with IFX, 61 were increased IFX, 29 were improved over moderate, and 13 had a remission. Improvement was significantly higher in second failure than in first failure (59.6% and 26.3%, respectively, $p = 0.006$). Twenty-four were switched 2nd bio after IFX escalation, and 16 were switched 2nd bio without escalation (ETN: 21, TCZ: 6, ADA: 4). Improvement rates were 80%, 100%, 75%, respectively. There was no distinction between the two. **<Conclusions>** Efficacy of IFX escalation was higher in second failure and 2nd bio was effective in first failure.

W30-5

The efficacy of the dose-escalation infliximab therapy for rheumatoid arthritis

Kotaro Otomo, Masaru Kato, Takashi Kurita, Toshio Odani, Yuichiro Fujieda, Shinji Fukaya, Tetsuya Horita, Shinsuke Yasuda, Tatsuya Atsumi, Takao Koike

Hokkaido graduate school of medicine, department of medicine II, Sapporo, Japan

Background: We have evaluated the efficacy of the dose-escalation infliximab (IFX) protocol for RA since 2009. **Methods:** 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. **Results:** 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. **Conclusion:** The dose-escalation IFX therapy is well tolerated for RA.

W30-6

Prognostic predictors of retention rate of infliximab

Masahiro Hanabayashi¹, Toshihisa Kojima¹, Koji Funahashi¹, Daizo Kato¹, Masatoshi Hayashi¹, Hiroyuki Matsubara¹, Hideki Takagi², Fumiaki Sugiura³, Nobunori Takahashi⁴, Takeshi Oguchi³, Atsushi

Kaneko⁴, Yuji Hirano⁵, Hiroyuki Miyake⁶, Hisato Ishikawa⁷, Yuichiro Yabe⁸, Takayoshi Fujibayashi⁹, Naoki Ishiguro¹

¹Department of Orthopedic Surgery and Rheumatology, Nagoya University Graduate School of Medicine, Nagoya, Japan, ²Department of Orthopedic Surgery, Nagoya Kyoitsu Hospital, ³Department of Orthopedic Surgery, Anjo Kosei Hospital, ⁴Dept. of Orthop. Surg. and Rheumatology, Nagoya Medical Center, ⁵Department of Rheumatology, Toyohashi Municipal Hospital, ⁶Department of Orthopedic Surgery, Ichinomiya Municipal Hospital, ⁷Department of Orthopedic Surgery, Nagano Red Cross Hospital, ⁸Department of Rheumatology, Tokyo Koseinenkin Hospital, ⁹Department of Orthopedic Surgery, Konan Kosei Hospital

Objective: To assess the association between DAS28-CRP at baseline and retention rate of infliximab (IFX) in RA patients.

Methods: 498 RA cases treated with IFX as 1st bio were extracted from multi-center study group (Tsurumi Biologics Communication: TBC). Cases were classified by tertile of DAS28-CRP (4.49, 5.33) at baseline and retention rate in each group were determined by Kaplan-Meier method.

RESULT: Discontinuation by adverse event had no significant difference between each group. Discontinuation by insufficient efficacy occurred more in higher disease activity group (Log Rank $p < 0.05$). The estimated retention rate by cause of insufficient efficacy at 24 months was 85% in lower group and 70% in higher group.

Conclusion: Disease activity at baseline influence on retention rate of IFX.

W31-1

Effect of TNF inhibitors on altered peripheral T cell differentiation in RA

Kazuhiro Kurasawa, Tetsuya Ohara, Satoko Arai, Takayoshi Owada, Reika Maezawa, Takeshi Fukuda

Clinical immunology, Dokkyo Medical University, Tochigi, Japan

Aims: To clarify abnormalities of memory T cell differentiation in RA and to determine whether TNFi correct the abnormality.

Methods: Flowcytometry analysis was performed on PBL from 143 RA patients and 37 controls using antibodies against CD4/8, CD45RA/CCR7 and CD28/CD27. In patients with clinical remission, longitudinal analysis was done. **Results:** Aging made naïve T cell decreased and memory T cells increased. RA itself induced naïve T cell expansion, effector -memory T cells reduction and increase in CD8 terminal differentiated T cells. TNFi correct altered CD4 and CD8 T cell differentiation, but MTX did only CD4 T cells.

Conclusion: In RA, peripheral T cell differentiation is altered. TNFi have potency to correct abnormal T cell differentiation, but MTX might have the less.

W31-2

Increasing the dose and reducing the dosing intervals of infliximab (IFX) in RA

Satoshi Ito¹, Hiroe Sato¹, Yoichi Toyoshima¹, Hiroshi Otani¹, Asami Abe¹, Hajime Ishikawa¹, Kiyoshi Nakazono¹, Ichiei Narita², Akira Murasawa¹

¹Niigata Rheumatic Center, ²Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences

To analyze the effects of increasing the dose/reducing the dosing intervals of IFX in RA patients, we evaluated 41 RA patients (12 men and 29 women) with an average age of 56.6 years (23-76 years)

who had received IFX on average 199.5 mg 6.8 times prior to dose escalation. At 7th injection after dose escalation, improvements in DAS28 (ESR), RF, MMP-3, and CRP were 4.2 ± 1.8 @ 2.5 ± 0.6 , $p < 0.001$; 61.1 ± 58.1 @ 22.9 ± 15.4 , $p < 0.05$; 179.5 ± 66.0 @ 122.0 ± 79.3 , $p < 0.05$; 1.42 ± 1.71 @ 0.25 ± 0.25 , $p < 0.05$, respectively. IFX was discontinued in 12 patients: 1 CR, 2 transferred to other hospitals, 5 switched to tocilizumab, and 4 AEs including 1 Pneumocystis pneumonia, 1 methotrexate pneumonia, 1 infusion reaction, and 1 gastric cancer. Dose escalation of IFX is beneficial in RA patients.

W31-3

Adding tacrolimus in RA patients with an inadequate response to infliximab

Yukio Yonemoto, Koichi Okamura, Tsutomu Kobayashi, Tetsuya Kaneko, Tsuyoshi Ichinose, Kenji Takagishi
Department of Orthopaedic Surgery, Gunma University Graduate School of Medicine

We add tacrolimus in rheumatoid arthritis patients with an inadequate response to infliximab therapies. Eight RA patients (6 women and 2 men) with IFX secondary failure took TAC addition combination therapy. All of the cases used methotrexate (average 7.5mg/week). The TAC dose was 1-3mg/day (average 1.9mg/day). DAS28 (3-ESR), CRP and ESR were improved after treatment in 5 of 8 cases and they satisfied clinical remission. There are a few reports TAC, MTX and IFX combination therapy, and it was thought that it is the one of the choices for IFX secondary failure.

W31-4

Effect of prednisolone premedication from initial infliximab administration.

Daizo Kato¹, Toshihisa Kojima¹, Masatoshi Hayashi¹, Koji Funahashi¹, Hiroyuki Matsubara¹, Masahiro Hanabayashi¹, Takayoshi Fujibayashi², Toki Takemoto², Masatoshi Kamori³, Tomone Shioura⁴, Seiji Tsuboi⁴, Naoki Ishiguro¹
¹Department of Orthopedic Surgery, Nagoya University School of Medicine, Nagoya, Japan, ²Department of Orthopedic Surgery, Konan Kosei Hospital, ³Mukaiyama Clinic, ⁴Department of Orthopedic Surgery, Shizuoka Kosei Hospital

[Background] Infliximab (IFX) gives rapid and sustained clinical response in rheumatoid arthritis (RA) patients. Yet, loss of drug efficacy is a common problem. [Aim] To investigate the effect of prednisolone (PSL) premedication prior to IFX administration from initial loading. [Method] 498 RA patients received IFX as first biologics were registered in TBC. 46 patients received 50mg of PSL premedication from initial IFX administration and 96 patients received 20mg of PSL with same manner. [Result] Retention rate of 50mg premedication group was significantly higher than that of 20mg premedication group and overall, and oral daily PSL dose was significantly reduced. [Conclusion] To sustain the effect of IFX, 50mg of PSL premedication from initial IFX administration may become useful option.

W31-5

Biologics in obese patients with rheumatoid arthritis is good for infliximab

Kensuke Kume, Kanzo Amano, Susumu Yamada
Department of Rheumatology, Hiroshima Clinic, Hiroshima, Japan

The purpose and methods) of the present medical treatment for obesity, but RA is known to be difficult, there is the most effective

biological products which have not been studied. This is a Retrospective study. Results) BMI > 30 MTX response rate of 24 weeks after the introduction of the 38 patients who used non despite MTX (DAS28 < 2.6) ratio was evaluated. Infliximab (21.2%), etanercept (11.6%), adalimumab (17.2%), tocilizumab (23.2%), respectively. Consideration) adalimumab for the small number of cases and tocilizumab, could not have enough statistics, may present with obesity infliximab for RA is the first choice.

W31-6

Infliximab provides benefit to RA patients with reduction of steroid.

Masaaki Usui, Keiya Yamana, Yukio Shigeyama
Center of Rheumatology, Okayama City Hospital, Okayama, Japan

Sixty-four RA patients (seventeen male and forty-seven female) were treated with infliximab in Okayama City Hospital. A follow-up duration was from 12 to 75 months, mean 31 months. Prednisolone (PSL) was given in forty-three patients and the mean dosage of 5.58mg/day. The mean of DAS28-CRP was improved from 4.17 points to 2.15 points at the follow up. The dosage of PSL was reduced in 39 patients and 11 patients discontinued the administration of PSL.

W32-1

Periarticular osteoporosis in early RA wrist joints. Analysis of quantitative CT

Kenrin Shi¹, Hideki Tsuboi², Akihide Nampei², Makoto Hirao¹, Yoshifumi Harada³, Hideki Yoshikawa¹, Jun Hashimoto¹
¹Department of Orthopaedic Surgery, Osaka University Graduate School of Medicine, ²Department of Orthopaedic Surgery, Osaka Rosai Hospital, ³Bone & Joint Research Laboratories, Teijin Pharma Limited

We studied periarticular osteoporosis in early RA, analyzing quantitative CT of wrist joints. 25 joints of 13 RA patients within 5 years from onset (mean age, 48.8 yrs; mean duration, 21.2 mts) were enrolled. After 3D reconstruction of quantitative CT, bone mineral density (BMD) and bone volume/total volume (BV/TV) were calculated by 3D-Teijin Bone Structure Analysis System. The relationships with joint findings, swelling and tenderness; plain radiograph findings, bone atrophy, erosion, etc; age and duration were examined. Mean BMD and BV/TV were 565.7mg/ml and 43.4%, respectively. BV/TV was significantly less in joints with tenderness, and both BMD and BV/TV were significantly less in those with bone atrophy. BMD and BV/TV demonstrated negative correlation with age, but without duration.

W32-2

Vertebral Strength in patients with RA -cortical shell and trabecular bone-

Taro Mawatari¹, Yasuharu Nakashima¹, Hisakata Yamada¹, Ken Okazaki¹, Jun-ichi Fukushi¹, Takashi Itokawa¹, Masanobu Ohishi¹, Yasutaka Tashiro¹, TM Keaveny², Yukihide Iwamoto¹
¹Department of Orthopaedic Surgery, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, ²O.N. Diagnostics, Berkeley, California

Vertebral strength and trabecular load distribution in RA patients were evaluated by finite element (FE) analysis of QCT scans. 29 RA patients (ave. 61.8yo, 21pt receiving glucocorticoid) without

a history of osteoporosis medication were enrolled and randomly divided into either an alendronate group (ALN, n=14) or an untreated control (CTL, n=15). Non-linear FE analysis was performed at baseline and after 12 months to compute vertebral compressive strength and bending stiffness, and to assess load distribution in the trabecular compartment. Both of the vertebral compressive strength and the bending stiffness were decreased by 10% or more in the CTL, but were maintained in the ALN. Trabecular load distribution was 42% at baseline and significantly decreased after 12 months.

W32-3

Risk factors for osteoporosis in Rheumatoid Arthritis patients - TOMORROW study-

Tadashi Okano¹, Masahiro Tada¹, Yuko Sugioka¹, Shigeyuki Wakitani¹, Kenji Mamoto¹, Tatsuya Koike²

¹Department of Orthopedic Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan, ²Department of Rheumatology, Osaka City University Graduate School of Medicine, Osaka, Japan

Background: We have started prospective cohort study (TOMORROW study). This study include 235 volunteers, 112 RA patients treated with biologic DMARDs, and 96 RA patients treated with non biologics. **Methods:** We analyzed concerning factors for osteoporosis at baseline. **Results:** Both the upper and lower limbs, the thoracic and lumbar vertebra significantly indicated a low value in the BMD in the RA group compared with the volunteer group ($p < 0.05$). The lean muscle was lower, and the amount of fat was higher in the RA patients. The BMD and the lean muscle correlated positively, and existed in a negative correlation with the amount of fat. **Conclusions:** RA patients showed different body composition compared to volunteers. The possibility that it was related to the reduction in BMD was suggested.

W32-4

Rheumatoid arthritis and osteoporosis, First report: Factors for osteoporosis

Ichiro Nakamura^{1,2}, Yasuhiko Koizumi^{1,2}, Makoto Tanokura^{1,2}, Katsumi Ito^{1,2}

¹Department of Rheumatology, Yugawara Kosei-nenkin Hospital, ²Working Group of Rheumatoid Arthritis

In 442 RA patients, bone density was measured. Average T-score for femoral neck was 74.1%, significantly lower than 80%. To determine factors affecting T-score for the femoral neck, multiple logistic regression analysis was performed. Covariates included age, sex, duration of RA, CRP, anti-CCP antibody, serum osteocalcin, urinary NTX, HAQ, presence or absence of lumbar compression fracture, amount of steroids, amount of MTX, and administration of bisphosphonate. We assumed these 12 factors for explanatory variables and T-score under 70%, the standard value for osteoporosis, for the dependent variable. The result showed that duration of RA, amount of steroids and presence or absence of lumbar compression fracture were significantly associated with development of osteoporosis in RA patients.

W32-5

Fracture risk assessment and osteoporosis treatment disparities in RA patients

Takefumi Furuya, Seiji Saito, Eisuke Inoue, Atsuo Taniguchi, Shigeki Momohara, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

To determine the proportion of patients with RA in our IORRA cohort (age ≥ 40 years, $n = 3970$) who are high risk for fractures using the FRAX. Among the patients with a 10-year risk of a major osteoporosis fracture $>20\%$ ($n = 723$, 42%), 453 (63%) and 320 (44%) reported taking any osteoporosis medications and taking bisphosphonates, respectively. The increasing fracture risk groups were significantly ($p < 0.001$) associated with oral glucocorticoid use, daily prednisolone dose, DAS28, J-HAQ, ESR. Among the patients with BMD ($n = 276$), the FRAX with BMD was significantly higher than those without BMD in women ($p < 0.001$). FRAX identified a substantial proportion of elderly RA patients who had a high risk of fractures. A substantial gap exists between fracture risk and osteoporosis treatment.

W32-6

TNF-I and bisphosphonate combination therapy inhibits RA joint destruction

Arisa Shimizu¹, Hiroyuki Yamashita¹, Yuichi Nishioka², Waka Nakata³, Hideharu Sugimoto³, Kenji Ito¹, Akio Mimori¹

¹National Center for Global Health and Medicine, ²Nishioka Clinic RA, Yamanashi, Japan, ³Department of Radiology, Jichi Medical University, Tochigi, Japan

Osteoclast takes a major role in destruction of joints in patients with rheumatoid arthritis (RA). Bi phosphonates reduce osteoclast numbers and activity, and TNF inhibitors also inhibit its activity. We studied whether combination therapy of TNF inhibitor and bisphosphonate slows the radiographic progression better than TNF inhibitor monotherapy. 38 patients with active RA were enrolled and 24 were treated with monotherapy, 14 with combination therapy. Modified Total Sharp Scores before and during the treatments were calculated, and their progression per year were statistically assessed. Although the monotherapy group showed significant progression from the baseline ($+5.28 \pm 3.73$, $p=0.01$), the combination therapy group showed no significant radiographic progression ($+0.26 \pm 5.16$, $p=0.85$).

W33-1

Radiographic changes of weight-bearing joints during TNF-blocking therapies

Isao Matsushita, Hiraku Motomura, Eiko Seki, Tomoatsu Kimura
Department of Orthopaedic Surgery, Faculty of Medicine, University of Toyama

Objective: The purpose of this study is to assess radiographic changes of weight-bearing joints in patients with rheumatoid arthritis during 5 years of TNF-blocking therapies. **Methods:** We evaluated the radiographic progression of 240 weight-bearing joints using Kaplan-Meier method during 5 years. The end point was defined as progression of damage. **Results:** Analysis of hip and knee joints indicated that 5-year survival rate was 93.5% in baseline grade 0/I joints, whereas there was gradual progression of damage in hip and knee joints with grade II. **Conclusions:** Weight-bearing joints with pre-existing damage, especially hip and knee joints, were predisposed to progressive destruction even under TNF-blocking therapies.

W33-2

Evaluation of cartilage degeneration in RA patients using T1-rho mapping MRI

Ken Okazaki¹, Hidetoshi Tsushima¹, Yasuhiro Nakashima¹, Taro Mawatari¹, Jun-ichi Fukushi¹, Yasutaka Tashiro¹, Yukihide Iwamoto¹

¹Department of Orthopaedic Surgery, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, ²Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University

Degeneration of cartilage matrix due to inflammation occurred more significantly in RA than in OA. We evaluated this degenerative change by T1-rho mapping MRI. Cartilage specimens were obtained from 9 RA patients and 11 OA patients during knee arthroplasty (38 specimens from RA and 106 from OA), and graded by macroscopic findings of degeneration (G0:normal, G1:softening, G2:fibrillation, G3:rough surface). T1-rho value was calculated at the relevant area of specimens. The value was correlated with the grading and with safranin-O staining in both RA and OA. In RA, the value was greater than the OA of same grading (G0:RA;48.2, OA;40.5, G1:RA;50.1, OA;47.8, G2:RA;57.5, OA;48.0). In RA, matrix depletion occurred more rapidly than OA. This method can quantitatively evaluate this early change.

W33-3

Association between bone cystic change by PCR and bone marrow edema by MRI in RA

Yasufumi Shindo¹, Yuji Akiyama¹, Noritsune Kouzu², Takuma Wada¹, Muneo Ota¹, Mayuko Sakamoto¹, Yuki Shimada¹, Akinori Yamamoto¹, Yoshihiro Yoshida¹, Kazuhiro Yokota¹, Yasuto Araki¹, Hiroshi Kajiyama¹, Haruhiko Akiba¹, Kyoichi Nakajima¹, Kojiro Sato¹, Yu Asanuma¹, Hiromi Oda⁴, Junji Tanaka³, Toshihide Mimura¹

¹Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University, Saitama, Japan, ²Kouzu Orthopaedic Clinic, ³Saitama Medical University division of Radiology, ⁴Saitama Medical University division of Orthopedics

Purpose. To examine whether Phase Contrast Radiography (PCR) can detect bone marrow edema on MRI in patients with rheumatoid arthritis (RA). **Patients.** Fifteen males, 23 females. 36 RA, 1 adult Still's disease, 1 mixed connective tissue disease. **Methods.** We examined radiography of hands on PCR in various combinations of S and G values to maximize the radiolucency which might be equivalent of bone marrow edema seen in RA by MRI. **Results.** Hyperlucent area in PCR was demonstrated most distinctly when both S and G values were set to high level. About two third of the bone marrow edema in MRI might be detected as hyperlucent lesions in PCR in this condition. **Conclusion.** It was suggested that PCR might detect bone marrow edema or its equivalent on MRI in RA.

W33-4

Evaluation of rheumatoid arthritis by low field compact MRI

Makoto Sugihara, Masanobu Horikoshi, Takeshi Suzuki, Tomoya Hirota, Shinya Hagiwara, Naoto Umeda, Yuya Kondo, Hiroto Tsuboi, Hiroshi Ogishima, Taichi Hayashi, Isao Matsumoto, Takayuki Sumida

Division of Clinical Immunology, Doctoral Program in Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba

Objective: To evaluate the activity of rheumatoid arthritis (RA) by low field compact MRI (cMRI). **Methods:** We have developed 0.3T cMRI. 235 patients were included. Bone erosion, bone marrow edema and synovitis were scored by cMRI scoring system (Mod Rheumatol 2009;358). **Results:** (1) 90 patients were RA without biologics, 77 were RA with biologics (29 infliximab, 21 tocilizumab, 18 etanercept, 6 adalimumab and 3 abatacept), 49 were undifferentiated arthritis (UA) and 21 were other arthropathy. (2) cMRI score were 47.4 ± 43.8 for RA without biologics, 68.5 ± 45.3 for RA with biologics ($p=0.005$), 11.6 ± 16.9 for UA ($p<0.001$) and 23.7 ± 38.0 for other arthropathy ($p=0.002$). **Conclusion;** cMRI might be useful tool to prospect disease activity of RA and distinguish RA from the other diseases.

W33-5

Effects of TNF-blockers on shoulder joints in patients with rheumatoid arthritis

Kazuhiro Sugimori, Isao Matsushita, Hiraku Motomura, Eiko Seki, Tomoatsu Kimura

Department of Orthopaedic Surgery, University of Toyama

We examined the joint damage of shoulder in patients with rheumatoid arthritis (RA) during TNF-blocking therapies. Thirty six shoulders (19 patients) were evaluated at baseline and 2 years after TNF-blocking therapies. The structural damage in shoulder joints was assessed using Larsen grade (LG), medial displacement index (MI), and upward migration index (UI) of humeral head. When LG was progressed, MI and UI decreased. According to ROC analysis about LG progression, the AUC of MI and UI change value were 0.75, 0.70, respectively. When we decided cut-off values of MI and UI change, the group without MI and UI change had fewer joints with baseline LG III-IV and more cases with good response significantly. MI and UI were useful for detailed evaluation of the joint destruction.

W34-1

Analysis of 10 patients with undifferentiated arthritis by utilizing hand MRI

Hiroo Hashimoto¹, Kiichi Komoto¹, Michiko Komatsu¹, Kazuhiko Moriwaki¹, Masami Hashimoto², Takehide Mitogawa², Fumio Otsuka³

¹Department of internal medicine, Innoshima General Hospital, Onomichi, Japan, ²Department of internal medicine, Onomichi Municipal Hospital, Onomichi, Japan, ³Okayama University Hospital, Okayama, Japan

Objective: We studied the diagnosis of early RA by using hand magnetic resonance (MRI) in patients with undifferentiated arthritis (UA). **Subjects:** 10 UA patients (mean age 66 years, M/F, 4/6). **Methods:** Severity of arthritis, laboratory data, and hand Gd-MRI were examined. Data were analyzed according to 1) early RA classification of Nagasaki University (2006), 2) ACR/EULAR new criteria of RA classification (2010) and ACR criteria of RA classification (1987). **Results:** (70%), (60%) and (20%) of the patients were fulfilled for the criteria of 1), 2) and 3), respectively. Hand MRI findings included bone erosion (40%), bone marrow edema (40%) and synovitis (70%). **Conclusion:** Systemic findings including clinical, sero-

logical and radiological examination are crucial for the diagnosis of early RA.

W34-2

Prediction of ongoing joint destruction in RA clinical remission by US

Ryusuke Yoshimi, Kaoru Takase, Maasa Hama, Kouji Kobayashi, Kayo Terauchi, Toshiyuki Watanabe, Reikou Watanabe, Sei Samukawa, Hiroshi Kobayashi, Atsushi Ihata, Atsuhisa Ueda, Mitsuhiko Takeno, Yoshiaki Ishigatsubo

Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine

Objective: To assess whether ultrasonography (US) predicts joint destruction during clinical remission of rheumatoid arthritis (RA). **Methods:** Hand X-ray and power Doppler (PD) US were monitored in 20 RA patients who had been in clinical remission for two years. The association between radiological joint destruction and total PD score in US was analyzed. **Results:** Progressive radiological destruction in any joints was found in some patients having more than 2 of total PD score in US at the entry, but not those having one or zero, during the 2 year observation. **Conclusion:** The results suggest that PDUS detects latent synovitis which causes joint destruction even in the clinical remission of RA patients. Thus, imaging remission in US is essential to reach "true remission" of RA.

W34-3

Power Doppler Sonography of MCP and PIP joints in rheumatoid arthritis

Ikuko Onishi¹, Masayuki Inoo¹, Yoshihiro Akashi², Satoshi Tohdo¹, Kunio Seto³, Noriyuki Kurata²

¹Utazu hama Clinic, ²Utazu Clinic

Objective. To evaluate the difference of MCP and PIP joints between dorsal side ultrasonography (US) and palmar side. **Methods:** We underwent gray-scale (GS) and power doppler (PD) US at 10 fingers (20 joints) in 80 patients : 13 RA patients haven't treated yet (group 1), 50 RA patients were treated with DMARDs or Biologics (group 2). 12 patients weren't RA (group 3). **Results:** Total each palmar PD grade were correlated with total each dorsal PD in 63 RA patients (group 1 and 2) ($r=0.40$, $p<0.01$). In patients of group 2, 80% palmar PD positive joints were corresponded with dorsal site. Tenosynovitis were detected on palmar than dorsal site in group 1. In group 2, patients who had tenosynovitis had no relation with disease activity.

W34-4

The impact of sonographer, machine and transducer on the synovial Doppler flow

Kei Ikeda¹, Yohei Seto², Shigeru Ohno³, Fumihiko Sakamoto⁴, Mihoko Henmi⁴, Jun Fukae⁴, Akihiro Narita⁴, Daiki Nakagomi¹, Kazuhide Tanimura⁴, Takao Koike³

¹Department of Allergy and Clinical Immunology, Chiba University Hospital, Chiba, Japan, ²Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, ³Yokohama City University Medical Center, Center for Rheumatic Diseases, Kanagawa, Japan, ⁴Hokkaido Medical Center for Rheumatic Diseases, Hokkaido, Ja-

pan, ⁵Department of Medicine, Hokkaido University Graduate School of Medicine, Hokkaido, Japan

Synovial blood flow in small (2nd MCP) and large (knee) joint in two RA patients was evaluated with semi-quantitative (0-3) and quantitative (pixel number) scores. The inter-rater reproducibility was remarkably high (ICC: 0.908-0.969). The Doppler signals differed significantly between two machines with quantitative measures (small joint $p=0.024$, large joint $p=0.005$, paired-t). The sensitivity of overused transducer in detecting synovial blood flow was significantly and markedly decreased both with semi-quantitative score (small joint $p=0.011$, large joint $p=0.024$, Wilcoxon signed-rank) and quantitative score (small joint $p=0.005$, large joint $p=0.015$, paired-t) as compared with brand-new one. Instrument factors, especially condition of transducer affect assessment of synovial Doppler flow.

W34-5

Musculoskeletal Ultrasound (US) in systemic lupus erythematosus (SLE)

Takehisa Ogura, Yuichi Izumi, Ayako Hirata, Norihide Hayashi, Reiko Miura, Ryuta Endo, Hideki Ito, Rie Kujime, Takehiko Ogawa
Division of Rheumatology, Toho University Ohashi Medical Center, Tokyo, Japan

OBJECTIVES: Although US examination is a valuable imaging tool in RA, its significance in SLE is not yet confirmed. To investigate articular manifestations in SLE using US technique. **METHODS:** Nine SLE patients with episode of joint symptoms (9 women) were recruited, and bilateral wrist, MCP, PIP and IP joints and extensor and flexor tendons were assessed for grey scale and power Doppler activity. **RESULTS:** Synovitis was detected in the wrists with 6 cases, in MCP joints with 3 cases, in PIP joints with one case and in IP with one case, respectively. Tendonitis was also found in 3 cases. There was no significant relationship between other clinical or immunological features and US-detected articular findings. **CONCLUSION:** US-detected synovitis was modestly frequent in the wrists with SLE.

W34-6

Ultrasonographic differences between elderly-onset seronegative RA and PMR

Takeshi Suzuki, Keiko Ishihara

Division of Rheumatology, Mitsui Memorial Hospital, Tokyo, Japan

Ultrasonographic differences between seronegative (both RF and ACPA negative) elderly-onset RA (EORA) and polymyalgia rheumatica were examined by reviewing the records of eight patients for each disorder. Numbers of the cases presented each synovial lesion were as follows (EORA:PMR): long head of biceps tendon, 4:5; subdeltoid bursa, 1:2; glenohumeral joint, 4:1; knee, 5:4; popliteal cyst, 1:3; radiocarpal joint, 8:5; MCP joint, 5:1; PIP joint 2:0; finger flexors, 4:2; extensor carpi ulnaris, 4:1; MTP joint, 3:0; talocrural joint, 2:1; ankle tendons, 5:1. Power Doppler signals tended to be detected inside of the synovial spaces in EORA patients. In PMR shoulders, hot erosions at insertion of supraspinatus tendon were frequently detected, while acromioclavicular arthritis was not observed.

W35-1

Predictable value of musculoskeletal ultrasonography in rheumatoid arthritis.

Keisuke Nishimura¹, Takashi Nakazawa¹, Shunichi Fujita¹, Natsuko Miura¹, Akio Morinobu², Daisuke Sugiyama³, Shunichi Kumagai³, Toshihiko Yokota¹

¹Department of Endocrinology and Rheumatology, Kurashiki Central Hospital, Kurashiki, Japan, ²Department of Clinical Immunology and Pathology, Kobe University Graduate School of Medicine, Kobe, Japan, ³Section of Evidence-based Laboratory Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

Objective: We investigated an imaging remission by musculoskeletal ultrasonography (MSK-US) in rheumatoid arthritis patients. **Methods:** We analyzed the MSK-US reports in rheumatoid arthritis patients. The definition of 'US imaging remission' is no power Doppler signal in involved joints. About the extracted 'imaging remission' cases, we examined if they are clinical remission, or continued their CR.

Results: In 25 of the US imaging remission cases, 23 cases were CR. We could follow up in 23 cases, and medications were tapered or stopped in 13 cases, and were not changed in 10 cases. The former were lasted remission in 7 cases, and 6 cases were relapsed. The latter were relapsed in only one. **Conclusion:** US imaging remission is not always a true remission.

W35-2

Availability of ultrasound in daily clinical practice for rheumatoid arthritis

Yohei Seto, Atsuo Taniguchi, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Though utility of musculoskeletal ultrasound (US) has been emphasized in evaluation of synovial inflammation in patients with RA, it is not clear when, who and how to apply US assessment in clinical practice, especially at busy outpatient clinic in Japan. The impact of US in daily outpatient setting is to be determined. In a rheumatology specialist clinic (RA patients 66%), various joint areas were evaluated mainly to confirm clinical findings at 28% of total 273 visits of RA patients (average 1.7 joints scanned which took 3.4 minutes per each session), resulting in 6.5% extension of time for the clinic. The data supported that US assessment is applicable in daily clinical setting.

W35-3

Musculoskeletal ultrasound as an educational curricular for the residents

Reo Yoshikawa¹, Satoshi Kamei¹, Sumie Moriyama¹, Yoshinori Masui¹, Haruka Tsuchiya², Takashi Ozaki², Junwa Kunimatsu¹, Yuko Takahashi², Akio Mimori², Hiroshi Kaneko³

¹Department of Internal Medicine, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan, ²Division of Rheumatic Diseases, Department of Internal Medicine, National Center for Global Health and Medicine, Tokyo, Japan, ³Department of Rheumatology, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan

Because new diagnostic criteria of rheumatoid arthritis (RA) having been proposed, an early diagnosis and an evaluation of disease activity are needed. Safe and convenient musculoskeletal ultrasound (MSK-US) is beneficial tool. We performed total 36 cases of

MSK-US supported by medical technologists together with applicant residents for half a year. The wrist was examined frequently (32 cases), and the purpose of MSK-US were diagnosis (17 cases) and an evaluation of diseases activity (27 cases). We performed the Doppler-echo in all cases. Main purpose was diagnosis and evaluation of disease activity. MSK-US is important with an aspect of not only the medical examination but also the postgraduate education for residents.

W35-4

The impact of ultrasound on the classification of RA with ACR/EULAR criteria

Daiki Nakagomi¹, Kei Ikeda¹, Ayako Okubo¹, Taro Iwamoto¹, Yoshie Suzuki¹, Hironori Kawashima¹, Kentaro Takahashi¹, Shigeru Tanaka¹, Hidefumi Wakashin¹, Hiroaki Takatori¹, Kotaro Suzuki¹, Katsuhiko Takabayashi², Hiroshi Nakajima¹

¹Department of Allergy and Clinical Immunology, Graduate School of Medicine, Chiba University, Chiba, Japan, ²Department of project information, Graduate School of Medicine, Chiba University, Chiba, Japan

In addition to ACR/EULAR classification criteria, ultrasonography (US) was performed on DAS 44 joints in 106 cases with possible diagnosis of rheumatoid arthritis (RA). The mean age was 51.6 year-old, 21 patients were male, and median duration of symptom was 6 months. Rheumatoid factor and anti-CCP antibody were positive in 51 and 34 cases, respectively. The numbers of cases who clinically fulfilled the ACR/EULAR criteria (CL-RA) and who fulfilled the criteria after replacing the joint involvement with US synovitis (US-RA) were 30 for CL-RA/ US-RA, 12 for CL-RA/ non-US-RA, 7 for non-CL-RA/ US-RA, and 57 for non-CL-RA/ non-US-RA, respectively. The result shows that the combined use of US may alter the RA classification by ACR/EULAR criteria in up to 18% of the patients assessed.

W35-5

The utility of ultrasonography as early diagnosis of rheumatoid arthritis

Shin-ya Kawashiri¹, Takahisa Suzuki¹, Yoshikazu Nakashima¹, Akitomo Okada¹, Junko Kita¹, Tomohiro Koga¹, Mami Tamai¹, Satoshi Yamasaki¹, Hideki Nakamura¹, Tomoki Origuchi², Atsushi Kawakami¹

¹Unit of Translational Medicine, Department of Immunology and Rheumatology, Graduate School of Biomedical Sciences, Nagasaki University, ²Nagasaki University School of Health Sciences, Nagasaki University

Purpose: We evaluated the utility of musculoskeletal ultrasonography (MSUS) as early diagnosis of RA. **Methods:** Thirty patients, who had undifferentiated and untreated joint symptoms of hand, were enrolled in this study. They were examined on joint findings by rheumatologist, laboratory data (CRP, ESR, IgM-RF, anti-CCP, MMP-3), bone X-ray, MSUS, and MRI of hands. We detected important factors of early diagnosis of RA. **Results:** Fifteen patients were diagnosed as early RA. High titers of IgM-RF and anti-CCP, PD \geq grade2 and bone erosion on MSUS and bone change on MRI were detected as predict markers of early diagnosis of RA. **Conclusion:** The findings of MSUS are important markers which accurate of early diagnosis of RA.

W35-6

A second survey for clinical application of musculoskeletal ultrasound in Japan

Maasa Hama, Kaoru Takase, Kouji Kobayashi, Kayo Terauchi, Toshiyuki Watanabe, Reikou Watanabe, Ryusuke Yoshimi, Atsushi Ihata, Atsuhisa Ueda, Mitsuhiro Takeno, Yoshiaki Ishigatsubo
Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

Our previous survey in 2008 revealed that insufficient educational opportunity prevented from spreading musculoskeletal ultrasound (MSUS) in rheumatologists of Japan, though the usefulness was recognized. We conducted the second survey using questionnaires which were sent to 200 rheumatologists at 2010. MSUS has been already used for daily practice in 49% of 115 responders, while 38% intended to use it in near future. Majority (81%) of MSUS users started it within the last 3 years. They learned the technique by themselves (23%), in training courses (46%) and by experts (27%), indicating that training courses provide the best opportunity to learn the technique. It is further necessary to establish educational program including standardization of scanning techniques and evaluation methods.

W36-1

Predictive factors of treatment efficacy by adalimumab in RA patients.

Hisaaki Miyahara, Masakazu Kondo
Fukuoka RA Biologic Treatment Study Group

Objectives: To investigate predictors of clinical efficacy in RA patients treated with adalimumab (ADA). **Methods:** 215 RA patients treated with ADA were evaluated. 67% of patients had concomitant treatment with methotrexate (MTX), and 35% of patients had other biologics in prior. Efficacy was evaluated based on DAS28ESR. **Results:** Average DAS28 was 5.1 at baseline and improved to 3.4 at 48 weeks. Based on the EULAR criteria, 29% had good, 43% had moderate, and 28% had no response at 48 weeks. In the patients with good response, concomitant treatment with MTX and no other treatment with biologics in prior were identified as predictors of low disease activity in a logistic multivariate analysis. **Conclusion:** ADA was most effective in biologics-naïve patients with concomitant MTX treatment.

W36-2

Efficacy of adalimumab for early RA patients from the multicenter study (TBC)

Takayoshi Fujibayashi¹, Toshihisa Kojima², Atsushi Kaneko³, Yuji Hirano⁴, Yosuke Hattori², Kenya Terabe⁵, Naoki Ishiguro²

¹Department of Orthopaedic Surgery, Konan Kosei Hospital, Konan, Japan, ²Department of Orthopaedic Surgery, Nagoya University Graduate School of Medicine, ³Department of Orthopaedic Surgery, Nagoya Medical Center, ⁴Department of Rheumatology, Toyohashi Municipal Hospital, ⁵Department of Orthopaedic Surgery, Fukuroi Municipal Hospital

We evaluated the efficacy of ADA for early RA using the data of the Tsurumi Biologics Communications (TBC). One hundred seventy five RA cases which were administered ADA after marketing were evaluated. We divided them into 22 cases of RA duration shorter than 2 years (group A) and 153 cases of RA duration over 2 years (group B). We investigated the mean age, the mean dose of

MTX, the ADA naïve ratio, the survival ratio at 52 weeks, and DAS28-ESR at 0 and 52 weeks. Regarding the mean age, the mean dose of MTX, and the ADA naïve ratio, there were no significant difference between both groups. Regarding the survival ratio at 52 weeks, group A was tendency to decrease. However DAS28-ESR of group A was significantly lower. We concluded that ADA might be more effective for early RA patients.

W36-3

Serum adalimumab concentrations and AAA: clinical efficacy of ADA, 2nd report

Misuzu Yamashita¹, Masamitsu Natsumeda¹, Koji Takasugi¹, Ryutaro Yamanaka¹, Kayo Ezawa¹, Kazuhiko Ezawa¹, Yoshihisa Nasu², Keiichi Nishida³

¹Department of Internal Medicine, Kurashiki Kosai Hospital, Kurashiki, Japan, ²Department of Orthopaedic Surgery, Kurashiki Kosai Hospital, Kurashiki, Japan, ³Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Objective and Methods: We evaluated the efficacy of adalimumab (ADA) and tacrolimus (TAC) combination therapy in 22 RA patients using EULAR response, ACR improvement, Δ DAS28 and Δ CDAI in relation to serum concentration of the drugs and anti-adalimumab antibodies (AAAs). **Results:** There was weak correlation between serum TAC levels and Δ DAS28. In 3 patients with high titer of AAA (>100 AU/ml), serum TAC levels were significantly lower than in patients without AAA. One of them showed better response with lower titer of AAA after dose increase of TAC. Another non-responder with AAA during ADA monotherapy achieved clinical remission with undetectable AAA after the addition of TAC. **Conclusion:** Enough serum TAC levels bring clinical improvement and regulatory effects on the development of AAAs.

W36-4

Relation between the effect of adalimumab (ADA) to RA and anti-ADA antibody

Goh Tsuji¹, Seiji Kawano², Akio Morinobu², Jun Saegusa², Daisuke Sugiyama², Masato Yagita³, Saori Hatachi³, Shunzo Namiuchi⁵, Yumiko Nobuhara⁵, Takashi Nakazawa⁴, Keisuke Nishimura⁴, Tomoko Nakamura⁶, Sho Sendo¹, Shunichi Kumagai¹

¹Department of Rheumatic Disease, Shinko Hospital, Hyogo, Japan, ²Department of Clinical Pathology and Immunology, Kobe University School of Medicine, ³Department of Medicine Division of Clinical Immunology and Rheumatology, Kitano Hospital The Tazuke Kofukai Medical Research Institute, ⁴Department of Endocrinology and Rheumatology, Kurashiki Central Hospital, ⁵Department of Rheumatology, Saiseikai Nakatsu Hospital, Osaka, Japan, ⁶Department of Rheumatology, Center Hospital, Hyogo Rehabilitation Centre,

[Background] In Japanese pre-marketing clinical trial anti-Adalimumab (ADA) Antibody (AAA) production in RA patients administered ADA was high frequency compared with the reports of the foreign countries. **[Purpose]** To clarify the relation between the clinical effect of ADA, AAA production and the ADA blood level. **[Patients and Methods]** 42 RA patients administered ADA to RA 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]** Eight patients produced AAA after ADA administering. In four of the eight patients the blood levels of AAA were increased four weeks after ADA

treatment. The levels of blood ADA and the effect of ADA were decreased in all eight patients.

W36-5

Timing to determine continuance of Adalimumab (ADM) treatment in RA patients

Takafumi Hagiwara, Takako Miura, Takeshi Nakamura, Kosuke Okuda, Hiroshi Sunami, Tsukasa Matsubara
Matsubara MayFlower Hospital, Rheumatology, Kato, Japan

Purpose: To evaluate efficacy of ADM therapy in maintenance of clinical remission (CR) in ADM patients. **Method:** 44 ADM treated patients. Groups: (A) continued ADM therapy for more than 1yr.; (B) dropped out of ADM therapy within 1yr. Groups were compared using DAS28-CRP (DAS).

Result: 25/35 continued therapy for ≥ 6 mo., 16/27 continued for 1yr. DAS compared 6mo. after initial treatment: 3.08 in (B), 4.88 in (A). Next, (A) was divided into two groups: patients maintaining CR 1yr. after initial treatment and those who failed to maintain CR. DAS 2mo. after initial treatment was compared. All comparison were statistically significant.

Conclusion: Continuance of ADM should be determined, at most at 6mo., and for maintenance of CR, continuance based on DAS scores, 2mo. after initial treatment.

W36-6

Examine of adalimumab efficacy to rheumatoid arthritis patients.

Shigeyoshi Tsuji¹, Takao Iwai¹, Koji Nomura², Hiroyuki Nakaya³, Yasuo Kunugiza⁴, Koichiro Takahi⁵, Hideo Hashimoto⁶, Masakazu Fujii³, Tetsuya Tomita⁴, Takashi Ikawa⁷, Suguru Osawa⁸, Yasuaki Aoki², Hideki Yoshikawa²

¹Department of Orthopaedic Surgery, Hoshigaoka Koseinenkin hospital, ²Dept.of Orthopaedic surgery, Japanese Red Cross Society Himemji Hospital, ³Dept.of Orthopaedic surgery, Garacia Hospital, ⁴Orthopaedics, Osaka university Graduate school of medicine, ⁵Dept.of Orthopaedic surgery, Toneyama national hospital, ⁶Dept.of Orthopaedic surgery, Rinku Genaral medical center, ⁷Osaka Rehabilitation Hospital, ⁸Dept.of Orthopaedic surgery, Sumitomo Hospital

[Purpose] Examination of clinical use of adalimumab (ADA) on multicenters use started treatment from August, 2008 was examined. **[Object]** 100 cases of patients treated with ADA were average 60.2 years old and the duration were 11.7 years were examine for this study. The combination with MTX was 60 cases and the average dosage was 6.2mg. **[Result]** Only 17 cases were stop treatment by adverse event or no response, however 83 cases were now continued the administration. Through 56 cases were able to assess on the improvement level of EULAR criteria, and 19 cases were Good Response and 23 cases were Moderate Response and no response was 14 cases. The DAS28 mean value has been improved from 4.91 to 3.21. The improvement of DAS28 was higher on using with MTX.

W37-1

The effect and safety of adalimumab in elderly RA patients

Yosuke Hattori¹, Atsushi Kaneko², Yuji Hirano³, Takayoshi Fujibayashi⁴, Kenya Terabe⁵, Toshihisa Kojima¹, Naoki Ishiguro¹

¹Department of Orthopaedic Surgery, Nagoya University Graduate School of Medicine, ²Department of Orthopaedic Surgery and Rheumatology, Nagoya Medical Center, ³Department of Rheumatology, Toyohashi Municipal Hospital, ⁴Department of Orthopaedic Sur-

gery, Konan Kosei Hospital, ⁵Department of Orthopaedic Surgery, Fukuroi City Hospital

When we use biologics (Bio) for elderly rheumatoid arthritis (RA) patients, including the combination of immunosuppressive drugs, we cannot but become careful. We examined the effect and safety of adalimumab (ADA) in elderly patients with RA in multicenter study (Tsurumi Biologics Communication; TBC). The object is 31 RA patients older than 70 years old (70-83, mean 74). We performed clinical evaluation in 52 weeks after the administration. The continuation rate is 67.7%. The mean DAS28-CRP was initially 4.74. It decreased to 2.86 after 52 weeks. The continuation rate rose for the MTX combination or the Bio Naive case. The discontinuation reason was effect 6 and safety 1, others 3. The effect and safety of ADA are provided in elderly RA patients.

W37-2

Serum adalimumab concentrations and AAA: clinical efficacy of ADA, 3rd report

Masamitsu Natsumeda¹, Misuzu Yamashita¹, Koji Takasugi¹, Ryutaro Yamanaka¹, Kayo Ezawa¹, Kazuhiko Ezawa¹, Yoshihisa Nasu², Keiichi Nishida³

¹Department of Internal Medicine, Kurashiki Kousai Hospital, Kurashiki, Japan, ²Department of Orthopaedic Surgery, Kurashiki Kousai Hospital, Kurashiki, Japan, ³Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Objective: To examine the association with the efficacy of adalimumab and serum adalimumab concentrations in addition to the correlation between body weight and serum adalimumab concentrations. **Methods:** We measured trough serum adalimumab level and anti-adalimumab antibodies together with clinical response variables (Δ DAS, Δ CDAI, EULAR response) in 50 RA patients treated with adalimumab. **Results:** There was weak negative correlation between body weight and serum adalimumab concentrations of 48 patients treated with 40mg/2W adalimumab. Serum adalimumab levels were below 17 μ g/ml in all patients whose Δ DAS or Δ CDAI did not improve. Patients whose serum adalimumab levels were below 5 μ g/ml showed poor EULAR response. **Conclusion:** Clinical efficacy needs enough serum adalimumab concentrations.

W37-3

The predictive factors for a year continuation of adalimumab in RA patients

Yuji Hirano¹, Atsushi Kaneko², Takayoshi Fujibayashi⁴, Yosuke Hattori³, Kenya Terabe⁵, Yukiyo Oishi¹, Toshihisa Kojima³, Naoki Ishiguro³

¹Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan, ²Department of Orthopaedic Surgery and Rheumatology, Nagoya Medical Center, Nagoya, Japan, ³Department of Orthopaedic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan, ⁴Department of Orthopaedic Surgery, Konan Kosei Hospital, ⁵Department of Orthopaedic Surgery, Fukuroi Municipal Hospital

The aim is to find the predictive factors to continue adalimumab (ADA) for one year in patients with RA using data of multicenter study (TBC). The continuation rates of ADA in 175 cases were 70.9% at 6 month and 61.1% at one year. Mean DAS28 was decreased from 5.40 at baseline to 3.27 at one year in continuation group (C-group). The rate of BIO-naive in C-group (67.3%) was

significantly lower than that of failure group (F-group) (51.5%). Although disease activity at baseline was similar in both groups, disease activity at 4 week in C-group was significantly lower than that in F-group. The predictive factors for continuation of ADA for one year were CRP, ESR, DAS28(ESR) and DAS28(CRP) at 4 week by ROC analysis.

W37-4

The safety and efficacy of adalimumab (ADA) in rheumatoid arthritis (RA)

Ayumi Okuyama, Koji Nishimura, Tsuneo Kondo, Takahiko Kurasawa, Eiko Nishi, Hirofumi Takei, Hayato Nagasawa, Koichi Amano

Division of Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan

Objective: To evaluate the safety and efficacy of ADA in RA patients at our department for 24 weeks. **Method:** ADA was 70 RA patients (55 females and 15 males) with the mean age of 61.2 and the mean duration period of 131 months, the mean MTX 7.5mg/w, the mean prednisolone 5.8mg/day. Twenty-six (37%) had previous treatment with biologics. **Result:** Sixty-seven percent completed the entire 24-week treatment. The LOCF analysis revealed that DAS28-ESR decreased from 5.27 to 3.19. The EULAR Good response (GR) rate and remission rate were 34% and 20%, respectively. **Conclusion:** The patients without previous biologics therapy had higher GR and remission rate than the patients with previous biologics. The severe adverse event was seen in one patient. ADA seemed to be more effective in biologics-naïve patient.

W37-5

Study of adalimumab treatment for patients with rheumatoid arthritis.

Chihiro Tanaka^{1,2,5}, Akira Hashiramoto^{2,5}, Yoshitada Sakai^{2,3}, Maki Kagitani², Yoshiko Kawasaki^{2,5}, Teppei Hashimoto^{1,2}, Nao Shibamura^{2,4}, Koji Tateishi¹, Takashi Yamane¹, Hironobu Yokoyama¹, Shigeru Matsuda¹, Miki Murata¹, Yasuhiro Terashima¹, Kohzoh Kohyama¹, Natsuko Nakagawa¹, Ryosuke Yoshiwara¹, Yasushi Tanaka¹, Kazuko Shiozawa¹, Shunichi Shiozawa^{2,5}

¹Rheumatic Disease Center, Konan Kakogawa Hospital, Kakogawa, Japan, ²The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan, ³Faculty of Health Science, Himeji Dokkyo University, Himeji, Japan, ⁴Kobe Kaisei Hospital, Kobe, Japan, ⁵Department of Rheumatology, Kobe University Graduate school of Medicine, Kobe, Japan

(Objective) To evaluate the effect of adalimumab (ADA) on patients with rheumatoid arthritis (RA). **(Methods)** A total of 189 patients with active RA were enrolled at Kobe University Hospital and Konan-Kakogawa Hospital. Patients' profiles were age 57.4 ± 12.9 (female 153, male 36), class 2.1 ± 0.6 and X-ray stage 2.85 ± 1.03 . When analyzed, patients were categorized into the first biologic-introduced group (group D) and the second or third biologic-introduced group (group S). **(Results)** In combination with MTX, ADA obtained significantly higher rate of both treatment-retention and clinical-remission, and the significant improvement in patients first-treated with solo ETN of S group. An increased effect of ADA was suggested in the combination use with additional 2 DMARDs.

W37-6

Efficacy of adalimumab as the first biologics for rheumatoid arthritis patients

Masao Sato¹, Masao Takemura², Ryuki Shinohe³, Katsuji Shimizu¹

¹Department of Orthopaedic Surgery, Gifu University School of Medicine, Gifu, Japan, ²Department of Informative Laboratory Medicine, Gifu University School of Medicine, Gifu, Japan, ³Department of Orthopaedic Surgery, Nishimino Welfare Hospital

OBJECTIVES: The aim of this study is to evaluate the efficacy of adalimumab (ADA) as the first biologics for patients with rheumatoid arthritis (RA). **METHODS:** The study population comprised 41 RA patients (11 men, 30 women). The mean age of the patients was 61 years (range 31-83 years). The patients were administered ADA (40mg) every 2 weeks and evaluated by DAS 28. **RESULTS:** The disease activity score (DAS) 28 at the baseline and at the evaluated endpoint were 6.67 and 3.05, respectively. The DAS 28 decreased significantly from baseline to at evaluated endpoint ($p < 0.0001$). Usage of MTX with ADA improved DAS 28 better than those of patients without MTX. **CONCLUSION:** ADA has shown high efficacy in RA as the first biologics. Furthermore, concomitant use of MTX was more effective in ADA therapy.

W38-1

Discontinuation of adalimumab in RA patients after attaining clinical remission

Shintaro Hirata, Kazuyoshi Saito, Ippei Miyagawa, Satoshi Kubo, Koshiro Sonomoto, Shunsuke Fukuyo, Kentaro Hanami, Sonosuke Yukawa, Shigeru Iwata, Masao Nawata, Shizuyo Tsujimura, Mikiko Tokunaga, Kunihiro Yamaoka, Yoshiya Tanaka

The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health Japan, Kitakyushu, Japan

To elucidate the ability of ADA-free remission, we discontinued ADA for 30 RA patients, maintained DAS28 < 2.6 for ≥ 24 wks without NSAIDs and glucocorticoids, in 121 patients, initiated ADA ≥ 1 yr before. Median age 62.5yr, female 80%, duration 25.5mo, stage I+II in 70%, dosing period of ADA 52 wks. Discontinued group had shorter duration and earlier stage. Mean DAS28 were 5.1 at starting ADA, and 1.9 at termination. Data at 24 and 52 wks after terminating ADA were available in 11 and 5 cases. Nine (82%) at 24 wks and 5 (100%) at 52 wks stayed in DAS28 < 3.2 . HAQ ≤ 0.5 was achieved in 26 (87%) at termination, 10 (91%) at 24 wks after, and 5 (100%) at 52 wks. All of 5 cases kept structural remission for 52 wks. These results suggest that ADA could be discontinued with preferred maintenance effect.

W38-2

Clinical and radiographic outcomes in bio-naïve RA patients on Adalimumab

Ko Katayama

Katayama Ortopedic Rheumatology Clinic

[Purpose] Clinical and radiographic outcomes were assessed in bio-naïve RA pts treated with adalimumab (ADA) (81% +MTX). [Methods] Out of 31 pts administered with ADA, 21 pts with ≥ 6 M treatment were analyzed (mean age: 59.5 yr-old; mean disease duration: 86.3 Ms). Efficacy endpoints included DAS28, mHAQ and changes in the mTSS. [Results] DAS28 improved from 6.4 to 4.3 (LOCF). EULAR responses were good in 5, moderate in 14 and no response in 2 pts. mHAQ decreased from 1.3 to 0.9. Annual change

in mTSS was reduced from 18.2±16.1 to 0.0±3.8 (baseline mean mTSS: 84.1). Greater improvements in DAS28 and mHAQ were seen in early RA while the radiographic effect was regardless of the disease duration. [Conclusion] Those effects were confirmed primarily in bio-naïve RA pts treated with ADA + MTX.

W38-3

The therapeutic effect and FDG uptake changes by Ada+MTX therapy for early RA

Koichi Okamura¹, Yukio Yonemoto¹, Kimihiko Takeuchi^{1,2}, Tsutomu Kobayashi¹, Kenji Takagishi¹

¹Department of Orthopaedic Surgery, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan, ²Department of Orthopaedic Surgery, Isesaki Fukushima Hospital, Isesaki, Gunma, Japan

We administered Ada and MTX to 5 RA patients (1 men, 4 women; average age: 36.2) whose disease duration was less than two years (average: 1.0 years), and evaluated disease activities of these patients by FDG-PET/CT before treatment and after 6 months later. The average MTX and PSL were 8.0mg/week, PSL 1.4mg/day. The average of CRP, ESR, MMP-3, DAS28 and DAS28-CRP before treatment were 2.34, 59.8, 252.9, 4.61 and 3.68; 6 months after treatment; 0.17, 19.6, 55.6, 2.11 and 1.64. Functional images of the maximal standardized uptake value (SUVmax) were produced for bilateral shoulder, elbow, wrist, hip, knee and ankle joints. The average of the sum of SUVmax was 23.4 before treatment; 17.1 after treatment. At the time of a last follow-up, 4 cases have achieved clinical remission (one case; Bio free).

W38-4

Serum adalimumab concentrations and AAA: clinical efficacy of ADA, 4th report

Masamitsu Natsumeda¹, Misuzu Yamashita¹, Koji Takasugi¹, Ryutaro Yamanaka¹, Kayo Ezawa¹, Kazuhiko Ezawa¹, Yoshihisa Nasu², Keiichi Nishida³

¹Department of Internal Medicine, Kurashiki Kousai Hospital, Kurashiki, Japan, ²Department of Orthopaedic Surgery, Kurashiki Kousai Hospital, Kurashiki, Japan, ³Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Objective: To compare the efficacy of adalimumab between anti-TNF switchers and naïve patients in addition to the relationship of serum adalimumab concentrations and anti-adalimumab antibodies (AAAs). **Methods:** We measured trough serum adalimumab level and AAAs together with EULAR response in 46 RA patients treated with adalimumab (switchers: 23 patients, naïve: 23 patients). **Results:** Compared with switchers, serum adalimumab concentrations of naïve patients were significantly higher, and more naïve patients showed good or moderate EULAR response. AAAs were detected more in switchers, especially infliximab switchers, than in naïve patients. **Conclusion:** Switchers showed less clinical improvement than naïve patients because of lower serum adalimumab concentrations and more production of AAAs

W38-5

Examination of rheumatoid arthritis patients who discontinued adalimumab therapy

Yosuke Hattori¹, Atsushi Kaneko², Yuji Hirano³, Takayoshi Fujibayashi⁴, Kenya Terabe⁵, Toshihisa Kojima¹, Naoki Ishiguro¹

¹Department of Orthopaedic Surgery, Nagoya University Graduate School of Medicine, ²Department of Orthopaedic Surgery and Rheumatology, Nagoya Medical Center, ³Department of Rheumatology, Toyohashi Municipal Hospital, ⁴Department of Orthopaedic Surgery, Konan Kosei Hospital, ⁵Department of Orthopaedic Surgery, Fukuroi City Hospital

We examined the case that reached discontinuation with rheumatoid arthritis (RA) patients who administered adalimumab (ADA) in multicenter study (Tsurumi Biologics Communication; TBC). RA patients are 175 examples. The continuation rate of 52 weeks is 61%. The reason of discontinuation is adverse event (n=18), loss of efficacy (n=37), others (n=13). We examined the risk factor which reached discontinuation for a patient background. A dermatopathy broke out 44% in adverse event to reach discontinuation. The accumulation incidence of the adverse event and the skin adverse event fell in the MTX combination group from the ADA monotherapy group (p=0.04, p=0.051). It is suggested that the skin adverse event decreased by using MTX together.

W38-6

Adalimumab therapy in patients of rheumatoid arthritis with renal insufficiency

Keiichi Sumida, Yoshifumi Ubara, Tatsuya Suwabe, Noriko Hayami, Yoshinari Hattori, Rikako Hiramatsu, Eiko Hasegawa, Masayuki Yamanouchi, Junichi Hoshino, Naoki Sawa, Kenmei Takaichi

Department of Nephrology and Rheumatology, Toranomon Hospital, Tokyo, Japan

Although many studies have reported the efficacy of adalimumab (ADA) in patients of rheumatoid arthritis (RA), there are few reports on the safety of ADA for patients with renal insufficiency. We evaluated renal function of patients with RA treated with ADA in our hospital. 50 patients with RA (11 male, 66.1±10.9 years old) were enrolled. The mean serum Cr and CCr calculated by Cockcroft-Gault formula (CG-CCr) were 0.69±0.29mg/dl and 34.2±20.5ml/min respectively. In 43 patients, CG-CCr was below 60ml/min, and 1 patient was on hemodialysis. The dropout of ADA observed in 21 patients was not due to renal insufficiency. The exacerbation of renal function was not observed during the treatment. Our results suggest that ADA is a safe treatment for the patients of RA with renal insufficiency.

W39-1

Comparison of infliximab, etanercept, adalimumab and tocilizumab in 1086 patient

Masao Nawata, Kazuyoshi Saito, Shintaro Hirata, Ippei Miyagawa, Shunsuke Fukuyo, Kentaro Hanami, Shigeru Iwata, Shizuyo Tsujimura, Kunihiro Yamaoka, Yoshiya Tanaka

Department of Medicine, University of Occupation and Environmental Health, Japan

We treated RA patients with 1086 (IFX471, ETN265, TCZ149, ADA201) biologics since 2002. Drug survival rates were as follows; IFX81%, ETN91%, ADA79%, TCZ80%, and the rate was highest in ETN. Concomitant MTX rates were as follows; IFX100%, ETN59%, and ADA94% and TCZ48%, and biologics naïve rates were as follows; IFX99%, ETN73%, ADA78% and TCZ42%. We compared treatment responses, remission rates, survival rates, adverse reaction and the incidence of infectious complications since July 2008 when these biologics were approved in RA. There was no

difference at the survival rates, adverse reaction and the incidence of infectious complications. The rates of Non-responder were lowest for ETN. Remission rates (about 5%) were high in IFX/ADA.

W39-2

Differences in Continuation Rate Among Four Biological Agents

Syunichi Imai¹, Ken Hasegawa²

¹Rheumatoid Arthritis Center, Minami Medical Health Cooperation,

²Department of Orthopaedic Surgery, Chiaki Hospital

Object: To investigate differences in the continuation rate among four biological agents. **Subjects and methods:** Through September 2010, at this hospital, 56 patients received infliximab (IFX), 43 etanercept (ETN), 30 tocilizumab (TCZ), 20 adalimumab (ADA). These patients were clinically assessed using the DAS28 (ESR) index and the CDAI. **Results and discussion:** After excluding patients who discontinued biological drug treatment or switched to a different biological agent, the continuation rate was 83.3% for TCZ, 50.0% for ADA, 41.9% for ETN, and 39.3% for IFX. As a general rule, at this hospital, TCZ is in the event of insufficient or complete lack of efficacy with TNF 2 agents, which made the high continuation rate for TCZ all the more noteworthy.

W39-3

Analysis of Patients Dropping Out of Biological Preparation Therapy

Makoto Tanokura^{1,2}, Ichiro Nakamura^{1,2}, Yasuhiko Koizumi^{1,2}, Katsumi Ito^{1,2}

¹Dept. of Rheumatology, Yugawara Kosei-nenkin Hospital, ²Working group for rheumatoid arthritis

At our hospital, treatment with naïve biological preparations has been applied to 154 patients with RA. Treatment with biological preparations was discontinued temporarily or completely in 57 of these 154 patients. The present study was undertaken to analyze the cases dropping out of biological preparation therapy. The reason for dropout was attenuation of efficacy in 22 cases, adverse reactions in 22 cases, poor responses in 7 cases, infection in 3 cases and malignant tumor in 3 cases. Among these 57 cases, treatment with biological preparations was discontinued completely in 22 cases. Of these 22 cases, 10 died and the remaining 12 are now being followed with other drugs (immunosuppressor + steroid in 9 cases, steroid alone in 2 cases and no medication in 1 case).

W39-4

Retention rates of biologics in rheumatoid arthritis and relevant risk factors

Ryoko Sakai^{1,2}, Yukiko Komano^{1,2}, Michi Tanaka^{1,2}, Hayato Yamazaki^{1,2}, Kaori Watanabe^{1,2}, Toshihiro Nanki^{1,2}, Ryuji Koike^{1,2,3}, Nobuyuki Miyasaka², Masayoshi Harigai^{1,2}

¹Department of pharmacovigilance, Tokyo Medical and Dental University Graduate School of Medicine, Tokyo, Japan, ²Department of Rheumatology, Tokyo Medical and Dental University Graduate School of Medicine, Tokyo, Japan, ³Faculty of Medicine Clinical Research Center, Tokyo Medical and Dental University Hospital, Tokyo, Japan

Objective: To investigate retention rates of infliximab (IFX) and etanercept (ETN), and reasons and risk factors for discontinuation of the drug in patients with rheumatoid arthritis (RA). **Method:** We analyzed patients who started IFX (n=371) or ETN (n=441) as the first biologics after their registration to the REAL. We observed

these patients up to 3 years. **Results:** The retention rate for ETN (69% at year 3) were significantly higher than that for IFX (62%) (p<0.001). Lack of efficacy was the most prevalent reason for the discontinuation in the both groups. Cox proportional hazards analyses identified age (HR 1.5), comorbidities (HR 1.8), number of previous DMARD (HR 1.5) and concomitant MTX at the baseline (HR 2.0) as independent risk factors for the discontinuation due to adverse events.

W39-5

Analysis of efficacy in cases biologic agents (Bio) were switched

Tomomi Yamashita¹, Keiko Funahashi¹, Takako Miura², Takafumi Hagiwara², Takeshi Nakamura², Kosuke Okuda², Tsukasa Matsubara^{1,2}

¹Department of Clinical Research, Matsubara Mayflower Hospital, Hyogo, Japan, ²Department of Rheumatology, Matsubara Mayflower Hospital, Hyogo, Japan

(Purpose) The purpose of this study was to investigate efficacy of each Bio after switching. **(Method)** We analyzed patients switching to IFX, ETN, TCZ, or ADA. Efficacy was assessed by DAS28-ESR (DAS) or CDAI. **(Results)** After switching, efficacy was measured by DAS, EULAR criteria showed improvement as moderate or good. 67% cases switching to IFX were effective, 79% for ETN, 86% for TCZ, and 42% for ADA. Efficacy of switching between TCZ and anti-TNF agents was compared by DAS and CDAI. Effective cases were 36% switching to anti-TNF agents by DAS, 27% by CDAI, for the cases of TCZ, 86% by DAS, 33% by CDAI. **(Discussion)** Efficacy of ADA was slightly lower, but others showed rather high efficacy after switching. To measure the efficacy of switching between TCZ and anti-TNF agents, CDAI is useful.

W39-6

Comparative study of 1st-line biologics based on Δ DAS and DAS_AUC

Hajime Miyazato, Tetsuhisa Motomura, Gen Shiraishi
Shunan Memorial Hospital, Department of Rheumatology

One biologic was used to treat various RA patients. Now that 5 biologics are covered by insurance, their proper usage depending on status is needed considering differences in molecular structure, half life or mode of action. As the first step, we studied which agents are suitable for 1st-line-use with data from our about 300 biologics-treated patients and examined 4 biologics marketed for more than 2 years in selected biologic-naïve patients. For anti-TNF agents, antibodies (IFX, ADA) and receptor (ETN) were compared by indicators (e.g. % DAS change (Δ DAS), DAS_AUC). TNF Receptor significantly controlled Disease Activity (Δ DAS: p=0.001, DAS_AUC: p<0.001), suggesting differences in efficacy, continuation rate, safety and cost effectiveness between 1st-line biologics.

W40-1

evaluation of renal function in RA —Japanese eGFR using Cr vs Cystatin C—

Michitomo Sakuma^{1,2}, Kensuke Koyama¹, Hirotaka Haro¹

¹department of orthopaedic surgery, yamanashi university, ²department of orthopaedic surgery, yamanashi prefectural central hospital

We evaluate renal function using Cr and CyC in RA patient. **(method)** 55 RA patients were treated with MTX or ETN therapy. Cr and CyC every 3~6months over measure time calculated eGFR using the conversion formula. We considered variation due to CRP,

DAS28CRP and dose of PSL MTX at the assessment day. (result) specimen number 218, eGFR has decreased with age, There was no CKD stage IV or more cases. The average of eGFR calculated each Cr and CyC is 85.9 and 103.6, CyC is high. At over CRP>1, DAS28CRP>2.3 eGFR (Cr) increases, eGFR (CyC) decreases, eGFR (CyC) treated PSL has decreased. (summary) In RA patients, eGFR (CyC) was high compared to eGFR (Cr). During CRP highs or treated with PSL, eGFR could not exactly evaluate renal function.

W40-2

A prediction model for gout using genetic polymorphisms

Wako Urano, Atsuo Taniguchi, Eisuke Inoue, Chieko Sekita, Naomi Ichikawa, Yumi Koseki, Hisashi Yamanaka
Institute of Rheumatology, Tokyo Women's Medical University

Objective: To investigate a prediction model for gout using genetic polymorphisms associated with serum uric acid levels.

Patients and Methods: We selected 10 genes, *PDZK1*, *GCKR*, *ABCG2*, *LRRC16A*, *LRP2*, *SLC2A9*, *SLC16A9*, *SLC17A1*, *SLC22A11* and *SLC22A12*, and examined the association of 12 polymorphisms on these genes using 153 Japanese male patients with gout and 532 male controls.

Results: The number of risk alleles in gout was significantly higher than that of controls ($P < 0.0001$). We also constructed a prediction models by incorporating the genetic information together with age, body mass index, serum triglyceride levels, and eGFR. In this model, the C statistics was 0.78, suggesting this model may be useful for the prediction of gout in Japanese males.

W40-3

Detection of a soluble form of folate receptor-beta in synovial fluids.

Taku Nagai¹, Masashi Tanaka¹, Yasuhiro Tsuneyoshi¹, Takemasa Matsuda², Nobuhiko Sunahara², Takami Matsuyama¹

¹Graduate school of Medical and Dental Sciences, Kagoshima University, ²Kagoshima Red Cross Hospital

Since we showed that folate receptor-beta (FRb) is expressed on most of RA synovial infiltrating macrophages, but not on monocytes and resident macrophages, the values of soluble FRb released from synovial infiltrating macrophages may reflect the total activity of synovial infiltrating macrophages. In this study, we report the ELISA detecting the soluble FRb in synovial fluids. The recombinant soluble FRb was produced from insect cells as a positive control. The values of the soluble FRb in synovial fluids from RA patients ($n=10$) were significantly higher (39.9 ± 19.9 units) as compared with those from OA patients ($n=4$, 18.8 ± 4 units). This study suggests that the values of the soluble FR-beta may be a novel biomarker of the synovial infiltrating macrophages.

W40-4

Comparative analysis of seven anti-CCP antibody assays in the diagnosis of RA

Kenichiro Onuma¹, Nobuhide Hayashi¹, Noriko Fukuzumi¹, Seiji Kawano¹, Shunichi Kumagai^{2,3}

¹Department of Clinical Laboratory, Kobe University Hospital, Kobe, Japan, ²Department of Clinical Pathology and Immunology, Kobe University Graduate School of Medicine, Kobe, Japan, ³The Center for Rheumatic diseases, Shinko Hospital

【Objective】To compare the diagnostic and analytical performances of 7 different anti-cyclic citrullinated peptide (CCP) antibody

kits. **【Methods】**Anti-CCP antibody titers were measured using sera from 79 patients with RA and 123 patients with rheumatic diseases other than RA. Reproducibility, sensitivity, specificity, correlation and concordance rate were compared among 7 different kits. **【Results】**Coefficient of variations of within-run and between-run reproducibility at 3 different concentrations for each kit were 0.7~7.1% and 0.6~8.3%, respectively. The ranges of sensitivity, specificity and concordance rates were 78.5~79.7%, 95.9~97.5% and 97.5~100%, respectively. **【Conclusion】**Our study showed that each kit has high specificity and is equally useful for the diagnosis of RA.

W40-5

The correlation between blood hyaluronic acid and DAS28 in tocilizumab therapy

Toyomitsu Tsuchida¹, Ayako Kubota²

¹Institute of Rheumatic Disease, Tsuchida Clinic, ²Orthopedic Surgery, School of Medicine, Faculty of Medicine, Toho University

Objective: We investigated the correlation between blood hyaluronic acid (HA) and joint destruction in 22 RA patients receiving tocilizumab (TCZ) for whom we were able to perform HA, DAS28, and MMP-3 measurements both before dosing and after six months of treatment.

Results: The patients had a mean age of 58.7 years, and 1, 7 and 14 of them were Stage II, III, and IV, respectively. Correlation analysis revealed a correlation between the HA level after six months of treatment and the baseline DAS28 ($r = 0.7604$). In addition, after six months of TCZ therapy all five of the subjects with abnormal HA levels were Stage IV.

Conclusions: It is possible that, in advanced stage, high disease activity patients, HA levels might have to be measured to determine the status of joint destruction.

W40-6

Efficacy of anti-CCP Ab for early diagnosis of RA in undifferentiated arthritis

Ikuko Tanaka^{1,5}, Motokazu Kai², Kunikazu Ogawa³, Hisaji Ohshima⁴, Shigenori Tamaki^{2,5}

¹Department of Laboratory Medicine, Fujita Health University School of Medicine, Toyoake, Japan, ²Department of Rheumatology, National Hospital Organization Mie Chuo Medical Center, Thu, Japan, ³Department of Orthopedic Surgery, National Hospital Organization Mie Chuo Medical Center, Thu, Japan, ⁴Department of Collagen Disease, National Hospital Organization Tokyo Medical Center, Tokyo, Japan, ⁵Nagoya Rheumatology Clinic

The aim of this study is to evaluate the efficacy of anti-CCP antibody (ACPA) as a diagnostic marker for early RA in undifferentiated arthritis. In 158 of 231 cases fulfilled 1987-ACR criteria, ACPA was positive, and in 214 of 220 other collagen disease ACPA was negative. Sensitivity of ACPA was 68% and specificity of ACPA was 97% in established RA or other collagen diseases. 114 of 156 cases unfulfilled 1987-ACR criteria were treated with DMARDs. ACPA was positive in 56 of 114 cases treated with DMARDs and was negative in 30 of 42 cases untreated with DMARDs. Sensitivity of ACPA was 49% and specificity of ACPA was 71% in early RA and undifferentiated arthritis.

W41-1

Analysis of Therapeutic Effect of Total Shoulder Arthroplasty

Kazuya Tamai¹, Miwa Akutsu², Kazuo Tomizawa², Katsuhisa Yoshikawa², Yutaka Nohara²

To evaluate the effect of total shoulder arthroplasty (TSA), we reviewed 17 shoulders in 15 patients (age, 52-87 years) who underwent TSA for rheumatoid arthritis (5 shoulders), osteoarthritis (5), cuff tear arthropathy (3), old trauma (2), and other pathologies (2). The follow-up period was 17 (6-50) months. Assessment with the Japanese Orthopaedic Association (JOA) score revealed that the pre-operative overall score of 39 points increased to 63 points postoperatively, providing an improvement ratio of 41%. Pain, function and range-of-motion components improved 55, 31 and 22%, respectively, indicating less improvement in function and range-of-motions. We conclude that TSA is effective in pain relief but unpredictable in restoring function and range-of-motions.

W41-2

Mid-term results of total elbow arthroplasty for rheumatoid arthritis

Taisei Kawamoto, Satoshi Iida, Hiromi Ataka
Matsudo city hospital

We evaluate the usefulness of New Type of total elbow arthroplasty including radius component, FINE ELBOW, for rheumatoid arthritis patients. From November 2002, twenty elbows in seventeen patients who had rheumatoid arthritis underwent primary total elbow arthroplasty. The mean age of the patients was 63.8 years. The prosthesis used was FINE ELBOW PROSTHESIS (Nakashima, Okayama, Japan) RESULTS: The J.O.A score improved from 43.9 (pre-operative) to 85.9 (post-operative) at the final examination. The most significant improvement in range of motion. The most prominent observation was reduction of elbow pain and improvement of elbow extension. CONCLUSION Total elbow arthroplasty with FINE ELBOW in rheumatoid arthritis patients can lead to improvement in range of motion, function and pain.

W41-3

The alternation of thumb deformity and dysfunction in rheumatoid arthritis

Shogo Toyama, Daisaku Tokunaga, Ryo Oda, Hiroaki Kobashi, Satoru Nakamura, Kan Imai, Toshikazu Kubo
Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine

[Introduction] The aim of this study is to assess alternation of thumb deformity and function in rheumatoid arthritis. [Materials and methods] We did assessments at the baseline and 5 years later. A total of 52 patients (100 hands) were available. Thumb deformity was determined according to the Stein classification. We reviewed function, joint destruction and disease activity. [Results] Type I deformity was most frequent, and deformity had increased in 5 years. Type II and III had strong dysfunctions but have not progressed. In contrast, Type I and MP had moderate dysfunctions and have severely progressed. [Discussion] Even long-term affected or well-controlled patients had increased dysfunction. We considered that an appropriate assessment and an early therapeutic intervention may be necessary.

W41-4

Clinical results of Avanta silastic metacarpophalangeal arthroplasty for RA

Kozo Morita, Kensuke Ochi, Yukio Horiuchi

We have been using the Avanta silastic finger joint prosthesis for patients over Larsen stage 3 rheumatoid arthritis of the metacarpophalangeal joint and who present with uncorrectable palmar dislocation of the MP joint or with subluxation with ADL disorders. 17 patients with RA (male 2, female 15) including 19 hands and 63 joints went under this surgery from 2001 and were followed for an average of 2.5 years. In 13 hands the replacement was performed in all 4 fingers. ROM, ADL, radiograms and the need for further treatment were reviewed. The average ROM of the MP joint was -15 degrees and 59 degrees for active extension and flexion, respectively. The final ROM, correction of the ulnar deviation and palmar luxation improved consequently. The patients were satisfied cosmetically also.

W41-5

Silicone implant arthroplasty for MP joints of fingers in rheumatoid patients

Kenzo Hashizume¹, Keiichiro Nishida¹, Yoshihisa Nasu², Ryuichi Nakahara¹, Taichi Saito¹, Tomoko Kanazawa¹, Toshifumi Ozaki¹
¹Okayama University Hospital, Department of Orthopaedic surgery, Okayama, Japan, ²Kurashiki Kosai Hospital

(Purpose) To investigate the clinical outcomes of silicone implant arthroplasty for the destroyed metacarpophalangeal (MP) joints of the fingers in rheumatoid (RA) patients. (Materials and Methods) Silicone implant arthroplasty of the MP joints of the fingers was performed in 8 hands of 7 RA patients (22 joints). Statistical differences between pre- and post-operative DASH score, FIM score, grasping power, pinch power, and VAS for patients' satisfaction were analyzed. (Results) Grasping and pinch power, and VAS for patients' satisfaction were significantly improved after the operation. (Conclusions) Silicone implant arthroplasty for the MP joints of the RA fingers can be expected to achieve good clinical outcomes, but should be performed earlier before severe ulnar deviation occurs.

W41-6

Swan-neck and buttonhole deformities in patients with rheumatoid arthritis

Ryo Oda, Daisaku Tokunaga, Shogo Toyama, Toshikazu Kubo
Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine

[Introduction] We studied functional deficiency and successive changes regarding swan-neck and buttonhole deformities. [Materials and Methods] We assessed total of 100 hands could be assessed. Nalebuff classification were performed in these patients. Hand evaluations were made using scores of ADL (JSSH) and modified Kapandji index (MKI). [Results] At baseline, swan-neck deformities were observed in 35.8%. 5 years later, these deformities progressed in 44.8%. Buttonhole deformities were observed in 11.5%. 5 years later, these progressed in 32.6%. Both scores of ADL and MKI worsened significantly with progression of these deformities. [Discussion] It is necessary to carry out appropriate therapeutic intervention from an early stage in order to enable such patients to maintain their finger function.

W42-1

Wrist arthrodesis using an intramedullary rod in rheumatoid arthritis

Katsutoshi Sunami, Katsuhiko Murakami, Kohei Miyake
Chugoku Central Hospital of the Mutual Aid Association of Public School Teachers

Arthrodesis of the wrist is a standard operation to treat severe rheumatoid arthritis.

We performed 4 wrist arthrodeses in 3 patients using Wrist Fusion Rod (WFR).

In all patients synovectomy, resection of the head of the ulna and reconstruction of ruptured extensor tendons were performed.

The mean age at operation was 57 years (33 to 69).

The mean postoperative follow-up was 13.5 months (3 to 33).

Postoperatively, pain relief and improved function was achieved in all the patients.

WFR provides good alignment, rigid internal fixation in combination with stapling.

W42-2

Arthrodesis of wrist joint for rheumatoid arthritis ~utility of locking plate~

Fuyuki Tominaga, Nobutaka Kaibara, Yukio Esaki, Goh Hirata, Hisaaki Miyahara

Department of Orthopedic Surgery, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan

The wrist joint arthrodesis is a useful treatment for severe joint deformity in rheumatoid arthritis (RA). We utilize the locking plate for fixation instead of medullary rod and other conventional methods. To evaluate our short time result, we investigated eight female RA patients that were operated from April 2007 to March 2010. To make a rigid fixation, we applied volar locking plate to dorsal site of wrist joint for internal fixation. Allogenic bone transplantation was applied to all cases. Bone union was observed without correction loss in seven cases within five months except for one pyogenic wrist joint arthritis caused by extension of infectious endocarditis. The locking plate is useful for wrist joint arthrodesis for rigid fixation and preferable result.

W42-3

Indication and clinical outcome of partial arthrodesis for rheumatoid wrists

Taichi Saito, Keiichiro Nishida, Kenzo Hashidume, Ryuichi Nakahara, Tomoko Kanazawa, Toshifumi Ozaki

Department of Orthopaedic Surgery, Okayama University Hospital

We investigated the clinical results of partial arthrodesis for the reconstruction of rheumatoid wrists. 46 wrists of 40 patients with RA treated by partial arthrodesis were included in the current study. Resection of distal end of ulna was accompanied in all cases. Wrist joints were preoperatively evaluated according to the Schulthess classification. Radio-lunate fusion was indicated for Type I (ankylosis) or Type II (osteoarthritis) wrists with preserved midcarpal joint. Radio-scapho-lunate fusion or Radio-lunate-triquetral fusion was indicated for Type III (disintegration) wrists. At the final follow-up, all patients showed excellent pain relief with increased grip strength and improved forearm rotation. Radiographic parameters were also improved by the surgery.

W42-4

Surgical Treatment for Rupture of all finger extensors in Rheumatoid Arthritis

Hiroshi Takamura¹, Mitsuyasu Iwasawa¹, Kimio Masuda¹, Takuo Juji¹, Toshihito Mori¹, Atsuhito Seki²

¹Department of Orthopaedic Surgery, Sagami National Hospital, Kanagawa, Japan, ²Department of Orthopaedic Surgery, National Center for Child Health and Development, Tokyo, Japan

Purpose: We evaluated clinical results of repair for all finger extensor ruptures in Rheumatoid hands, and examined the postoperative active ranges of metacarpophalangeal joint.

Method: Ruptures of all finger extensor tendons were treated in 6 hands. The clinical outcome was assessed with active ranges of metacarpophalangeal joint, and the patient satisfaction was evaluated with a visual analog scale.

Result: Patients were satisfied when the extension lag of metacarpophalangeal joint is less than 30° and the flexion of metacarpophalangeal joint is more than 60°.

Conclusion: For satisfactory result, we should set the goal range of motion of metacarpophalangeal joint in each patient and the setting that flexion is more than 60° and extension is more than -30° is significant.

W42-5

Reconstruction of ruptured extensor tendons in rheumatoid hands

Koji Tateishi¹, Hironobu Yokoyama¹, Shigeru Matsuda¹, Yasuhiro Terashima¹, Kohzoh Kohyama¹, Natsuko Nakagawa¹, Kinue Matsuo²

¹Department of Orthopaedic Surgery, Kohnan Kakogawa Hospital, Hyogo, Japan, ²Department of Rehabilitation, Kohnan Kakogawa Hospital, Hyogo, Japan

We reported the outcome of reconstruction of ruptured extensor tendons followed by postoperative exercise using dynamic splints in patients with RA. Between January 2001 and December 2005, 50 ruptured extensor tendons were reconstructed in 27 patients with RA (21 women and 6 men). Dynamic splints were worn at the third postoperative day when active exercise of MCP and wrist joint was also started and DAS-28 was calculated before and after surgery. Full extension of MCP joints is unsatisfactory in cases with multiple tendon ruptures but that of MCP joint is significantly improved in cases with one or two tendon ruptures. Although early aggressive exercise using dynamic splints was performed postoperatively, palmar flexion of wrists is restricted in cases with multiple tendon rupture.

W42-6

Surgical treatment of carpal tunnel syndrome in the patients with RA

Hajime Ishikawa, Akira Murasawa, Kiyoshi Nakazono, Satoshi Ito, Asami Abe, Hiroshi Otani, Hiroe Sato, Yoichi Toyoshima

Department of Rheumatology, Niigata Rheumatic Center, Shibata, Japan

Surgical treatment of CTS was performed on 36 hands in 32 patients with RA. The average period between the onset of pain and surgery was 4.5 mos.. The average DAS28-ESR (4) was 3.31, and the severity of CTS according to Shinoda's classification was grade 1a: 5 hands, 1b: 1, 2a: 16, 2b: 12, 3a: 2, 3b: 0. Clinical results, evaluated using Kelly's criteria, were excellent in 27 hands, good in 9, and fair and poor in no. The average recovering period after the sur-

gery was 6 mos. without recurrence of pain. In 6 hands in which the nerve action potential could not be detected, sensory disturbance remained postoperatively, excepting one hand. The outcome of surgery for CTS in the patients with RA was generally good irrespective of the disease activity or the severity of CTS.

W43-1

Clinical features of "IgG4 related disease" and its surrounding diseases

Masamitsu Tatewaki, Kazuhiro Kurasawa, Satoko Arai, Takayoshi Owada, Reika Maezawa, Takeshi Fukuda
pulmonary Medicine and Clinical immunology, Dokkyo Medical University, Tochigi, Japan

To analyze pathophysiology of "IgG4-related disease", we examined clinical features of patients with serum high IgG4 levels ($>105\text{mg/dl}$) and sclerosing lesions (group A, $n=24$), those with high IgG4 without sclerosing lesions (group B, $n=21$) and those with sclerosing lesions and normal IgG4 (group C, $n=7$). Serum IgG4 levels were 633 ± 649 in group A and 338 ± 330 mg/dl in group B. In group B autoimmune diseases and allergic diseases were found in 10 and 6 of the patients, respectively. Systemic lymphadenopathy and interstitial pneumonia were frequently detected in patients of group A and B. These findings indicate that conditions of serum elevated IgG4 levels, regardless of sclerosing lesions, are associated with immune dysregulation and/or systemic inflammation.

W43-2

Clinical analyses of patients with IgG4-related disease in our hospital

Masao Katayama, Michita Suzuki, Kyoko Takano, Eiji Nagasawa
Division of Rheumatology, Department of Internal Medicine, Nagoya Medical Center, National Hospital Organization, Nagoya, Japan

Clinical analyses were performed in 10 patients with IgG4-related disease in our hospital. The male:female ratio was 4:6. The average age was 51.4 ± 13.4 years. 3 patients with Mikulicz's disease (MD), 4 with IgG4-related multiorgan lymphoproliferative syndrome (IgG4+MOLPS) and 3 with retroperitoneal fibrosis were diagnosed. 1 patient with MD complicated with autoimmune pancreatitis. IgG4+MOLPS included 2 patients with tumor in the ophthalmologic region, 1 with tumor of the upper lip and 1 with systemic lymphadenopathy. The average of serum IgG4 was 1109.5 mg/dl ($144\text{--}2950$ mg/dl). 8 patients were treated with glucocorticoids and responded favorably to them. 1 patient with upper lip tumor was treated with surgery. One patient with systemic lymphadenopathy has no treatment.

W43-3

A longitudinal survey of serum IgG4 concentrations in IgG4 related disease

Ichiro Mizushima¹, Kunihiro Ogane¹, Takashi Kato¹, Kazunori Yamada², Masami Matsumura², Mitsuhiro Kawano²

¹Division of Nephrology and Rheumatology, Department of Internal Medicine, Ishikawa Prefectural Central Hospital, Ishikawa, Japan,

²Division of Rheumatology, Department of Internal Medicine, Kanazawa University Graduate School of Medicine, Ishikawa, Japan

Objective: To investigate the clinical significance of serum IgG4 concentrations in IgG4 related disease (IgG4-RD). **Methods:** We measured IgG4, IgG and IgE concentrations in the sera of 30 pa-

tients with IgG4-RD. Each value was compared before and after clinical events such as treatment and recurrence. **Results:** 26 patients were treated with corticosteroid. After treatment, significant decrease of serum IgG4 concentrations, IgG4/IgG ratio and clinical improvement were observed. Recurrence occurred in 8 cases and IgG4 concentrations significantly rose again. Decline of IgG4 concentration occurred concurrently with clinical improvement in the cases without steroid treatment. **Conclusion:** Serum IgG4 concentration might be useful as an indicator of response to therapy and recurrence in IgG4-RD.

W43-4

Analysis of useful factors to differentiate IgG4-related disease

Takahide Ikeda, Noriko Takahashi, Hideyuki Okada, Hiroyuki Morita, Tatsuo Ishizuka

Department of General Internal Medicine, Gifu University Graduate School of Medicine

Objective: We investigated effective clinical factors to diagnosis of IgG4-related disease. **Methods:** We have examined sex, age, BMI, temperature, blood examination test and proteinuria as an independent valuable, and a diagnosis of IgG4-related disease as a dependent variable in 5 IgG4-related diseases and 31 other diseases by the logistic-regression analysis. **Result:** The average age in 5 IgG-related diseases (cases with autoimmune pancreatitis, Mikulicz's disease, retroperitoneal fibrosis) was 60 years. The average serum IgG4 level was 1041 mg/dl. There were no significant independent variables except for log (IgG4) (odds ratio 0.108). **Conclusion:** IgG4-related diseases have recognize the various organ lesions, but IgG4 levels was essential for the diagnosis of IgG4-related disease.

W43-5

Respiratory involvement of IgG4-related disease

Shoko Matsui¹, Mitsuhiro Kawano², Koichiro Shinoda¹, Reina Ogawa¹, Hiroyuki Hounoki¹, Hirofumi Taki¹, Kazuyuki Tobe¹, Yasushi Kakuchi², Ichiro Mizushima², Kazunori Yamada², Yasufumi Masaki³, Hisanori Umehara³

¹First Department of Internal Medicine, University of Toyama, ²Division of Rheumatology, Department of Internal Medicine, Kanazawa University Graduate School of Medicine, ³Hematology and Immunology, Kanazawa Medical University

Aims: The aim of this study is to investigate the clinical characteristics of the patients with IgG4-related respiratory disease. **Methods:** A retrospective study in Toyama and Kanazawa University Hospital was performed. **Results:** Twenty-nine patients (male 21: female 8) were identified. The mean age was 64. Chest CT presented diffuse or local pulmonary infiltration, tumor-like lesions, and various other findings. Mean serum IgG and IgG4 were 3538 mg/dl and 1142 mg/dl, respectively. Hyper serum IgE was observed in 90% and hypo-complementemia was observed in 38% of them. **Conclusion:** Our study suggests that respiratory involvement in IgG4-related disease is not rare, and show various conditions. A large scale study is required to clarify the feature of IgG4-related respiratory disease.

W43-6

Analysis of IgG4-related Diseases with Retroperitoneal Fibrosis

Kentarō Doe, Kazuhisa Nozawa, Katsura Hōhtatsu, Shouseki Lee, Hirofumi Amano, Naoto Tamura, Yoshinari Takasaki

Herein, we report analysis of clinical manifestations in 3 cases having IgG4-related diseases with retroperitoneal fibrosis. Affected organs were retroperitoneal, renal, and salivary gland (Mikulicz's disease). Each case was having the 1-3 organ manifestations and serum IgG4 level and IgG4/total IgG ratio were tended to increase depending on number of the affected organs. Steroid (PSL: 35-40 mg/day) was almost effective for disease amelioration. We performed a lip biopsy for diagnosis because of difficulty of performing biopsy from retroperitoneal or renal lesions. One of three cases, who even lacked salivary gland manifestations, revealed an infiltration of IgG4 positive plasma cells. We propose that lip biopsy should be considerable when the histological samples are difficult to obtain.

W44-1

Long-term effect of infliximab in patients with Ankylosing spondylitis

Kurusu Tada¹, Naoto Tamura¹, Shigeto Kobayashi², Hisashi Inoue³, Yoshinari Takasaki¹

¹Rheumatology and Internal Medicine, Juntendo University School of Medicine, ²Internal Medicine, Juntendo Koshigaya hospital, ³Orthopaedics, Juntendo University School of medicine

We previously reported the efficacy of infliximab for treatment of patients with active ankylosing spondylitis. All patients were responded immediately to infliximab, but some cases were found to attenuate the effects. We thought to be caused by a low dose administered of infliximab at long intervals. So we increase the dose of infliximab, reduce interval and pretreatment prior to administration of infliximab to prednisolone. then their disease activity tended to decrease.

W44-2

Sisters cases of sacroiliitis

Kazuhiro Hatta, Ryuichi Sada, Teruhisa Azuma, Hiroyasu Ishimaru
General Medicine, Tenri Hospital

Although Ankylosing spondylitis are more frequently seen in male. Sacroiliitis is seen also in female patient in daily clinical situation. We report sisters cases of sacroiliitis. A 25 year-old female were seen to our clinic because of severe lumbago. Her past history was JRA in her childhood. Schober test was positive, and Xp and CT showed complete ankylosis of bilateral sacroiliac joints. Her younger sister also complaint severe lumbago and came to our clinic. She suffered from JRA at the age of four. X ray showed bilateral sacroiliitis and Achilles tendinitis. Sacroiliitis is one major lesion of SNSA (Seronegative spondyloarthropathy), we should bear in mind this disease when we see lumbago patients.

W44-3

Treatment and assessment for psoriatic arthritis

Junichi Fujisawa¹, Naoki Kondo², Takahiro Netsu², Naoto Endo², Katsumitsu Arai³, Takehiro Murai⁴, Hiroshige Sano⁵, Tadamasa Hanyu⁶

¹Carrier Support Center for Resident, Niigata University Medical and Dental Hospital, Niigata, Japan, ²Division of Orthopedic Surgery, Department of Regenerative and Transplant Medicine, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, ³Division of Orthopedic Surgery, Niigata Prefectural Central Hospital, Niigata, Japan, ⁴Division of Orthopedic Surgery, Niigata

Cancer Center Hospital, Niigata, Japan, ⁵Division of Orthopedic Surgery, Niigata Prefectural Tokamachi Hospital, Niigata, Japan, ⁶Division of Rheumatology, Nagaoka Red Cross Hospital, Niigata, Japan

Aim: To investigate the treatment and assessment for psoriatic arthritis (PsA). **Patients and methods:** Eighteen patients were enrolled in this study. The average age was 55.1 years and average duration of the disease was 14.4 years. To assess the PsA, we chose DAS28. **Results:** In the treatment, Methotrexate was taken in twelve patients. Five patients had good response, four patients had moderate response and three patients had no response. Three patients took cyclosporine and all had no response in this study. Another three patients have no drug treatment (one patient had had gold therapy) and they have already remitted. **Conclusions:** In this study, Methotrexate was effective, especially in the peripheral type, in the treatment of PsA. DAS28 was very useful for assessing the activity of PsA.

W44-4

efficacy of biologics against pustulotic arthro-osteitis and psoriatic arthritis

Takashi Ogasawara, Hideyuki Tachibana, Manabu Tanabe, Yumiko Seno, Sayuri Kataoka, Akiko Tochimoto, Mutsuto Tateishi, Takashi Yamada

Tokyo Metropolitan Ohtsuka Hospital

Biologics such as adalimumab (ADA) and tocilizumab (TCZ) are utilized for the treatments of various arthropathies. We report the clinical course of 3 patients using ADA or TCZ. A woman aged 58, diagnosed as SAPHO syndrome after several years of steroid against seronegative rheumatoid arthritis (RA), got ADA and methotrexate (MTX). Her palmoplantar pustulosis and inflammation values were almost disappeared, however, osteomyelitis of hands remained. A woman aged 67 suffered from systemic eruption, severe anemia, and polyarthritis by psoriasis. Each symptom improved by steroid and TCZ, and additional MTX result in the complete recovery of skin lesions. 61-years-old RA and psoriasis woman was treated by ADA and MTX and she got satisfaction with improved arthropathy and eruptions.

W44-5

HLA profile in SAPHO syndrome.

Taku Yabuki, Mari Ushikubo, Kazuhide Gomi, Hirotohi Matsumoto, Kumiko Akiya, Hisaji Ohshima

Department of Connective Tissue Diseases, Tokyo Medical Center, Tokyo, Japan

Background) While SAPHO syndrome consists with osteoarthritis and skin diseases, its clinical entity and genetic background remain to be clarified. **Purpose)** To clarify HLA profiles in SAPHO syndrome. **Subjects & Methods)** In 7 patients with SAPHO syndrome (mean age; 46.1), HLA haplotypes were analyzed. **Results & Conclusion)** HLA B27 was positive in only one patient. HLA A2 and B61 were seen in 6 and 3 patients, respectively. Because it is suggested that HLA A2 may be associated with psoriatic arthritis, further analysis of the genetic backgrounds is expected for establishment of the clinical entity of SAPHO syndrome.

W44-6

Treatment results of patients with SAPHO syndrome

Hiroki Yabe¹, Masato Moriguchi¹, Tadashi Sakurai¹, Tomomi Tsutsumi¹, Aya Oda¹, Taku Yabuki², Hisaji Ohshima², Kensuke Ochi³, Takahiro Koyanagi³, Yukio Horiuchi², Chihiro Terai¹

¹Jichi Medical University Saitama Medical Center, Division of Rheumatology, ²Department of Internal Medicine, National Hospital Organization Tokyo Medical Center, ³Department of Orthopaedic Surgery, Kawasaki Municipal Kawasaki Hospital

We reviewed retrospectively the treatment results of 26 cases with SAPHO syndrome (2003-2009). The age at diagnosis ranged from 16 to 74 yo (mean: 52.9). Sternocostoclavicular hyperostosis was recognized in 25 cases. Pustular dermatitis such as PPP was seen in 22 cases. Most patients had intermittent attacks of pain, and oral NSAIDs were needed in all cases. SSZ and/or MTX were prescribed in 6 cases and PSL in 8 cases. Pain relief more than 50% was observed in 2 cases (33%) out of SSZ/MTX group, and in 5 cases (63%) out of PSL group. In SAPHO syndrome, pain-attacks tended to be controlled in those patients treated with oral PSL. However, none in both groups achieved drug-free remission. The new treatment methods such as biological preparations may be considered for incurable SAPHO cases.

W45-1

MMP-3 could be implicated in the pathogenesis of interstitial lung disease of RA

Yoshinobu Koyama¹, Kenji Fujii¹, Toshiyuki Ota², Ayumi Uchino¹

¹Center for Rheumatic Diseases, Iizuka Hospital, Fukuoka, Japan, ²Department of Laboratory and Transfusion Medicine, University of Occupational and Environmental Health, Fukuoka, Japan

Objectives: To identify MMP-3 have implication for the pathogenesis of ILD in RA.

Methods: Newly diagnosed RA patients (n=86) were enrolled. The correlations between a loss of DLCO and DAS-28, laboratory data such as ESR, CRP, MMP-3, SAA, RF and ACPA were evaluated.

Results: Although RF, ACPA, DAS28, CRP or SAA seemed to be no direct impact on %DLCO, a weak association was found on ESR ($P<0.05$). The serum level of MMP-3 was the most significant index correlating with a loss of DLCO ($P<0.01$). The relative risk of DLCO<50% for RA patients with MMP-3 \geq 450ng/ml was 5.14.

Conclusion: MMP-3 is possible to play an important role in the developing of ILD associated with RA. The correction of inappropriate expression of MMP-3 would be worth to discuss for preventing progression of ILD in RA patients.

W45-2

Lobular panniculitis as a characteristic skin manifestation in RA

Takehiko Ogawa, Takehisa Ogura, Ayako Hirata, Norihide Hayashi, Yuichi Izumi, Hideki Ito, Reiko Miura, Kana Ogawa
Division of Rheumatology, Toho University Ohashi Medical Center

Objectives: To clarify clinical characteristics of lobular panniculitis occurring in RA. **Methods:** We reviewed the medical records of 8 RA patients with lobular panniculitis, together with 110 RA patients without episode of panniculitis. **Results:** The eruptions were erythematous and partially hirsute indurations, which were quite similar among those 8 patients. Panniculitis arose over the periarticular extensor surfaces of the forearms or the distal legs, which had the most active synovitis. Compared with RA patients without pan-

niculitis, proximal joints were more frequently affected and mean number of tender joints was significantly smaller, whereas CRP levels were higher in patients with panniculitis. **Conclusion.** Panniculitis may be a characteristic and notable skin manifestation in RA.

W45-3

Cutaneous nodules in patients with rheumatoid arthritis

Tadashi Nakamura¹, Syu-ichi Higashi¹, Kunihiro Tomoda¹, Michishi Tsukano¹, Hironori Kudoh¹

¹Kumamoto Center for Arthritis and Rheumatology, Kumamoto, Japan, ²Clinical Pathology, Kumamoto University Hospital

We report a case of 57-year-old Japanese woman with an overlap syndrome of both rheumatoid arthritis (RA) and autoimmune hepatitis, who developed multiple skin nodules. An extensive biopsies of the nodules revealed rheumatoid neutrophilic dermatitis, showing panniculitis without vasculitis, combining with granulomatous formation histopathologically. Since cutaneous nodules in patients with RA are very complex, differential diagnosis should be done according to disease activities, medications used, and pathological findings. We suggest that the differences in histopathological findings of cutaneous nodules in patients with RA depend on their immunological conditions based on disease activities including therapeutic effects.

W45-4

Malignant lymphoma in rheumatoid arthritis: clinical analysis of 5 cases

Tomoyuki Ito¹, Takako Saeki¹, Tadamasa Hanyu²

¹Internal medicine, Nagaoka Red Cross Hospital, Nagaoka, Japan, ²Rheumatology, Nagaoka Red Cross Hospital, Nagaoka, Japan

We describe 5 patients (4 female, 1 male) with Stage 2 rheumatoid arthritis (RA) who developed malignant lymphoma (ML) during methotrexate (MTX) treatment (mean duration 26.6 months; mean dose at ML diagnosis 6.8 mg/week). The mean period from RA onset until ML diagnosis was 55.4 months, and 4 patients were over 60 years old at ML diagnosis. In all 5 cases, the mean total DAS28 score for all visits indicated moderate disease activity. Four patients had non-Hodgkin lymphoma (NHL) and 1 had Hodgkin lymphoma (HL); EBV was present in 3. Initial treatment involved MTX withdrawal alone in 4 patients, 2 of whom achieved CR and 2 PR. However, all 4 suffered relapse and needed chemotherapy. The possibility of ML developing in patients with active RA receiving MTX should be borne in mind.

W45-5

Geriatric syndrome and medical problems in elderly patients in RA

Hiroo Kuroda¹, Jun Koide², Osamu Namiki³

¹Department of Rheumatology, Jiseikai Memorial Hospital, Tokyo, Japan, ²Department of Rheumatology, Kamiitabashi Hospital, Tokyo, Japan, ³Department of Orthopedic Surgery, Kamiitabashi Hospital, Tokyo, Japan

[Objective] To study organic involvements in elderly RA patients and problems with the health care system. [Subjects] The subjects were 8 RA patients with an average age of 83 years. Three patients had received treatment with DMARDs. [Results] The patients were found to have various complications, including cerebral infarction, arrhythmia, cardiac failure, respiratory failure, renal failure, HPS and lower limb necrosis. [Conclusions] Early diagnosis and ad-

vances in treatment have enabled RA remission. On the other hand, however, many elderly patients also have geriatric syndrome. Accordingly, such patients require further consideration with respect to medical problems specific to the elderly, including ideal healthcare, end-of-life care, and financial problems.

W45-6

A prospective study of tuberculosis in patients with RA by *Nin-Ja* for 7 years

Yasuhiko Yoshinaga¹, Tetsushi Aita¹, Susumu Nishiyama¹, Shoji Miyawaki¹, Akira Okamoto², Shigeto Tohma³

¹Rheumatic Disease Center, Kurashiki Medical Center, Kurashiki, Japan, ²Department of Rheumatology, Himeji Medical Center, National Hospital Organization, Himeji, Japan, ³Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami Hospital, National Hospital Organization, Sagami, Japan

Objective: To evaluate the incidence of tuberculosis (TB) in patients with rheumatoid arthritis (RA) prospectively. **Methods:** We calculated the standardized incidence ratio (SIR) of TB from the clinical data on National Database of Rheumatic Disease by iR-net in Japan (*NinJa*) prospectively from 33 facilities for 7 years. **Results:** Among 39296 RA patients registered from 2003 to 2009, 34 patients developed TB. The SIR of TB in RA patients was 2.67 (95%CI:1.77-3.57). 34 patients developed TB were old with the mean age 62.8 years old, and had longer duration of RA with the mean duration 12.0 years. **Conclusion:** The incidence of TB in patients with RA was higher than general population, especially in older patients with longer duration of RA.

W46-1

Frequency of autoantibodies in normal subjects in health screening consultation.

Yoshiharu Amasaki¹, Akira Furusaki¹, Izumi Yasuda², Akira Sagawa³

¹Tonan Hospital, KKR Sapporo Medical Centre, ²Yamanote-doori Yagi Hospital, ³Akira Sagawa Rheumatology Clinic

Frequency and significance of the autoantibodies in the healthy subjects were examined. For 2,093 subjects in the multiphasic health screening test at our institute (1,508 men and 585 women), we measured RF, anti-CCP antibody (Ab), antinuclear Ab (ELISA and FANA method), as well as various disease-specific autoantibodies. Subjects positive for autoantibodies were further followed by questionnaire survey for their outcome two years after measurement. In healthy subjects, prevalence of RF, anti-CCP Ab, antinuclear antibody (ELISA / FANA) were 7.2 %, 1.2 %, and 8.7 / 17.7 % respectively. As for the disease-specific autoantibody, anti-SS-A antibody was the most frequent, with 1.6% of prevalence, and six subjects (17.6%) were appeared to be diagnosed as having Sjogren's syndrome.

W46-2

A critical role of CD4⁺CD25⁺LAG3⁺ regulatory T cells in suppression of B cells

Tomohisa Okamura, Keishi Fujio, Mihoko Shibuya, Shuji Sumitomo, Akiko Okamoto, Hirofumi Shoda, Kazuhiko Yamamoto

Department of Allergy and Rheumatology, Graduate School of Medicine, the University of Tokyo, Japan

We previously reported CD4⁺CD25⁺LAG3⁺ regulatory T cells (Tregs) that characteristically expressed early growth response gene-2 (Egr2), a zinc-finger transcription factor. Recent case-control association study revealed that polymorphisms in the *EGR2* influence SLE susceptibility in humans.

Here, we examined the role of CD4⁺CD25⁺LAG3⁺ Tregs in lupus pathogenesis. Adoptive transfer of CD4⁺CD25⁺LAG3⁺ Tregs, but not CD4⁺CD25⁺ Tregs, suppressed the progression of nephritis and autoantibody production in MRL/lpr lupus prone mice. Moreover, CD4⁺CD25⁺LAG3⁺ Tregs from C57BL/6 mice also suppressed B cell antibody production both *in vitro* and *in vivo*.

These results indicate that CD4⁺CD25⁺LAG3⁺ Tregs play a critical role in preventing the development of autoantibody-mediated autoimmune diseases.

W46-3

Identification of FLRT2 as a novel autoantigen for AECA using retrovirus vector

Tsuyoshi Shirai, Hiroshi Fujii, Kyohei Nakamura, Ryu Watanabe, Yumi Tajima, Naruhiko Takasawa, Tomonori Ishii, Hideo Harigae
Department of Hematology and Rheumatology, Tohoku University Graduate School of Medicine, Sendai, Japan

Objective: Most reported antigens of AECA are intracellular proteins. The aim is to identify autoantigen expressed on cell surface. **Methods:** Sera were screened for AECA activity with human umbilical vein endothelial cell (HUVEC) by FACS. cDNA library of HUVEC was inserted into retroviral vector and stably transfected to rat myeloma cells. cDNA expressing cells were FACS sorted with AECA IgG and cloned. **Results:** By FACS sorting with IgG from lupus patient that had AECA activity, 2 clones were isolated and both have fibronectin leucine-rich transmembrane 2 (FLRT2). HUVEC expressed FLRT2 and IgG of this patient bound to FLRT2 expressing cells. **Conclusion:** We identified membrane protein FLRT2 as a novel autoantigen for AECA. This system is useful for identification of cell surface autoantigen.

W46-4

Identification of epitopes of the anti-ACE2 autoantibodies in SLE patients

Shiori Haga¹, Yuko Takahashi², Yukihito Ishizaka¹, Akio Mimori²

¹Department of Intractable Diseases, Research Institute, National Center for Global Health and Medicine, ²Division of Rheumatic Diseases, National Center for Global Health and Medicine

We have found serum autoantibodies against angiotensin-converting enzyme 2 (anti-ACE2 Ab) in vasculopathy patients (Takahashi *et al.*, 2010). In this study, we identified the epitopes of the antibodies. **Methods:** We performed epitope mapping for anti-ACE2 Ab in the SLE patient with the highest antibody titer and lowest ACE2 activity among 18 vasculopathy patients analyzed. Then, we investigated epitopes shared in other patients, in absorption experiments with the corresponding peptides. **Results:** Two epitopes on ACE2 were identified. We also detected the shared epitopes in 5 patients and observed that the antibodies against these sites are involved in ACE2 dysfunction. The data may help to elucidate a pathogenesis of the inhibitory antibodies against ACE2 in vasculopathy patients.

W46-5

Rheumatoid factor and anti-Sm antibodies in subjects with anti-U1RNP antibodies

Kunio Takada, Mitsuyo Matsumoto, Masahiro Nakashima, Takashi Nakanishi, Hideyuki Horikoshi, Tomoaki Higuchi, Takahiro Yoshikawa, Kimihiro Suzuki

Division of Rheumatology, Department of Internal Medicine, National Defense Medical College, Saitama, Japan

71 subjects (4 males and 67 females) with anti-U1RNP were divided into RF(+) group and RF(-) group. The frequencies of systemic sclerosis (SSc), interstitial pneumonia (IP), and Raynaud's phenomenon (RP) in RF(+) group were significantly higher. Meanwhile, the frequency of persistent proteinuria or lupus nephritis (LN) and anti-Sm in the RF(+) group were significantly lower. Clinical features in the RF(+)anti-Sm(-)positive group and the RF(-)anti-Sm(+) group showed having systemic lupus erythematosus (SLE). The frequency of LN in the RF(-)anti-Sm(+) group was highest among groups. The frequencies of SSc, IP, and RP in the RF(+)/anti-Sm(-) group were highest among groups. The RF(-)anti-Sm(+) group showed intermediate. To examine RF and anti-Sm is benefits to diagnosis.

W46-6

Analysis of disease-specific modifications on a antigen for anti-RNP antibodies

Kouhei Nagai¹, Manae S. Kurokawa¹, Teisuke Uchida¹, Yukiko Takakuwa², Seido Ooka², Mitsumi Arito¹, Kazuki Okamoto¹, Tomohiro Kato¹

¹Clinical Proteomics and Molecular Medicine, St. Marianna University Graduate School of Medicine, ²Division of Rheumatology and Allergy, Department of Internal Medicine, St. Marianna University School of Medicine

[Introduction] Unusual modifications on autoantigenic proteins are proposed to be involved in the production of autoantibodies. Therefore, we tried to detect the disease-specific modifications on a snRNP68k, a major antigen of anti-RNP antibodies. [Methods] PBMCs were collected from patients with MCTD, SLE, and RA, and from healthy donors. Proteins from the cells were separated by 2-DE, and snRNP68k were detected by western blot. [Results] About twenty spots of snRNP68k were detected on the gels. Intensity of a spot (pI 7.5 and 67 kDa) was greater in the MCTD and the SLE groups than in the RA and the healthy groups. Phosphorylation level of the spot was lower than the other spots. These indicate that the de-phosphorylation of snRNP68k may be involved in the anti-RNP production.

W47-1

Assessment of HRQoL (SF-36) in 314 patients with SLE: A cross-sectional study

Sayumi Baba, Yasuhiro Katsumata, Yasushi Kawaguchi, Yuko Okamoto, Takahisa Gono, Masanori Hanaoka, Masako Hara, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University

Objective. To assess the health-related quality of life (HRQoL) in Japanese patients with systemic lupus erythematosus (SLE).

Methods. A cross-sectional study was conducted on 428 patients with SLE. Participants completed the Medical Outcomes Survey Short-Form 36 (SF-36) and underwent clinical and laboratory examination to evaluate disease activity and damage.

Results. A total of 314 patients returned the questionnaire. The median physical (PCS) and mental (MCS) component summary scores were 43, and 45, respectively, both of which were lower than Japanese standards. Comparing these data and disease duration, SLEDAI or damage index (DI), only PCS and DI were significantly correlated.

Conclusion. HRQoL was impaired in Japanese patients with SLE. SLE-related damage influenced physical QoL.

W47-2

Assessment of disease damage in 314 patients with SLE: A cross-sectional study

Yasuhiro Katsumata, Yuko Okamoto, Yasushi Kawaguchi, Sayumi Baba, Takahisa Gono, Masanori Hanaoka, Masako Hara, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Objective. To assess the disease damage in Japanese patients with SLE.

Methods. A cross-sectional study was conducted on 428 patients with SLE. Participants completed the Lupus damage index questionnaire (LDIQ) and underwent clinical and laboratory examination to evaluate disease damage.

Results. A total of 314 patients returned the questionnaire. Median duration of disease was 10 years. Median current dose of prednisolone was 10 mg/day. Median SLICC/ACR damage index (DI) and LDIQ score were 0 and 1, respectively and significantly correlated. There was a significant correlation between disease duration and DI.

Conclusion. The large cross-sectional study revealed the disease damage and its characteristics in Japanese patients with SLE. Disease duration and damage were significantly correlated.

W47-3

Cardiovascular involvement in 80 autopsies of systemic lupus erythematosus

Takayuki Kon¹, Ken Yamaji¹, Kaoru Sugimoto¹, Michihiro Ogasawara¹, Kazuo Kempe¹, Hiroshi Tsuda², Hiroshi Hashimoto³, Yoshinari Takasaki¹

¹Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo, Japan, ²Department of Geriatric General Medicine, Juntendo Tokyo Koto Geriatric Medical Center, Juntendo University School of Medicine, ³Juntendo University

Pathological and clinical features and treatments of 80 autopsied patients of SLE between 1960 and 2009 were investigated. We divided into two groups, those up to 1984 (Group A) and after 1985 (Group B). Cardiovascular involvement was detected in 58.8%. The most frequent findings were myocarditis (20.0% of all, 27.1% in Group A, 9.4% in B), myocardial infarction (16.3%, 4.2%, 34.4%) and atherosclerosis (6.3%, 2.1%, 12.5%). A total dosage of steroid (convert as prednisolone) was 12.5g (Group A) and 41.3g (B), there was significant difference. Advances in therapeutic techniques decreased myocarditis, and treatment or prolongation of prognosis increased myocardial infarction and atherosclerosis. It's rare case that cardiovascular disease was cause of death in SLE, but prudent management is important.

W47-4

Factors associated with quality of life in patients with SLE

Makio Furukawa¹, Chikako Kiyohara², Takahiko Horiuchi¹, Hiroshi Tsukamoto¹, Hiroaki Niino¹, Yojiro Arinobu¹, Kentaro To¹, Koichi Akashi¹

¹Department of Clinical Immunology, Rheumatology, and Infectious Diseases, Kyushu University Hospital, Fukuoka, Japan, ²Department of Preventive Medicine, Kyushu University Faculty of Medical Sciences, Fukuoka, Japan

We assessed Health-related Quality of Life (HRQOL) in 115 outpatients with SLE using SF-36. The means \pm SD of each subscale using Norm-based scoring were Physical functioning (PF): 39.57 \pm 17.94, Role physical (RP): 40.55 \pm 14.98, Bodily pain (BP): 36.40 \pm 3.73, General health perception (GH): 40.33 \pm 10.94, Vitality (VT): 45.66 \pm 10.40, Social functioning (SF): 42.67 \pm 13.91, Role emotional (RE): 44.14 \pm 13.51 and Mental health (MH): 46.66 \pm 9.86. We identified risk factors: ever Cyclosporin use (OR:4.90, P=0.004) for low PF, irregularity of sleeping (OR:24.94, P=0.006), $Plt > 23.4 \times 10^4$ (OR:4.32, P=0.004) and 517012 years (OR:0.20, P=0.005) and ESR>15mm/h (OR:3.85, P=0.004) for low BP, and TG>163mg/dl (OR:4.38, P=0.004) for low GH.

W47-5

Clinical study of systemic lupus erythematosus (SLE) in our center

Motoko Ishida, Tomoya Miyamura, Karin Shimada, Yoshiro Horai, Soichiro Takahama, Rumi Minami, Masahiro Yamamoto, Eiichi Suematsu

Department of Internal Medicine and Rheumatology, Clinical Research Center, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan

To investigate the relationship between the activity and laboratory data of SLE at onset and the prognosis. We enrolled 158 patients (15 males, 143 females) with SLE who had been diagnosed in our center, during March 2000 to August 2010. The average age was 41.0 yo, SLEDAI point was 2 to 51 (median 11). At onset, 18 cases revealed neuropsychiatric symptoms (NPSLE), while 17 cases showed lupus nephritis (LN). During the course, 6 cases developed NPSLE and 13 cases LN. The aPL positive rate of NPSLE (24 cases) was 75%, C1q positive rate of LN (30 cases) was 66%. Steroid therapy had been started in 111 cases (70%), 4 cases died during the period. The causes of all death were exacerbation of SLE. These data suggested that NPSLE had much frequency of aPL positivity, while LN had C1q positivity.

W47-6

Outcome of 68 cases with silent lupus nephritis: A case-control study

Masanori Hanaoka, Yasuhiro Katsumata, Yasushi Kawaguchi, Daisuke Wakasugi, Takahisa Gono, Sayumi Baba, Yuko Okamoto, Masako Hara, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Objective. Although histological renal lesions in patients with clinically silent lupus nephritis (SLN) are usually mild with a good outcome, proliferative glomerulonephritis can be present. We investigated the outcome in patients with SLN, focusing on classes III and IV. **Methods.** We retrospectively studied 180 renal biopsies in patients with SLE performed from 1994 through 2005. **Results.**

Among the 68 cases with SLN, 25, 26, 8, 3 and 6 had classes I, II, III, IV and V, respectively. All the cases with classes III and IV received high-dose steroids: none received cyclophosphamide. Clinically overt nephritis has never developed in these patients until 2010. **Conclusion.** SLN with classes III and IV were occasionally seen but their renal outcome was favorable without aggressive therapy with IVCY.

W48-1

The effect of tocilizumab on bone metabolism in rheumatoid arthritis patients

Isao Matsuura¹, Mieko Yamagata¹, Daisuke Kashiwakuma¹, Shunsuke Furuta¹, Kei Ikeda², Hiroshi Nakajima², Itsuo Iwamoto¹, Shoji Yoshida¹

¹Research Center for Allergy and Clinical Immunology, Asahi General Hospital, Chiba, Japan, ²Department of Allergy and Clinical Immunology, Chiba University, Chiba, Japan

【Purpose/Methods】 Although recent studies have shown the beneficial effect of anti-TNF drugs on bone metabolism in RA patients, there are not many published data on the effect of anti-IL-6 receptor antagonist TCZ. Before and after TCZ therapy, 26 RA patients were measured 1,25 (OH)₂VD, bone ALP (BAP), NTX and bone mineral density (BMD). 18 patients were females. Mean age was 60.5 year old. Mean disease duration was 7.5 years. Median dose of prednisolone was 5.0 mg/day. **【Results】** NTX and BMD did not changed significantly. On the contrary, 1,25(OH)₂VD statistically increased after TCZ therapy from 47.2 to 56.2 pg/ml (p=0.035). And also BAP increased from 58.1 to 102.6 U/l (p=0.001). **【Conclusion】** TCZ may have the beneficial effect on bone metabolism in RA patients.

W48-2

The effect of tocilizumab on bone metabolism in rheumatoid arthritis

Masayasu Kitano, Sachi Tsunemi, Sachie Kitano, Kazuyuki Fujita, Mika Okabe, Takuya Hino, Chieri Kanda, Ryota Okazaki, Mai Morimoto, Aki Nishioka, Masahiro Sekiguchi, Naoto Azuma, Naoki Hashimoto, Kiyoshi Matsui, Hajime Sano
Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine

We investigated the effects of tocilizumab (TCZ) on biochemical markers of bone metabolism, MMP-3 and osteopontin (OPN) in patients with rheumatoid arthritis (RA). 19 patients with RA received TCZ. We evaluated the effectiveness using DAS28-ESR. Next, we measured osteocalcin, NTx, MMP-3 and OPN at baseline, 4 and 12 weeks. As a results, NTx, MMP-3 and OPN levels at 12 weeks decreased significantly from baseline (19.1nmol BCE/l vs 15.85nmol BCE/l; p<0.01, 310.8ng/ml vs 159.2ng/ml; p<0.01 and 138.4ng/ml vs 89.2ng/ml; p<0.05 respectively). Osteocalcin levels in patients with low disease activity were higher than other patients at 4 weeks (6.65ng/ml vs 3.62ng/ml; p<0.05). In conclusion, these findings suggest that TCZ therapy improves systemic bone metabolism in patients with RA.

W48-3

Yearly radiographic progression of RA patients treated with TCZ or ADA.

Daisuke Hoshi, Kumi Shidara, Eri Sato, Naoki Sugimoto, Mariko Kitahama, Yohei Seto, Toru Yamada, Eiichi Tanaka, Ayako Nakajima, Atsuo Taniguchi, Shigeki Momohara, Hisashi Yamanaka

【Objective】To investigate yearly radiographic change of RA patients treated with tocilizumab (TCZ) or adalimumab (ADA) using Total Sharp Score (TSS). **【Methods】**We examined change of TSS by biological treatment in 62 RA patients who received TCZ (n=35) or ADA (n=27). We compared yearly progression of TSS (Δ TSS) in both groups. **【Results】**In TCZ/ADA group, mean age 56.6/48.9, female 91/85%, DAS28 5.39/4.86, J-HAQ 1.50/0.98, duration 10.3/8.3 years, MTX use 69/89%, prednisolone use 71/63%, biologics naïve 60/59%, TSS at baseline 154.2 \pm 73.6/105.9 \pm 72.5, and Δ TSS 2.3 \pm 3.5/2.9 \pm 5.4 were demonstrated. MTX was more frequently used in both groups to the patients with Δ TSS<0.5 group than those with Δ TSS>3 group. **【Conclusion】**Both TCZ and ADA equally inhibit the radiographic progression in RA patients.

W48-4

Radiographic efficacy of tocilizumab therapy in large joints

Hiraku Motomura, Isao Matsushita, Eiko Seki, Tomoatsu Kimura
Department of Orthopaedic Surgery, Faculty of Medicine, University of Toyama

Objective: To assess the influence of tocilizumab therapy on large joints in patients with rheumatoid arthritis. **Methods:** Changes in clinical variables and radiological findings in 151 large joints (24 hip joints, 25 knee joints, 25 ankle joints, 25 subtalar joints, 26 shoulder joints, 26 elbow joints) of 13 consecutive patients with rheumatoid arthritis were investigated at baseline and at 1 year of tocilizumab therapy. **Results:** Five joints of the 151 large joints showed radiographic progression of joint damage after 1 year of Tocilizumab therapy. All hip and knee joints showed baseline Larsen grade 0-II and the inhibition of the radiographic progression. **Conclusion:** Our results suggest that the radiographic progression in most large joints is inhibited by tocilizumab therapy.

W48-5

Imaging assessments after 52 weeks in synovitis in RA patients using tocilizumab

Akira Sagawa
Sagawa Akira Rheumatology Clinic

Objective: To assess changes in synovitis in RA patients treated with tocilizumab (TCZ) by ultrasonography. **Methods:** Ultrasonography was performed every TCZ dosing, and Intensity of synovitis was assessed semiquantitatively graded 0 to 3. **Results:** Before TCZ dosing, 35.3% of the patients were Grade 2 or 3, but this fell to 7.3% after three months, and to 6.3% after one year. In addition, comparison of patients who had not received biological agents (bio-naïve) to patients who had (bio-failure) revealed G0 from an early stage in the bio-naïve, and that both were about the same (63%) at one year. Accordingly, the bio-naïve exhibited significant improvement in terms of the numbers of swollen/tender joints, as well. **Conclusions:** TCZ was effective at inhibiting synovitis in RA patients over one year.

W48-6

Relation between the evaluation using the joint echo and disease activity index

Tomone Shioura, Seiji Tsuboi
JA Shizuoka Kouseiren Shizuoka Kousei Hospital

[Object and Method] Tocilizumab administration was started in our hospital and it was aimed at 13 examples to which evaluation by

a joint echo was performed at the time of the follow up for the 12th week. The evaluation by joint echo assessed the sum total of the blood flow of fingers and wrist s joint by 0 to 66point using power Doppler. The correlation value of the point with DAS28, CDAI, SDAI and each of that component were considered. [Result] It was the time of a start, the number of enlargement joints, a rate of an improvement, etc. for the 12th week that Echo point and significant correlation were accepted. [Conclusion] Although it was thought from now on that a joint echo spread increasingly, the appraisal method and scoring were considered that the further examination is required.

W49-1

The rate of clinical and functional remission with Tocilizumab therapy

Hiroshi Oka¹, Kusuki Nishioka², Yousuke Nishioka³

¹Institute of Medical Science, St. Marianna University School of Medicine, ²Institute of Medical Science, Tokyo Medical School, ³Toranomonkai Nishioka clinic

(Purpose) To evaluate efficacy and safety of Tocilizumab (TCZ) therapy for active Rheumatoid arthritis (RA) patients for 24 weeks. (Methods) Clinical remission (CR) was defined as less than 2.6 point of DAS₂₈ESR4(DAS) and functional remission (FR) was defined as less than 0.5 point of mHAQ score. (Results) 34 RA patients were enrolled in this study. The DAS score was significantly decreased from 4.35 \pm 0.22 to 2.34 \pm 0.18 after TCZ therapy (p<0.0001). The overall rate of CR was 58.8% and FR was 73.5%. There was no difference between biologics naïve group and switched group. The rate of FR with Methotrexate (MTX) combination group was higher than those of TCZ alone group. There was no serious side effects in this study. (Conclusion) TCZ was effective and safe therapy, especially with combination of MTX.

W49-2

Clinical and Physical Function Indices Associated with Tocilizumab Treatment

Seiya Miyamoto¹, Yoichi Kataoka², Moto Kobayashi¹, Yuichiro Narita¹, Yoichi Shimada³

¹Nakadori General Hospital, Akita, Japan, ²Joto Orthopedic Clinic, ³Dept. of Orthopedic Surgery Akita University Graduate School of Medicine

[Objective] To study changes in clinical and physical function indices associated with Tocilizumab (TCZ) treatment. [Subjects/Methods] Of 19 patients (pts) who began TCZ treatment in Nov 2008, 12 pts who continued treatment for 6 consecutive months or more (mean age, 57 yr) were examined. DAS28ESR and HAQ-DI were used as indices.

[Results] DAS28ESR improved from 4.7 at start to 1.9 on Month 6. HAQ-DI decreased from 0.75 at start to 0.48 on Month 4, but increased to 0.69 on Month 6. Three pts showed improvement in DAS28ESR but not in HAQ-DI; 2 were in Stage III or IV, probably having damaged-HAQ, and the other had advanced osteoarthritic changes of the left hip joint and showed improvement in HAQ-DI after left total hip arthroplasty.

[Conclusion] TCZ improved DAS28ESR and HAQ-DI.

W49-3

Weight-bearing joints of patients receiving Tocilizumab

Masanobu Ohishi^{1,2}, Hisaaki Miyahara², Yukio Esaki², Goh Hirata², Nobutaka Kaibara², Yukihide Iwamoto¹

¹Department of Orthopaedic surgery, Graduate School of Medicine, Kyushu University, ²Department of Orthopaedic Surgery and Rheumatology, National Hospital Organization Kyushu Medical Center

Weight-bearing joints of the patients receiving Tocilizumab (TCZ) were studied. Bone and synovium were collected during total joint replacement. Organization by collagen fibers in the synovium and fibrosis of the bone marrow were observed. Neither in the synovium nor bone were the infiltration of inflammatory cells observed. Multilayered osteoblasts was not so obvious as in cases with Etanercept treatment. Radiologically, 46% of the joints which underwent surgery showed progression of destruction before the operations. Among the 14 joints which did not undergo operation, joints rated Larsen grade 1 or 2 showed no progression, while one joint which was rated grade3 aggravated to grade4. Adequate timing of TCZ therapy is important to regulate the joint destruction of weight-bearing joints.

W49-4

Rheumatoid Arthritis Patients

Tomoko Watanabe¹, KwangSeok Yang², Yoshinari Takasaki¹, Hiroshi Tsuda²

¹Division of Rheumatology, Department of intermedicine, Juntendo University School of Medicine, ²Juntendo Tokyo Koto Geriatric Medical Center, Tokyo, Japan

【Title】The efficacy of Tocilizumab (TCZ) for the aged Rheumatoid Arthritis (RA) patients in our hospital.

【Introduction】We have evaluated the efficacy of TCZ for the aged RA patients.

【Objects】Twenty-nine aged RA patients, who were treated with TCZ for 24 weeks or longer.

【Methods】29 patients were divided into two groups: the longer 65 (aged group) and aged less than 65 (non-aged group). We evaluated the efficacy of TCZ treatment by using Disease Activity Score (DAS) 28 ESR (4) and EULAR criterion was assessed. **【Results】**There is no significant difference between the two groups.

【Conclusion】TCZ treatment is very good efficient in the aged as well as the non aged if we choose and observe subjects very carefully.

W49-5

Tocilizumab therapy in HBsAg negative and anti-HBs/HBc positive patients with RA

Yoshinori Masui¹, Junwa Kunimatsu¹, Leo Yoshikawa¹, Sumie Moriyama¹, Yo Ueda², Yuji Yoshida², Yuko Takahashi², Hiroyuki Yamashita², Akio Mimori², Hiroshi Kaneko³

¹Department of Internal Medicine, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan, ²Division of Rheumatic Diseases, Department of Internal Medicine, National Center for Global Health and Medicine, Tokyo, Japan, ³Department of Rheumatology, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan

Using of biologics in hepatitis B virus (HBV) patients is contraindication. The patients who were HBs Ag-negative but anti-HBc Ab-positive were considered to be clinically cured. However, HBV reactivation was reported even in those patients after immunosuppressants including anti-TNF blockades. The safety of tocilizumab (TCZ) administration in those patients has not been fully established. We administrated TCZ for 9 active RA who were positive anti-HBs/HBc Ab but not HBs Ag. Although TCZ was discontinued in 1

case because of bacterial infection, HBV-DNA remained undetectable in all patients. Our study suggests that TCZ may be safe for HBs Ag-negative and anti-HBs/HBc Ab-positive persons.

W49-6

an investigation of the patients who discontinued Tocilizumab from TBC data-base

Kiwamu Saito¹, Atsushi Kaneko², Atsuhiko Fukai², Nobunori Takahashi², Daihei Kida², Tomotaro Sato², Yuichiro Yabe⁴, Tomone Shioura⁵, Nobuyuki Asai⁶, Tomonori Kobayakawa⁷, Toshihisa Kojima³, Naoki Ishiguro³

¹saito clinic orthopedics and rheumatology, ²National Hospital Organization, Nagoya Medical Center, ³Nagoya University, ⁴Tokyo Koseinenkin Hospital, ⁵Shizuoka Kosei Hospital, ⁶Nakatsugawa Municipal General Hospital, ⁷Toyohashi Municipal Hospital

【purpose】To study those patients who discontinued Tocilizumab(TCZ). **【method】**Data from TBC(Tsurumi Biologic Communication) was investigated retrospectively. **【results】**TCZ was administered to 183 patients. 11 patients was lost follow-up. In the 172 patients, 25 patients (14.5%) was discontinued TCZ. 4 was discontinued by infection. 10 was not by infection (2 out of 10 was by high CRP level). 7 was by insufficient efficacy. 4 was not by adverse effect (one patient had noticed being pregnant and discontinued TCZ after that. The baby hadn't had any problem.) **【conclusion】**TCZ was discontinued in 14.5% of patients in the TBC data base. High CRP level was characteristic reason for TCZ and farther investigation is necessary.

W50-1

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

Motohiko Aidu¹, Hiroshi Fujii¹, Rika Kawamura¹, Satoshi Hara¹, Yasushi Kakuchi¹, Kazunori Yamada¹, Masami Matsumura¹, Mitsuhiro Kawano¹, Yasuo Katsuki^{1,2}, Shinichi Kato³, Satoshi Nakazaki³, Takashi Murayama³, Kunihiro Ogane⁴, Ichiro Mizushima⁴, Takashi Kato⁴

¹Division of Rheumatology, Department of Internal Medicine, Kanazawa University Graduate School of Medicine, ²Yawata Medical Center, ³Ishikawa Worker Medical Association, ⁴Ishikawa Prefectural Central Hospital

(Objective)The aim of this study was to define a diagnostic potential of serum IL-6 concentration for infectious disease under Tocilizumab therapy.

(Methods)35 RA patients receiving Tocilizumab were undertaken. Disease activity and Serum IL-6 levels were monitored every month. IL-6 levels were measured in case of infection. The relationship between IL-6 concentration and disease activity or infectious disease was analyzed.

(Results)Serum IL-6 levels were elevated after administration of Tocilizumab and decreased gradually as the disease activity was ameliorated. Some patients showed no elevation of IL-6 levels. IL-6 levels were markedly elevated in case of infection.

(Conclusion)Serum IL-6 level might be a good marker to diagnose RA activity or infectious disease under Tocilizumab therapy.

W50-2

Tocilizumab-induced neutropenia in patients with rheumatoid arthritis

Sei Muraoka, Koutarou Shikano, Makoto Kaburaki, Nahoko Tanaka, Kaichi Kaneko, Tatsuhiro Yamamoto, Yoshie Kusunoki, Hirahito Endo, Shinichi Kawai
Toho University Omori Medical Center, Rheumatic Disease Center, Tokyo, Japan

[Objective] To clarify the effects of Tocilizumab (TCZ) 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 TCZ. [Method] Fourteen patients with RA (1M/13F, mean±SD 61±14 y.o.) under TCZ therapy were included in this retrospective study, they were compared with patients (n=124) under TNF inhibitors. [Results] Mean NCs after TCZ and TNF inhibitors were decreased 34.8 % and 25.1 %, respectively. Patients under TCZ and TNF inhibitors with NCs < 2000 /μL were 50.0% and 10.5%, respectively. Severe infection was not observed in patients under TCZ therapy. [Conclusion] Although NCs were decreased by TCZ, incidence of infection was not increased in RA patients.

W50-3

Clinical significance of early change of WBC count in RA therapy by tocilizumab

Yasushi Tanaka, Kazuko Shiozawa, Ryosuke Yoshihara, Miki Murata, Chihiro Tanaka, Takashi Yamane, Noriaki Yo, Shigeaki Imura, Natsuko Nakagawa, Kohzoh Kohyama, Yasuhiro Terashima, Shigeru Matsuda, Hironobu Yokoyama
Rheumatic disease center, Konan Kakogawa Hospital, Kakogawa, Hyogo, Japan

Objective: To examine the change of white blood cell (WBC) count as a predictor of the disease activity of RA treated with Tocilizumab (TCZ). Method: 40 RA patients treated with TCZ over 6 months were enrolled and divided into two groups by the ratio of the decrease of WBC count after 4 or 8 weeks of the first TCZ treatment. 1st group was that of WBC count decreased more than 20%, and 2nd group was one of others. Disease activity was assessed by DAS28-CRP<2.3. Results: DAS28 improved significantly in the 1st group after 12wks of initiation of TCZ therapy compared with the 2nd group (6/19 vs 4/19, p=0.033). In addition, DAS28 after 24wks did not have significant difference (15/19 vs 14/19, p=0.433). Conclusion: Early decrease of WBC count in TCZ therapy of RA suggests the possibility of remission.

W50-4

Usefulness of MMP-3 for efficacy evaluation of tocilizumab based on IL-6 level

Hiroshi Fujinaga¹, Kozo Takahashi¹, Toshiaki Kogure², Tatsuya Nogami³, Hiroaki Hikami³

¹Department of Internal Medicine and Japanese Oriental Medicine, Toyama Prefectural Central Hospital, Toyama, Japan, ²Department of Japanese Oriental Medicine, Gunma Central General Hospital, Maebashi, Japan, ³Department of Japanese Oriental Medicine, Toyama University Hospital, Toyama, Japan

Objective: Blood IL-6 concentration during administration of tocilizumab (TCZ) shows actual IL-6 production in the human body and is useful as a biomarker during treatment but routine measurement is difficult because it is not covered by health insurance. Use-

fulness of MMP-3 in evaluation of TCZ effects is clear from the relation with clinical symptoms. We analyzed the relation between IL-6 and MMP-3 during TCZ administration.

Subjects: Subjects were 13 patients (one man and 12 women) treated with TCZ with mean disease duration of 13 years and history of use of biological agents in 92%.

Results: IL-6 and MMP-3 showed a positive correlation with a correlation coefficient of 0.76 (P=0.002).

Conclusion: MMP-3 values during TCZ treatment are assumed to reflect disease activity and IL-6 values.

W50-5

Relationship between efficacy of Tocilizumab and levels of CRP

Toshihisa Kojima¹, Yuichiro Yabe², Masatoshi Hayashi¹, Koji Funahashi¹, Daizo Kato¹, Hiroyuki Matsubara¹, Tomonori Kobayakawa³, Kiwamu Saito⁴, Tomone Shioura⁵, Atsushi Kaneko¹, Yuji Hirano¹, Naoki Ishiguro¹

¹Department of Orthopedic Surgery, Nagoya Univ. School of Medicine, ²Department of Orthopedic Surgery & Rheumatology, Tokyo Koseinenkin Hospital, ³Department of Orthopedic Surgery & Rheumatology, Toyohashi City Hospital, ⁴Department of Orthopedic Surgery, Nagoya Medical Center, ⁵Department of Orthopedic Surgery, Shizuoka Kosei Hospital

Objective: To investigate the relationship between the clinical efficacy and the time of the normalization of the serum CRP in RA patients treated with TCZ in TBC registry. Methods: 69 patients treated with TCZ were divided into 2 groups by the time of the normalization of the serum CRP from the introduction of the TCZ therapy (A:4week-/B:4week+). Efficacy was evaluated as TJC, SJC, GH, MMP-3 every 6 months. Result: TJC, SJC, GH, MMP-3 was significantly decreased at 6 and 12 month, respectively in both groups. GH of the group A was greatly improved than the group B. Conclusion: Monitoring of CRP during TCZ treatment is useful to assess the trough levels of TCZ. Early normalization of CRP and its maintenance could be important to control disease activity with TCZ.

W50-6

Change of muscle strength, mass, markers in RA patients treated with tocilizumab

Akihide Nampei¹, Makoto Hirao², Kosuke Ebina³, Hideki Tsuboi⁴, Kenrin Shi², Hideki Yoshikawa², Jun Hashimoto⁵

¹Department of Orthopaedic Surgery, Osaka Rosai Hospital, ²Department of Orthopaedics, Osaka University Graduate School of Medicine, ³Department of Orthopaedic Surgery, Osaka Police Hospital, ⁴Department of Orthopaedic Surgery, National Hospital Organization Osaka Minami Medical Center, ⁵NHO Osaka Minami Medical Center

RA patients decrease muscle mass and muscle strength. The reason was considered as low activity from pain and joint destruction, and increased resting energy expenditure from inflammatory cytokine. We investigated muscle strength, muscle mass, and muscle markers sequentially against RA patients treated with tocilizumab. Grip strength and pinch strength were increased significantly at 3 months and 6 months respectively. Lean body mass was tended to increase, but not significantly. Creatine Kinase (CK) was not changed significantly, but Creatinine (Cr) was increased significantly at 6 months. and the ratio Cr/CystatinC was increased at 1 month

significantly and persisted. It is possible that tocilizumab not only suppress the inflammation, but also improve the muscle metabolism.

W51-1

Treatment with biologics and risk of malignancy in rheumatoid arthritis

Masayoshi Harigai^{1,2,3}, Toshihiro Nanki^{1,2}, Michi Tanaka^{1,2}, Ryoko Sakai^{1,2}, Kaori Watanabe^{1,2}, Hayato Yamazaki^{1,2}, Ryuji Koike^{1,2,3}, Nobuyuki Miyasaka²

¹Department of Pharmacovigilance, Tokyo Medical and Dental University, ²Department of Medicine and Rheumatology, Tokyo Medical and Dental University, ³Clinical Research Center, Tokyo Medical and Dental University Hospital

Object: To investigate risk of malignancy in Japanese patients with rheumatoid arthritis (RA) treated with biologics. **Methods:** As of March 2010, 7,740 Japanese patients with RA who ever used infliximab or etanercept were registered to the SECURE (Safety of Biologics in Clinical Use in Japanese Patients with Rheumatoid Arthritis in Long-Term) study. Standardized incidence ratios (SIRs) of malignancy were calculated using Japanese general population as a reference. **Results:** 131 malignancies were reported including 99 non-hematological and 31 hematological malignancies. The latter contained 29 cases of malignant lymphoma. SIRs for all, non-hematological, and hematological malignancies, and lymphoma were 0.99, 0.77, 5.1, and 8.2 for female, and 0.83, 0.68, 4.3, and 5.9 for male, respectively.

W51-2

SNP algorithm for prediction of progression of joint destruction in RA patients

Tsukasa Matsubara¹, Satoru Koyano², Yoshitada Sakai³, Keiko Funahashi², Takafumi Hagiwara¹, Takako Miura¹, Kosuke Okuda¹, Akira Sagawa⁴, Takeo Sakurai⁵, Hiroaki Matsuno⁶, Tomomaro Izumihara⁷, Eisuke Shono⁸

¹Matsubara Mayflower Hospital, ²Research Institute of Joint Diseases, ³Himeji Dokkyo University, ⁴Sagawa Akira Rheumatology Clinic, ⁵Inoue Hospital, ⁶Matsuno Clinic for Rheumatic Diseases, ⁷Izumihara Rheumatic and Medical Clinic, ⁸Shono Rheumatology Clinic

Purpose: We established a SNP algorithm for prediction of joint destruction in RA patients. **Patients and Methods:** 125 RA patients whose disease duration was within 5 years were enrolled. RA joint destruction was classified by Sharp score. We scored a relationship between each SNP and progress of joint destruction, the estimated total score of 10 SNPs (estimated scoring in each SNP was as follows: homo allele in the majority in severe joint destruction (S) group: +1 point, hetero allele: 0 point, and homo allele in the majority of mild joint destruction (M) group: -1 point). **Results:** 88.1% of the S group scored ≥ -1 point, and 86.7% of the M group scored ≤ -2 points with this algorithm. **Conclusion:** This SNP algorithm may be useful in initially distinguishing severe joint destruction.

W51-3

PPAR agonists enhance generation of human regulatory T cells with TSA or ATRA

Hitoshi Hasegawa, Lei Jin, Takuya Matsumoto, Sachiko Onishi, Koichiro Suemori, Masaki Yasukawa

Department of Bioregulatory Medicine, Ehime University Graduate School of Medicine

Purpose: The identification of molecules controlling Treg function is important in understanding autoimmune diseases such as RA. Previously, we reported that human TGF- β -induced Treg (iTregs) with PPAR agonists had high expression of Foxp3 and suppressive function. Thus, we report that trichostatin A (TSA) and retinoic acid (ATRA) enhance the generation of iTregs with PPAR α and γ agonists. **Methods:** PPAR agonist-treated iTregs with TSA or ATRA were examined Foxp3 expression and suppressive function. **Results:** PPAR agonists with TGF- β elicited Foxp3 DNA demethylation and induced potent Foxp3 expression. Moreover, TSA and ATRA enhanced iTregs generation synergistically with PPAR agonists. **Conclusion:** Human iTregs can be generated efficiently by combining PPAR agonists with TSA or ATRA.

W51-4

Effect of FKBP5 gene for the osteoclast differentiation

Miho Kimura¹, Reiko Matsushita¹, Atsushi Hashimoto², Tatsuo Nagai¹, Shunsei Hirohata¹

¹Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa 228-8555, Japan, ²National Hospital Organization Sagami National Hospital

Abnormality of bone marrow in rheumatoid arthritis (RA) has been reported. Previously, we reported that bone marrow CD34 positive cells from RA patients have higher FKBP5 mRNA expression. In order to examine whether FKBP5 has an important role for osteoclast differentiation, we created FKBP5 transfectant of mouse macrophage RAW264.7 cell line and cultured under the stimulation of RANKL. TRAP staining and the pit formation assay showed that FKBP5 transfectant generated differentiation of a larger numbers of osteoclasts with higher ability of pit formation, compared with control. Moreover, this response was inhibited by NF κ B inhibitor, N-acetyl cysteine. These results indicate that FKBP5 promotes osteoclast differentiation through the activation of NF κ B cascade in RAW264.7 cells.

W51-5

Plasma and synovial fluid miRNAs as potential biomarkers of rheumatoid arthritis

Koichi Murata, Hiroyuki Yoshitomi, Shimei Tanida, Hiromu Ito, Takashi Nakamura

Department of Orthopaedic Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan

INTRODUCTION: We investigated the existence of synovial fluid miRNAs, and potential of plasma and synovial fluid miRNAs as biomarkers of rheumatoid arthritis (RA).

METHODS: We measured concentration of miR-16, miR-132, miR-146a, miR-155 and miR-223 in plasma from RA, osteoarthritis (OA) and healthy controls (HCs) and synovial fluid from RA and OA by real-time PCR (n=30, each).

RESULTS: Synovial fluid miRNAs were present, revealed distinct expression pattern from plasma miRNAs and were likely to originate mainly from synovial tissues. Plasma miR-132 of HC was significantly higher than that of RA or OA, with high diagnosability. Plasma miR-16, miR-146a, miR-155, and miR-223 inversely correlated with tender joint count.

CONCLUSION: Plasma and synovial fluid miRNAs are potential biomarkers of RA.

W51-6

Re-evaluation of HLA-DRB1 allele classifications in Japanese RA patients

Kenichi Shimane^{1,2}, Yuta Kochi², Ryo Yamada⁴, Naoyuki Kamatani³, Kazuhiko Yamamoto^{1,2}

¹Department of Allergy and Rheumatology, the University of Tokyo Hospital, Tokyo, Japan, ²Laboratory for Autoimmune Diseases, Center for Genomic Medicine, Institute of Physical Chemical Research (CGM, RIKEN), Tokyo, Japan, ³CGM, RIKEN, Yokohama, Japan, ⁴Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan, ⁵Human Genome Center, Institute of Medical Science, the university of Tokyo, Tokyo, Japan

Purpose: Several classifications of role of HLA-DRB1 alleles in RA-susceptibility have been proposed based on shared epitope (SE) hypothesis. We re-evaluated these classifications in Japanese.

Methods: We genotyped HLA-DRB1 for 2410 RA patients and 911 controls by using WAKFlow kit. We tested the association of DRB1 with RA-susceptibility by χ^2 test. We examined the classifications proposed by Matthey, Vires and Tezenas.

Results: Besides SE alleles, DRB1*0901 is a significant risk allele for RA in Japanese. Among SE alleles, there is a hierarchy in their effects on RA predisposition, which was not correspondent to that seen European populations.

Conclusion: Our results suggested heterogeneity of DRB1 in RA predisposition, and a new classification may be needed for Japanese population.

W52-1

The phenotype of CD4+ T cells which recognize an autoantigen BiP-derived epitope

Hirofumi Shoda, Keishi Fujio, Kazuhiko Yamamoto
Dept. of Allergy and Rheumatology, Graduate School of medicine, the Univ. of Tokyo, Tokyo, Japan

We identified an autoantigen-derived HLA-DR4 epitope, BiP336-355.

The phenotypes of BiP336-355-HLA-DR4-tetramer (BiP-Tet)+ CD4+ T cells from healthy volunteers (HV) and rheumatoid arthritis (RA) were analyzed by FACS and RT-PCR. The proliferation of PBMCs in response to BiP336-355 was examined by 3H-thymidine uptake.

BiP-Tet+ CD4+ T cells existed 0.23% in HV and 0.52% in RA. BiP-Tet+ cells consisted of naive and memory T cells, not Treg cells. BiP-Tet+ T cells in HV showed Th1 phenotypes, whereas those in RA highly produced IL-17 in peripheral blood and synovium. PBMCs from HV showed less proliferation than those from RA.

Induction of IL-17-producing BiP-Tet+ T cells is a key step in the pathogenesis of RA.

W52-2

Arthritogenicity of Anx7 revealed by phosphoproteomics of RA synoviocytes

Mitsumi Arito¹, Kosuke Matsuo², Koji Noyori², Hiroshi Nakamura³, Manae S. Kurokawa¹, Kayo Masuko¹, Kouhei Nagai¹, Kazuki Okamoto¹, Kazuo Yudo⁵, Moroe Beppu⁴, Tomoyuki Saito², Tomohiro Kato¹

¹Clinical proteomics and Molecular Medicine, St. Marianna University Graduate School of Medicine, ²Department of Orthopedic Sur-

gery, Faculty of Medicine, Yokohama City University, Yokohama, ³Department of Joint diseases and Rheumatism, Nippon Medical School, ⁴Department of Orthopaedic Surgery, St. Marianna University School of Medicine, ⁵Department of Frontier Medicine, Institute of Medical Science, St Marianna University Graduate School of Medicine

To identify novel molecules involved in the pathogenesis of rheumatoid arthritis(RA), we here applied differential phosphoproteomic analysis to articular synoviocytes between RA and osteoarthritis (OA). Focusing on annexin VII (Anx7), one of the highly phosphorylated proteins in RA by the analysis, we prepared *Anx7*-transgenic mice to evaluate their susceptibility to collagen-induced arthritis (CIA). As a result, the *Anx7* transgene altered CIA-resistant C57BL/6 mice to CIA-susceptible ones. Further, the administration of anti-Anx7 antibodies (Abs) suppressed CIA even in CIA-susceptible DBA/1J mice. *In vitro*, the knockdown of Anx7 by siRNA caused down-regulation of IL-8 secretion. These results indicate that Anx7 participates in the pathogenesis of RA, through in part the secretion of IL-8.

W52-3

The effect of connexin43 for pro-inflammatory cytokines in rat FLSs

Shinji Tsuchida¹, Yuji Arai¹, Ryu Terauchi^{1,2}, Kuniaki Honjo¹, Shuji Nakagawa¹, Hiroaki Inoue¹, Ryo Oda¹, Daisaku Tokunaga^{1,2}, Toshikazu Kubo¹

¹Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, ²Department of Biomaterials and Biomechanics, Kyoto Prefectural University of Medicine, Kyoto, Japan, ³Department of Microbiology and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine

Connexin43 (Cx43) was the main protein in gap junction which were specialized connections between cells in a tissue. The levels of Cx43 in synovial tissue were higher in rheumatoid arthritis than in osteoarthritis. We investigated whether Cx43 gene silencing in fibroblast-like synoviocytes (FLSs) of rat *in vitro* by RNA interference enhanced pro-inflammatory cytokines such as tumor necrosis factor- α , interleukin-1 β , and interleukin-6. The Cx43 mRNA levels were highly expressed into FLSs by stimulation of LPS. Cx43 gene silencing by siRNA could effectively inhibit the gene expressions of those pro-inflammatory cytokines in rat FLSs. These results suggest that the siRNA targeting Cx43 gene could be a useful tool for treating inflammatory joint.

W52-4

IL-6 Promotes Pathological Angiogenesis by Modulating Angiopoietin Balance in RA

Ken Kayakabe, Takashi Kuroiwa, Noriyuki Sakurai, Hidekazu Ikeuchi, Toru Sakairi, Akito Maeshima, Keiju Hiromura, Yoshihisa Nojima

Department of Medicine and Clinical Science, Gunma University Graduate School of Medicine, Maebashi, Japan

Objective: To explore a role of IL-6 in RA angiogenesis. Methods: Endothelial cells (HUVEC) and synovial fibroblasts from RA patients (FLS) were co-cultured with IL-6. EC growth and EC-EC adhesion were assessed by CD31 and VE-cadherin stain. Results: Compared with control, IL-6 (100 ng/ml) induced 2.5-fold increase of CD31 positive area. EC stimulated with IL-6 exhibited irregular

shape and decreased cell-cell adhesion. In the supernatants of co-culture, IL-6 up-regulated VEGF and Ang-2, while decreased Ang-1. In RA synovial fluids, IL-6 was positively correlated with VEGF, while VEGF negatively with Ang-1. Conclusion: IL-6 not only up-regulates VEGF but also down-regulates Ang-1 signaling. These effects may synergistically promote the pathological angiogenesis in RA

W52-5

Relationship between angiogenesis factors and proinflammatory cytokines in RA

Eigo Takahashi, Daitaro Kurosaka, Kenichiro Hirai, Ken Yoshida, Isamu Kingetsu, Akio Yamada
Division of Rheumatology, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan

Objective: To investigate the relationship between serum levels of angiogenesis-related factors and proinflammatory cytokines in rheumatoid arthritis (RA) patients. **Method:** The subjects were 70 patients with RA who fulfilled the ACR 1987 criteria. Serum levels of angiogenesis-related factors and proinflammatory cytokines were measured by ELISA. **Result:** Serum levels of vascular endothelial growth factor (VEGF) and angiopoietin-1 (Ang-1) were correlated with IL-6. Serum level of angiopoietin-2 (Ang-2) was correlated with IL-6 and IL-8. **Conclusion:** Serum angiogenesis-related factors were correlated with serum proinflammatory cytokines in RA patients, might play an important role in joint inflammation of RA patients.

W52-6

Effect of biological agents on the in vitro IL-17 production of PBMC

Satoko Tejima, Toshihiro Tono, Tatsuo Nagai, Sumiaki Tanaka, Shunsei Hirohata
Department of rheumatology and Infectious Disease, Kitasato University School of Medicine, Sagamihara, Japan

We investigated the effects of IFX, ETN and TCZ on the IL-17 production of PBMC. PBMC, CD4+ T cells and CD14+ monocytes from healthy donors were cultured with pharmacologically attainable concentrations of biological agents or control IgG. The concentrations of IL-17 in the culture supernatants were measured. The expression of CD80 and CD86 of monocytes was measured by flow cytometry. IFX and ETN, but not TCZ, suppressed the IL-17 production of SEB stimulated PBMC and the expression of CD80 and CD86 of SEB stimulated monocytes. IFX and ETN didn't influence the IL-17 production of CD4+T cells activated with immobilized anti-CD3. The data indicates that TNF α antagonists suppress IL-17 production through the modulation of monocyte function, whereas TCZ does not influence IL-17 production.

W53-1

Analysis of SNPs in untreated newly diagnosed Japanese RA patients.

Tetsuya Nishimoto, Noriyuki Seta, Yuko Kaneko, Masataka Kuwana, Tsutomu Takeuchi
Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

To determine the significance of SNPs in Japanese RA patients, we genotyped FCRL3-169, STAT4+56293, CTLA4+49, PA-DI4+163, IRF5+198, and TRAF1+16860, and examined their asso-

ciation with RA susceptibility, clinical profiles, and response to treatments. Case-control comparisons using 99 RA patients from a SAKURA data base and 53 healthy controls revealed that PA-DI4+163 G allele was associated with RA susceptibility. Stratified analysis indicated that STAT4+56293 G allele and IRF5+198 T allele were increased in patients with shared epitope, and that FCRL3-169 A allele was associated in patients who were positive for MMP-3 and refractory to treatments. Therefore, all SNPs except CTLA4+49 were associated with RA susceptibility, clinical profiles, or response to treatments in Japanese RA patients.

W53-2

Chronic renal disease in patients with rheumatoid arthritis

Ryosuke Hanaoka, Harutsugu Okada
Department of Rheumatology, Kamitsuga General Hospital, Tochigi, Japan

OBJECTIVE: To evaluate the prevalence and associations of chronic kidney disease (CKD) in patients with rheumatoid arthritis (RA).

METHODS: Renal function was assessed by estimated glomerular filtration rate (eGFR) in 87 RA patients and 1583 controls for this cross-sectional study. CKD was defined as reduced eGFR of less than 60 ml/minute per 1.73 m². Logistic-regression analysis was used to test the independence of the associations between CKD and each variables.

RESULTS: Prevalence of CKD was significantly higher in RA patients than controls. Multivariable analysis revealed significant associations between CKD and RA, hypercholesterolemia, hypertension, hyperuricemia, and hyperglycemia.

CONCLUSIONS: CKD is associates with RA as well as classic cardiovascular risk factors.

W53-3

Rheumatoid arthritis and osteoporosis, Second report: Factors for BMD changes

Ichiro Nakamura^{1,2}, Yasuhiko Koizumi^{1,2}, Makoto Tanokura^{1,2}, Katsumi Ito^{1,2}

¹Department of Rheumatology, Yugawara Kosei-nenkin Hospital,

²Working Group for Rheumatoid Arthritis

In 237 RA patients, BMD was measured and the annual rate of change was assessed. BMD at femoral neck and lumbar was significantly decreased. Average reduction of BMD at femoral neck was 3.8%. To determine factors affecting changes in BMD at neck area, multiple logistic regression analysis was performed. Covariates included age, sex, duration of RA, CRP, anti CCP antibody, serum osteocalcin, urinary NTX, HAQ, presence of lumbar compression fracture, amount of steroids, amount of MTX, and administration of biological agents. We assumed these 12 factors for explanatory variables and increase or decrease in BMD for dependent variables. The result showed that the absence of a lumbar compression fracture and administration of infliximab were significantly associated with increase in BMD.

W53-4

The cross-talk between BMP-2 and S1P signaling for osteoblast differentiation

Chieri Kanda¹, Tsuyoshi Iwasaki², Sachie Kitano¹, Sachi Tsunemi¹, Masahiro Sekiguchi¹, Masayasu Kitano¹, Hajime Sano¹

¹Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, ²Department of Pharmacy, Hyogo University of Health Sciences

(Purpose) We previously demonstrated that S1P signaling induced osteoblast differentiation. The present study we investigated the role of S1P signaling on bone morphogenic proteins (BMPs) induced osteoblast differentiation. (Methods) BMPs induced osteoblast differentiation was examined by Runx2, ALP and osteocalcin expressions of C2C12 cells using RT-PCR and ELISA. The effects of pertussis toxin (PTX) and MEK1/2 inhibitor on osteoblast differentiation were also examined. (Results) Both S1P and FTY720 enhanced BMPs induced osteoblast differentiation. These enhancing effects were inhibited by PTX and MEK1/2 inhibitor. (Conclusion) These results indicate that cross-talk between S1P signaling via MEK/ERK cascade and BMPs signaling synergistically induces osteoblast differentiation.

W53-5

Efficacy of raloxifen on reducing fractures rate of steroid-treated RA patients

Hisanori Nakayama¹, Futoshi Hagiwara², Hiromi Hayakawa², Toshihiro Matsui¹, Shigeto Tohma²

¹Department of Rheumatology, Sagamihara National Hospital, National Hospital Organization, ²Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, National Hospital Organization

Objective. To evaluate the efficacy of raloxifen (RLX) on reducing the risk for fractures of steroid administered RA patients as compared with bisphosphonate (BP) or active vitamin D (VD). **Methods.** We carried out intervention trial of 100 RA patients (mean age:61), They were divided into three groups, BP group (62): alendronate or risedronate+ VD, RLX gr. (13): RLX+ VD, VD gr. (25): VD alone. **Results.** Mean observation term was 41 months. 22 patients had occurred incidental fractures, BP gr.: 11 patients, RLX gr.: 2 pts, VD gr.: 9 pts. The incident rate of new fractures at 48 month was 18.0% for BP gr., 17.9%, for RLX gr., and 45.0% for VD gr., relatively. **Conclusions.** RLX was superior to VD and not inferior to BP in prevention of incidental fractures in steroid treated RA patients.

W53-6

Serum Fetuin A and osteoporosis in patients with rheumatoid arthritis

Hiroe Sato^{1,4}, Yoichi Toyoshima¹, Hiroshi Otani¹, Asami Abe¹, Satoshi Ito¹, Hajime Ishikawa¹, Kiyoshi Nakazono¹, Takeshi Kuroda², Masaaki Nakano³, Ichiei Narita⁴, Akira Murasawa¹

¹Department of Rheumatology, Niigata Rheumatic Center, Niigata, Japan, ²Niigata University, Health administration center, Niigata, Japan, ³Niigata University, School of Health Care, Faculty of Medicine, Niigata Japan, ⁴Division of Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

Serum Fetuin A takes part in tissue mineralization by forming complexes with calcium (Ca) and phosphate (P) and it is rich in bone tissue. Fetuin A is negatively correlated to inflammation. We measured serum Fetuin A levels in 193 women with rheumatoid arthritis (RA). Serum Fetuin A levels were positively correlated to age, CRP, ESR, DAS28, MMP-3 and adjusted Ca levels. Bone mineral density, P, hemoglobin, albumin and total cholesterol were negative-

ly correlated to Fetuin A levels. In elderly patients over 70 years old, undercarboxylated osteocalcin (ucOC) was positively correlated to serum Fetuin A levels. Serum Fetuin A levels negatively correlated to the disease activity. In elderly women with RA, Fetuin A levels were positively correlated to ucOC.

W54-1

A retrospective study of pulmonary manifestations in rheumatic diseases

Michi Tanaka^{1,3}, Ryoko Sakai¹, Yukiko Komano^{1,3}, Toshihiro Nanki^{1,3}, Ryuji Koike^{2,3}, Masayoshi Harigai^{1,3}, Nobuyuki Miyasaka³

¹Department of Pharmacovigilance, Graduate School of Medical and Dental Sciences, Tokyo Medical Dental University, Tokyo, Japan, ²Clinical Research Center, Tokyo Medical Dental University Hospital, Tokyo, Japan, ³Department of Medicine and Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical Dental University, Tokyo, Japan

Object: To clarify prognosis of the patients with pulmonary manifestations including interstitial pneumonitis (IP), pulmonary arterial hypertension (PH), pulmonary hemorrhage, pulmonary granulomatosis, and infections, we conducted a retrospective study. **Methods:** We identified patients with RA, SLE, PM/DM, SSc, MCTD, microscopic polyangiitis (MPA), and Wegener's granulomatosis (WG) who had been admitted to the participating hospitals for the treatment of the pulmonary manifestations between 2004 and 2007. **Results & Discussion:** Accumulated 2-year survival rates were 87, 88, and 82% for IP, PH, and pulmonary infections, respectively. More than 90% of the deceased patients had IP (n=45) or pulmonary infections (n=55), indicating poor prognosis of the patients with these complications.

W54-2

Prognosis factors of polymyositis/dermatomyositis with interstitial lung disease

Takashi Kurita¹, Shinsuke Yasuda¹, Kotaro Otomo¹, Yusaku Kanetsuka¹, Michihito Kono¹, Yuka Shimizu¹, Toshio Odani¹, Yuichiro Fujieda¹, Masaru Kato¹, Tetsuya Horita¹, Tatsuya Atsumi¹, Takao Koike¹

¹Department Medicine II, Hokkaido University Graduate School of Medicine, ²Department of Radiology, Hokkaido University Graduate School of Medicine

Background: Interstitial lung disease (ILD) is a serious complication in polymyositis (PM) and dermatomyositis (DM). **Aim:** To clarify the prognosis factors of PM/DM with ILD. **Methods:** We examined 41 PM/DM patients admitted to our hospital for initial treatment in the past 10 years. The primary endpoint of this study was relapse or death. **Prognosis factors** were analyzed retrospectively. **Results:** DM had significantly shorter event free survival as compared with PM (Log-rank; p= 0.047). The frequencies of severe infections were not different in both groups. The multivariate COX regression analysis revealed DM was the independent prognosis factor. No significant correlations were found in sex, smoking, CT findings, age or autoantibody. **Conclusion:** DM was a poor prognosis factor in PM/DM with ILD.

W54-3

Therapeutic response of interstitial pneumonia in myositis or scleroderma

Haruka Tsuchiya, Yuko Takahashi, Hiroyuki Yamashita, Hiroshi Kaneko, Akio Mimori

A chart review over 14 years for 48 patients with progressive IP and PM, DM, amyopathic DM (ADM), or SSc. Patients: 38 patients with myositis (9 PM, 32 DM, and 8 ADM) and 10 with SSc (12 cases). Results: In 26 of the 27 cases that received steroid monotherapy, the patient survived. In the remaining 34 cases, combination therapy with additional cyclosporine (CsA) or tacrolimus (TAC) and/or IVCY was used to treat intractable IP. Steroids+CsA or TAC were effective in 18/26 cases of PM/DM/ADM. Steroids + IVCY were effective in 2/2 cases of SSc. Diffuse alveolar damage developed in 4 ADM patients and in 5 DM patients and was lethal in 7 patients. This non-comparative study suggests the efficacy of adjunctive CsA or TAC therapy for IP in PM/DM and of adjunctive IVCY to treat IP in SSc patients.

W54-4

Outcome of combination therapy with CyA and PSL in DM-A/SIP

Kenichiro Hata, Tohru Takeuchi, Takuya Kotani, Koji Nagai, Shigeki Makino, Toshiaki Hanafusa
Osaka Medical College

Objective: We report outcome of combination therapy with cyclosporine-A (CyA) and prednisolone (PSL) in acute/subacute interstitial pneumonia with dermatomyositis. Methods: Survival rate, laboratory findings for 24 months were assessed in 19 DM-A/SIP patients who were treated with CyA (4mg/kg) and PSL (0.75-1.0mg/kg). Result: Survival rate was 82.4%. The number of death was 3, 2 were aggravation of interstitial pneumonia (IP), one was infection. Recurrence of IP was one. Serum creatinine level 24 months after the therapy was 1.8 times higher than before the therapy. Conclusion: Combination therapy with CyA and PSL is effective in remitting and maintaining DM-A/SIP, but more cases are needed to assess the possibility of decreasing the dose of CyA or changing into other immunosuppressant.

W54-5

Incidences of pulmonary arterial hypertension in connective tissue diseases

Sumiaki Tanaka, Eisuke Ogawa, Kenta Hoshi, Junichi Tanaka, Tatsuhiko Wada, Tatsuo Nagai, Jun Okada, Shunsei Hirohata
Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine

To clarify the incidence of PAH in patients with connective tissue diseases, we performed a prospective study of the 451 patients enrolled from 2006 until 2010. The diagnosis of PAH was performed using ultrasound cardiography, followed by confirmation using heart catheterization. At the enrollment, 8 patients were excluded due to the presence of PAH. Thus 443 patients were followed during 373 person-years, and 5 patients (dcSSc:2, lcSSc:1, SLE 1, MCTD:1) were diagnosed as definite PAH. The incidence of PAH was significantly high in dcSSc (27 per 1000 person-years) and low in SLE (6) than other patients (lcSSc:15, MCTD:12). The incidence of PAH in anti-RNP antibody positive was 11. The data indicate that the incidence of PAH in dcSSc is much higher than that in MCTD and lcSSc.

W54-6

Basic analyses for development of novel therapeutic strategy for PAH

Noritada Yoshikawa^{1,2}, Chikao Morimoto^{1,2}, Hiroto Tanaka^{1,2}

¹Department of Rheumatology and Allergy, Research Hospital, Institute of Medical Science, University of Tokyo, ²Division of Clinical Immunology, ACRC, IMS, University of Tokyo

To further improve the outcome of PAH patients, it may be effective to directly interrupt hypertrophy and irreversible remodeling of right ventricle. Because P-TEFb is the key molecule for development of cardiac hypertrophy and HEXIM1 can inhibit P-TEFb, we developed cardiac muscle-specific HEXIM1 transgenic mice, and which have attenuated hypoxia-induced PAH and RVH. We infected HEXIM1-expressing adenoviruses into cultured cardiomyocytes and revealed that overexpression of HEXIM1 could inhibit endothelin-1-induced hypertrophic cell growth, expression of cardiac hypertrophic genes, and P-TEFb activation and hypoxia-induced HIF1 protein and VEGF mRNA expression. Thus, we speculate that HEXIM1 may be a candidate for preventing RVH with PAH via suppressing several signal cascades.

W55-1

Comparative efficacy in GPI-induced arthritis by imatinib and nilotinib

Naotsugu Akashi^{1,2}, Isao Matsumoto¹, Yoko Tanaka¹, Asuka Inoue¹, Kayo Yamamoto¹, Naoto Umeda¹, Yuki Tanaka¹, Taichi Hayashi¹, Daisuke Goto¹, Takayuki Sumida¹

¹Division of Clinical Immunology, Doctoral Program in Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, ²Translational Sciences Department, Development Division, Novartis Pharma K.K.

[Objective] The present study investigated the effect of imatinib and nilotinib on the GPI-induced arthritis (GIA) mice. [Methods] 1) Immunized mice were treated with each from day 0, 7, 14 after immunization to day 26. 2) Anti-GPI antibody in serum of 1) mice was assayed. 3) Splenocytes on day 3, 7, 14 were cultured with each, and cytokines in supernatant were assayed. 4) Lymph nodes on day 10 were cultured with each to assess cell proliferation. [Results] 1) Imatinib given from day 0 and nilotinib from day 0, 7 suppressed GIA. 2) Imatinib suppressed antibody production. 3) Imatinib inhibited TNF- α , IL-6, IL-17 and IFN- γ production, however nilotinib suppressed only IL-17 and IFN- γ . 4) Imatinib and nilotinib inhibited proliferation of CD4⁺ T cells. [Conclusion] Imatinib and nilotinib prevent GIA.

W55-2

Study results of oral Jak inhibitor tasocitinib in patients with active RA

Yoshiya Tanaka¹, Hisashi Yamanaka², Hiroyuki Nakamura³, Tsutomu Takeuchi⁴

¹The first Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, ²Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, ³Pfizer Japan Inc., Tokyo, Japan, ⁴Division of Rheumatology, School of Medicine, Keio University, Tokyo, Japan

Tasocitinib is a novel, oral JAK inhibitor that is being investigated as a targeted immunomodulator and a DMARD for RA. The dose-response of tasocitinib (1 to 15mg BID, monotherapy) compared to PBO was estimated in pts with active RA and DMARD-IR

by double-blind, placebo-controlled study. Total 317 pts were received at least one dose. The primary endpoint, ACR20 response rates at wk12 were significantly higher for pts who received all tasocitinib doses compared to PBO. The efficacy was rapid and clear dose-dependency was observed. The efficacy was greatest with the 10 and 15 mg BID. The common AEs were nasopharyngitis, hyperlipidaemia and LDL-increased. 15 SAEs in 9 pts were observed. Thus, tasocitinib was well tolerated and efficacious over PBO in patients with active RA despite DMARD.

W55-3

JAK inhibitor, Tasocitinib regulates rheumatoid arthritis by inhibiting Th1/17

Keisuke Maeshima^{1,2}, Kunihiro Yamaoka², Kazuhisa Nakano², Shigeru Iwata², Masanobu Ohishi⁴, Hisaaki Miyahara⁴, Shinya Tanaka³, Kazuyoshi Saito², Koji Ishii¹, Hironobu Yoshimatsu¹, Yoshiya Tanaka²

¹Department of Internal Medicine I, Faculty of Medicine, Oita University, Oita, Japan, ²The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, ³Department of Orthopedic Surgery, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, ⁴Department of Orthopedic Surgery and Rheumatology, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan

Recent clinical studies have proven the effects of JAK inhibitor (CP-690,550;Tasocitinib) in rheumatoid arthritis (RA) patients. However, the exact mechanism remains unclear. We conducted a study utilizing synovial tissue from RA patients. Tasocitinib suppressed IL-17 and IFN- γ production from synovial CD4⁺ T cells without affecting IL-6, IL-8 production. In addition, IL-6 and IL-8 production by RA synovial fibroblasts and CD14⁺ monocytes were not affected. Treatment of a humanized model mouse implanted with RA synovium and cartilage with Tasocitinib decreased serum levels of human IL-6 and IL-8 and suppressed invasion of synovial tissue into cartilage. Our results suggested that the effects of Tasocitinib in RA are mediated through the specific suppression of Th1/17 cells.

W55-4

Decreased IL-17 production in patients treated with a JAK inhibitor

Kunihiro Yamaoka, Satoshi Kubo, Koshiro Sonomoto, Keisuke Maeshima, Koichi Oshita, Shintaro Hirata, Masao Nawata, Kazuyoshi Saito, Yoshiya Tanaka

The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan

Although, JAK inhibitor;tasocitinib is effective on rheumatoid arthritis (RA), mechanism of action is unapparent. CD4⁺ T cells were collected from 9 RA patients at week 0 and 12 with tasocitinib. Relevance between IFN- γ /IL-17 production *in vitro* and clinical outcomes was evaluated. IL-17 was suppressed at week 12 in 8 cases, although there was no certain trend for IFN- γ production. DAS28, CDAI and SDAI improved in all cases, whereas a single case with increased IL-17 shown the least improvement. Previously, we have reported that tasocitinib decreased IL-17 production by synovial CD4⁺ T cells. We have shown here that tasocitinib decreases IL-17 production from peripheral CD4⁺ T cells, suggesting that tasocitinib decrease RA disease activity by inhibiting IL-17 production by CD4⁺ T cells.

W55-5

The role of the JAK/ STAT signaling pathway in rheumatoid synovitis

Kiyoshi Migita, Izumi Yasumori, Taiichiro Miyashita, Takafumi Torigoshi, Satoru Motokawa

NHO Nagasaki Medical Center, Omura, Japan

Objective We investigated the molecular effects of JAK inhibitor on the JAK/STAT signaling pathways in rheumatoid synovitis.

Method Fibroblast-like synoviocytes (FLS) were stimulated with oncostatin M (OSM). Protein phosphorylation of FLS was assessed by Western blot. **Results** OSM was found to be a potent inducer of IL-6 in RA-FLS. OSM stimulation elicited phosphorylation of JAKs and STATs suggesting activation of the JAK/STAT pathway in FLS. CP690,550 completely abrogated the OSM-induced production of IL-6, as well as OSM-induced JAK/STAT activation. **Conclusions** These findings suggest that IL-6-type cytokines contributes to rheumatoid synovitis through activation of the JAK/STAT pathway and Inhibition of these pathways by CP690,550 could be important in the treatment of RA.

W55-6

A new type antiinflammatory drug targetting steroid receptor coactivator

Hirofumi Mitsui^{1,3}, Kazuki Okamoto¹, Manae S. Kurokawa¹, Mitsumi Arito¹, Kouhei Nagai¹, Kazuo Yudo², Moroe Beppu³, Tomohiro Kato¹

¹Dept. of Clin. Proteomics & Mol. Med., St. Marianna Univ. Schl. Med., Kawasaki, Japan, ²Dept. of Front. Med., Inst. of Med. Sci., St. Marianna Univ. Schl. Med., Kawasaki, Japan, ³Dept. of Orthop. Surg., St. Marianna Univ. Schl. Med., Kawasaki, Japan

We found a small nuclear protein (abbreviated as MTI-II), which is a new member of the glucocorticoid-receptor/coactivators complex. MTI-II plays an important role both in hormone action and in anti-inflammation. MTI-II is utilizable as a therapeutic agent for RA. MTI-II is a small protein, therefore it does not move into the cell by itself. To solve this problem, we have constructed a fusion protein of MTI-II with protein transduction domain (H11RM) and examined whether H11RM could have the anti-inflammatory activity *in vitro* and *in vivo*. H11RM successfully penetrated into HeLa cells and inhibited the transactivation activity of NF- κ B in the HeLa cells when H11RM was added to the culture medium. An international patent of this work (PCT/JP2005/011851, Kazuki Okamoto) has been applied.

W56-1

Analysis of postoperative infection in RA patients

Tohgo Nonaka, Fumiaki Nishisaka, Masao Akagi, Kanji Fukuda, Chiaki Hamanishi

Department of Orthopaedic Surgery, Kinki University School of Medicine

We analyzed the postoperative infection in the biological use group and non-use group in RA patients. For

341 RA patients who enforced orthopaedic surgical treatment in this course and divided it into biological use group (67 cases) and non-use group (274 cases), and examined the postoperative complications such as postoperative infection. The case that accepted postoperative, infection in non-use group was 6 cases, but the postoperative infection in the use group was not recognized. However, the wound healing delay was accepted in non-use group by 18 cases,

and it was recognized in 8 cases in the use group. In this study, biological use did not become the risk of the postoperative infection. It will be thought that prospective study including various kinds of factors is necessary.

W56-2

Post operative infection in RA patients with biologics treatment

Ken Sabanai, Hisayoshi Inoue, Makoto Kawasaki, Katsumi Sato
Department of Orthopaedic Surgery, Tohoku Rosai Hospital, Sendai, Japan

〈Background〉 Although there is concern about the postoperative infection by using biologics in the RA patients, it is still unclear. We clarified whether the postoperative infection was related with the use of biologics in RA patients in our hospital. 〈Materials and methods〉 Between Jan. 2007 and Aug. 2010, 19 patients with biologics treatment and 236 patients without biologics treatment were performed surgical treatments. We examined the rate of postoperative infection among the RA patients. 〈Results〉 The postoperative infection was occurred in 3 of 19 patients with biologics treatment, the infection rate was significantly higher than that of the patients without biologics treatment. The symptom of infection in our cases was relieved by the surgical debridement and using antibiotics.

W56-3

A case of infected total knee arthroplasty in a patient treated with etanercept

Itaru Furuichi
National Hospital Organization Ureshino Medical Center, Saga, Japan

We experienced the inflammation case of total knee arthroplasty under etanercept medication. A case was the 70-year-old man of RA under kidney dialysis treatment and etanercept medication. We performed total knee replacement, and it was symptomatic relieve. In six months post-operation, an inflammation view appearance in the left knee following pneumonia, and we accept neutrophilia by joint puncture, and we did debridement immediately. We carried out the remission of the symptomatic, but bacterial proof was not made during progress. When a primary causative organism is not proved, the judgement of "there is another cause which is in a sterile state and causes inflammation" or "although it is bacterial infection, we cannot find bacteria" is very difficult.

W56-4

Deep surgical site infection of lumbar spine after introduction of tocilizumab

Takahiro Makino¹, Hideki Tsuboi¹, Hiroyasu Fujiwara¹, Shosuke Akita², Shiro Ohshima², Kazuo Yonenobu¹

¹Department of Orthopaedic Surgery, National Hospital Organization Osaka Minami Medical Center, Osaka, Japan, ²Department of Rheumatology, National Hospital Organization Osaka Minami Medical Center, Osaka, Japan

A 74-year-old woman with rheumatoid arthritis (RA) underwent lumbar surgery for spinal stenosis. Tocilizumab (TCZ; 400mg, every 4 weeks) was started for treatment against RA after 2 months postoperatively. At 7 months after beginning of TCZ, severe low back pain was occurred. WBC count, fraction of neutrophil, and CRP level slightly increased after the onset of low back pain, however, magnetic resonance imaging revealed pyogenic spondylitis and epidural abscess around operated area. Coagulase-negative staphylo-

coccus was detected at these sites. Because TCZ suppresses systemic inflammatory strongly, it is quite difficult to detect deep surgical site infection (SSI) by laboratory data only. We must take care of SSI in patients treated with TCZ, even if laboratory data is normal.

W56-5

prosthetic infection of TEA in the patients administered the biological agent.

Tsuyoshi Ichinose^{1,2}, Takeo Sakurai^{2,3}, Yasuyuki Tamura², Yoshihiro Yamashina², Takenobu Iso³, Koichi Okamura¹, Yukio Yonemoto¹, Hiroshi Inoue^{2,3}, Kenji Takagishi¹

¹Department of Orthopaedic Surgery, Gunma University Graduate School of Medicine, ²Inoue Hospital, ³Gunma RA Clinic

We report the prosthetic infection in the patients administered the biological agent.

Sixty-three years old woman and 71 years old woman administered the etanercept were operated the total elbow arthroplasty in 2005, 2009 respectively. The swelling and tenderness of the operated elbow appeared without trauma. We diagnosed them with prosthetic infection. The antibiotic drug was administered in both cases. After the treatment, the symptoms were improved and the etanercept was administered again in one case, remission has not been observed. There were a few reports regarding the prosthetic infection in the patients administered the biological agent. The clinical courses of our patients suggest that the exclusion of these patients is not necessary for the administration of the biological agent.

W56-6

TEA for RA after the Infectious Open-wound with a Mutilans Deformity

Osami Suzuki, Tomoyuki Nakasa, Mitsuo Ochi
Department of Orthopaedic Surgery, Hiroshima University

A sixty-one years old woman, who has rheumatoid arthritis for 30 years, had a spontaneous open-wound around the right elbow joint. The roentgenogram revealed a mutilans deformity and the lateral epicondyle of the humerus penetrated the wound. At the first operation, debridement and temporally wire fixation were performed to suppress the infection. Seven months later, she underwent a total elbow arthroplasty using a linked type prosthesis at the second operation. Two months later, irrigation and resuture of the wound was carried out at the third operation because the wound closing had been delayed. Although a reconstruction using some implants after an infection of the joint should be undertaken with caution, it is useful to improve a function.

W57-1

The role of angiotensin II (Ang II) on lymphocytes from SLE patients

Yumi Tajima, Kyohei Nakamura, Ryu Watanabe, Tsuyoshi Shirai, Hiroshi Fujii, Naruhiko Takasawa, Tomonori Ishii, Hideo Harigae
Division of Hematology and Rheumatology, Tohoku University Graduate School of Medicine

(Purpose) We evaluate the role of Ang II on human lymphocytes.

(Method) Peripheral blood mononuclear cells (PBMCs) were obtained from SLE and healthy subjects. The expression of angiotensin II type 1 receptors (AT1Rs) and the influence of Ang II on the differentiation and apoptosis of PBMCs was examined by flow cytometry and immunoblot.

(Result) AT1Rs were expressed on B, NK cells and monocytes in healthy subjects. AT1Rs on T cells were expressed by anti-CD3 stimulation. The apoptosis of T cells was inhibited but the differentiation of B and T cells was not affected by Ang II. The expression of AT1Rs on B, NK cells and monocytes was significantly low in SLE.

(Conclusion) We demonstrated that Ang II might be functional in lymphocytes and play a pathophysiological role in SLE.

W57-2

Association between CD4, CD8 T cell and pathogenesis of SLE induced by IFN α

Eriko Honda¹, Yuko Hirohata¹, Shunichi Shiozawa^{1,2,3}

¹Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan, ²Department of Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, ³The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

OBJECTIVE: We have shown that IFN α transgenic mice (IFN α Tg) induces the production of dsDNA antibody and renal diseases akin to human SLE. In these mice, activated CD4 and CD8 T cells were dominant in spleen. We investigated the contribution of T cells to the pathogenesis of SLE.

METHODS: Anti CD4 and CD8 antibodies were injected in IFN α Tg. Autoantibodies and serum immune complex (IC) were measured. Splenic lymphocytes were examined under flow cytometry and kidney lesions were evaluated.

RESULTS: Anti CD4 antibody treatment decreased anti ds-DNA antibody and IC in sera, memory CD8 T cell was also significantly decreased. Alopecia were ameliorated either by anti CD4 or anti CD8 antibody treatment.

CONCLUSION: Activated CD4 T cell induces both autoantibodies and IC-mediated glomerulonephritis.

W57-3

High expression of BCMA on autoantibody producing RP105-negative B cells in SLE

Syuichi Koarada, Yoshifumi Tada, Hisako Inoue, Rie Suematsu, Sachiko Soejima, Akihito Ohta, Kohei Nagasawa
Division of Rheumatology, Saga University

RP105(-) B cells produce autoantibodies in SLE. The phenotype of the cells were investigated. RP105(-) B cells from SLE patients were activated 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 rheumatic diseases. sCD40L induced cell death in both RP105(-) and (+) B cells in vitro. Whereas RP105(+) B cells were not rescued from cell death by BAFF/APRIL, which, however, maintained survival of RP105(-) B cells. In vitro activation with sCD40L and BAFF resulted in reduction of BAFF-R and increase of BCMA expression on RP105(-) B cells. The results suggest that RP105(-) B cells are possibly regulated by BCMA and BAFF/APRIL.

W57-4

Identification of IL-21 production in peripheral blood of patients with SLE

Mizuho Suzuki, Taichi Hayashi, Isao Matsumoto, Takayuki Sumida

Division of Clinical Immunology, Doctoral Program in Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba.

OBJECTIVE: To clarify the pathogenesis of systemic lupus erythematosus (SLE), we examined IL-21 production and its producing cells in the peripheral blood mononuclear cells (PBMCs) of SLE patients. **METHODS:** PBMCs were obtained from 10 patients with SLE and 10 healthy subjects (HS). 1) After isolation of CD4⁺ T cells, IL-21 mRNA production was quantified by RT-PCR. 2) IL-21 producing cells in the PBMC such as CD4⁺ ICOS^{high} CXCR5⁺ cells were quantified by FACS analysis. **RESULTS:** In PBMCs, 1) IL-21 mRNA expressions in CD4⁺ T cells of SLE patients were higher than those of HS. 2) CD4⁺ ICOS^{high} CXCR5⁺ cells were increased in SLE patients. **CONCLUSION:** The increase production of IL-21 in peripheral blood T cells of SLE patients possibly affect to the generation of SLE.

W57-5

Demethylation of *CD40L* promoter in autoantibody-inducing CD4⁺ T cell

Toshiyuki Haruna¹, Ken Tsumiyama¹, Shunichi Shiozawa^{1,2,3}

¹Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan, ²Department of Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, ³The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

Objective: Our 'self-organized criticality theory' explains that generation of autoantibody-inducing CD4⁺ (*ai*CD4⁺) T cell is the key for SLE. Here we investigated the methylation status of the *CD40L* gene promoter in the *ai*CD4⁺ T cell.

Methods: Genomic DNA was isolated from CD4⁺ T cell of the mice immunized 12x with ovalbumin (OVA). The methylation status of the CpG motifs in the *CD40L* promoter region was analyzed by using bisulfite sequencing.

Results: The CpG motifs in the *CD40L* promoter was significantly demethylated in CD4⁺ T cell of the mice immunized 12x with OVA as compared with those of control mice.

Conclusion: The result suggests that the demethylation of *CD40L* promoter in *ai*CD4⁺ T cell contributes to the pathogenesis of SLE.

W57-6

The help of autoantibody-inducing CD4⁺ T cell and cross-presentation cause SLE

Yumi Miyazaki¹, Ken Tsumiyama¹, Shunichi Shiozawa^{1,2,3}

¹Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan, ²Department of Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, ³The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

Objective: Our 'self-organized criticality theory' shows that the generation of autoantibody-inducing CD4⁺ (*ai*CD4⁺) T cell is the key for the cause of SLE. Here we investigated the contribution of *ai*CD4⁺ T cell-help and antigen cross-presentation to the induction of lupus kidney disease. **Methods:** We transferred pre-mature CD8⁺ T cell of the mice immunized 8x with OVA into the mice immunized 12x with KLH. These recipients were immunized 1x with OVA and KLH, followed by treating with chloroquine to inhibit cross-presentation. **Results:** When cross-presentation was inhibited, both IFN γ ⁺CD8⁺ T cell and proteinuria were decreased. **Conclusion:** The *ai*CD4⁺ T cell-help and antigen cross-presentation are

sine qua non for the generation of CTL and subsequent lupus kidney disease.

W58-1

Interferon α causes SLE by expanding CD3⁺ CD4⁻ CD8⁻ double negative T cell

Eriko Honda¹, Chieri Akiyama¹, Akira Hashiramoto^{1,2,3}, Shunichi Shiozawa^{1,2,3}

¹Department of Biophysics, Graduate School of Health Science, Kobe University, Kobe, Japan, ²Department of Medicine, Graduate School of Medicine, Kobe University, Kobe, Japan, ³The Center for Rheumatic Disease, Kobe University Hospital, Kobe, Japan

OBJECTIVE; We have shown that IFN α transgenic mice (IFN α Tg) induces production of anti-dsDNA antibody and renal diseases akin to human SLE. In these mice, activated effector T cells were dominant in spleen. We here investigated T cell subsets contributing to the pathogenesis of SLE.

METHODS; Lymphocytes isolated from kidneys of IFN α Tg were examined under flow cytometry and infiltration of lymphocytes to glomerulus by immunohistochemistry.

RESULTS; Active CD4⁻ CD8⁻ double negative (DN) T cell of IFN α Tg infiltrated to glomerular lesions. Furthermore, DN T cell induced *de novo* glomerulonephritis when transferred into naïve recipients.

CONCLUSION; The DN T cells increased by IFN α cause IC-mediated glomerulonephritis in murine SLE.

W58-2

Expression and role of IRAK in B cells of normal subjects and SLE patients

Hiroaki Niiri¹, Siamak Jabbarzadeh-Tabrizi¹, Shun-ichiro Ota¹, Kumiko Noda¹, Naoyasu Ueda¹, Atsushi Tanaka¹, Kentaro To¹, Yasushi Inoue¹, Yojiro Arinobu², Hiroshi Tsukamoto¹, Takahiko Horiuchi¹, Koichi Akashi¹

¹Department of Clinical Immunology, Rheumatology, and Infectious Diseases, Kyushu University Hospital, Fukuoka, Japan, ²Center for Cellular and Molecular Medicine, Kyushu University Hospital, Fukuoka, Japan

TLR signaling potentially leads to T-cell-independent breakdown of B cell tolerance that is closely related to the development of autoimmunity. IRAK-1 and IRAK-3 regulate TLR signaling in non-B cells positively and negatively, respectively. We here demonstrate that in the absence of stimuli, IRAK-3 was exclusively expressed in naïve B cells, while IRAK-1 was expressed in both naïve and memory B cells. Of note, BCR stimulation significantly downregulated IRAK-3 expression by a calcium-dependent mechanism, while it up-regulated IRAK-1 expression in B cells. IRAK-3 knockdown augmented TLR-induced activation in B cells. IRAK expression was altered in SLE B cells. These results suggest that the balance of IRAK-1 and IRAK-3 expression is critical for maintenance of B cell tolerance in humans.

W58-3

Study on the genetic background in the induction of SLE

Manabu Izumikawa¹, Ken Tsumiyama¹, Shunichi Shiozawa^{1,2,3}

¹Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan, ²Department of Medicine, Kobe Uni-

versity Graduate School of Medicine, Kobe, Japan, ³The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

Objective: Our 'self-organized criticality theory' explains that generation of autoantibody-inducing CD4⁺ (*ai*CD4⁺) T cell is the key for SLE; *ai*CD4⁺ T cell induces autoantibodies and CTL and tissue injuries. Here we examined the contributing genetic background to this theory.

Methods: BALB/c and C57BL/6 mice were immunized 12x with OVA. Autoantibodies, IFN γ -producing CD8⁺ T cell in spleen and proteinuria were examined.

Results: Upon repeated immunization with OVA, autoantibodies were induced in both BALB/c and C57BL/6 mice. Further, IFN γ -producing CD8⁺ T cell and proteinuria were equally increased in both mice.

Conclusion: Regardless of genetic background, SLE is caused when host's immune 'system' is over-stimulated to levels that surpass system's self-organized criticality.

W58-4

The genomic and epigenomic analysis in monozygotic twin discordance in SLE

Hiroshi Furukawa¹, Toshihiro Matsui², Hisanori Nakayama², Kota Shimada², Tatsuoh Ikenaka³, Akiko Komiya⁴, Hirokazu Takaoka², Hidekazu Futami², Naoyuki Tsuchiya⁴, Shigeto Tohma¹

¹Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami National Hospital, National Hospital Organization, ²Department of Rheumatology, Sagami National Hospital, National Hospital Organization, ³Department of Rehabilitation, Sagami National Hospital, National Hospital Organization, ⁴Molecular and Genetic Epidemiology Laboratory, Doctoral Program in Life System Medical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba

The genomic and epigenomic analyses in monozygotic twin discordance in systemic lupus erythematosus (SLE) were performed to find genes playing important roles in the pathogenesis of SLE. SNP and CNV typing was done in the twin using illumina 610Q. Discordances of SNP and CNV were observed in 35 SNPs and 5 CNVs (985kb). CpG methylation and gene expression were also analyzed with illuminaHM27 and Agilent whole genome 4X44K, respectively. CpG methylation levels were different more than 15% in 123 genes. Gene expression levels were different more than 2 folds in 758 genes. Both of CpG methylation and gene expression levels were different in 11 genes that could be candidate genes playing important roles in the pathogenesis of SLE.

W58-5

Association of HLA-DRB1 with SLE-susceptibility and sub-phenotype in Japanese

Kenichi Shimane^{1,2}, Yuta Kochi², Naoyuki Kamatani³, Ryo Yamada^{2,4}, Kazuhiko Yamamoto^{1,2}

¹Department of Allergy and Rheumatology, the University of Tokyo Hospital, Tokyo, Japan, ²Laboratory for Autoimmune Diseases, Center for Genomic Medicine, Institute of Physical Chemical Research (CGM, RIKEN), Tokyo, Japan, ³CGM, RIKEN, Yokohama, Japan, ⁴Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan, ⁵Human Genome Center, Institute of Medical Science, the university of Tokyo, Tokyo, Japan

Objective: To examine role of HLA-DRB1 in SLE-susceptibility and sub-phenotype in Japanese.

Methods: We genotyped HLA-DRB1 for 656 SLE patients and 911 controls by using WAKFlow kit. We tested associations of DRB1 with SLE-susceptibility and sub-phenotype by χ^2 tests. We performed k-means analysis to cluster the patients by autoantibody status.

Results: We identified DRB1*1501, *0901, *0802 and *0401 as SLE susceptibility alleles. The heterozygote DRB1*0901/*1501 conferred increased risk for SLE, the early onset and incidence of proliferative glomerulonephritis. In the cluster analysis, DRB1*0901 was associated with the subgroup characterized by higher positive rate of anti-Sm antibody.

Conclusion: Multiple DRB1 alleles confer risk of SLE and may affect the sub-phenotype in Japanese.

W58-6

Independent association of *MTMR6-C8orf12* and *FAM167A-BLK* with SLE in Japanese.

Naoyuki Tsuchiya¹, Ikue Ito¹, Yuya Kondo², Taichi Hayashi², Isao Matsumoto², Takayuki Sumida², Satoshi Ito^{2,3}, Makio Kusaoi⁴, Yoshinari Takasaki⁴, Hiroshi Hashimoto⁵, Keigo Setoguchi⁶, Tatsuo Nagai⁷, Shunsei Hirohata⁷, Hiroshi Furukawa⁸, Shigeto Tohma⁸

¹Doctoral Program in Life System Medical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan, ²Doctoral Program in Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan, ³Department of Rheumatology, Niigata Rheumatic Center, Shibata, Japan., ⁴Department of Internal Medicine and Rheumatology, Juntendo University, Tokyo, Japan., ⁵School of Medicine, Juntendo University, ⁶Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan., ⁷Department of Rheumatology and Infectious Disease, Kitasato University School of Medicine, Sagami-hara, Japan, ⁸Clinical Research Center for Allergy and Rheumatology, National Hospital Organization, Sagami-hara National Hospital, Sagami-hara, Japan.

Objective: *FAM167A-BLK* region is associated with SLE in Japanese. *XKR6* and *C8orf12*, also located in 8p23.1, have been associated in Caucasians. Here we examined whether these genes independently contribute to SLE.

Methods: A case-control study was performed on 31 tagSNPs encompassing *MTMR9-BLK* as well as 2 SNPs in *XKR6* previously associated in Caucasians.

Results: *MTMR9-C8orf12* region showed independent association. In contrast, *XKR6* was not associated. *XKR6* SNPs were in moderate linkage disequilibrium (LD) with *BLK* in Caucasians, but the LD was weak in Japanese.

Conclusion: In 8p23.1, two independent genetic effects, one in *FAM167A-BLK* and the other in *MTMR9-C8orf12*, are present in Japanese. The association of *XKR6* in Caucasians might be caused by LD with the causative allele in *BLK*.

W59-1

Chronotherapy with methotrexate in RA patients

Hideto To¹, Hiroaki Ida², Emi Sonemoto³, Sasaki Hitoshi¹, Yukitaka Ueki³, Katsumi Eguchi⁴

¹Department of Hospital Pharmacy, Nagasaki University Hospital, ²Division of Respiriology, Neurology, and Rheumatology, Department of Medicine, Kurume University School of Medicine, ³Sasebo Chuo Hospital, Center for Rheumatic disease, ⁴Sasebo City General Hospital

Purpose: In order to prove the utility of chronotherapy, we studied the dosing time-dependent effects of methotrexate (MTX) in

rheumatoid arthritis (RA) patients. **Patient and Methods:** MTX was administered once a day at bedtime to Japanese RA patients to estimate DAS28, MHAQ, and adverse effects. **Results and Conclusion:** The DAS 28 was significantly improved at all observed points compared with the baseline after chronotherapy, and 23.5% of patients attained clinical remission for 3 months. The MHAQ was markedly decreased by 3 months chronotherapy. In this study, there were no severe adverse effects. Choosing an optimal dosing time that is associated with the 24 hour rhythms of RA symptoms is therefore expected to lead to effective MTX therapy for RA.

W59-2

The Low-dose MTX therapy ~ efficacy and pharmacokinetics

Yoshinobu Koyama¹, Takeshi Kawaguchi¹, Toshiyuki Ota², Ayumi Uchino¹

¹Center for Rheumatic Diseases, Iizuka Hospital, Fukuoka, Japan,

²Department of Laboratory and Transfusion Medicine, University of Occupational and Environmental Health, Fukuoka, Japan

[Purpose] To re-verify the efficacy of low-dose MTX treatment, and analyze the pharmacokinetics.

[Method] The persistence and remission rate after 12M of low-dose MTX therapy in 131 RA pts (DAS \geq 3.6) were calculated. The significant factors that correlate with AUC were also evaluated.

[Result] The persistence rate after 12M was 53%, the average dose was 6.7mg/wk, and the remission rate for DAS28-ESR/CRP was 15.3%/36.1%. Among a BSA, Cre, and cystatin C, eGFR (BSA corrected / uncorrected), and CCr, the eGFR (uncorrected) was the most significant factor that correlated with AUC. On the other hand, serum Cre was not reach to significance.

[Discussion] Increasing the dose of MTX more than 8mg/wk is not always necessary. The maximum dose should be considered with evaluating eGFR (uncorrected).

W59-3

The effect of an escalating dose of MTX on RA relapsing after one of biologics

Katsunori Ohnishi

Ohnishi Internal Medicine and Rheumatology Clinic

Biologics are good candidates inducing remission of RA. MTX is a counterpart of biologics as well as an anchor DMARD, the effect of which is dose-dependent. Restriction of dose, however, has not been considered beneficial both to RA patients and rheumatologists in Japan. The analysis was performed to evaluate the effect of an escalating dose of MTX on RA relapsed after temporarily responded by one of biologics with EULAR criteria. More than 8mg/week of MTX reduced DAS28ESR from 3.78 to 2.93, DAS28CRP from 3.30 to 2.48. The numbers of tender and swollen joints were improved from 2.00 to 0.92 and from 2.77 to 1.92, respectively. The level of ESR and CRP were from 30.2mm/hr. to 18.6 and from 1.18mg/dl to 0.48. The score of mHAQ was brought to 1.18 at the end of the observation from 0.51.

W59-4

The incidence of MTX lymphoproliferative disorders in RA patients

Yuji Yoshida, Yuko Takahashi, Hiroyuki Yamashita, Hiroshi Kaneko, Akio Mimori

The incidence of methotrexate lymphoproliferative disorders (MTX-LPD) in RA patients was estimated. Patients: Our complete database of 586 RA patients registered between 1990 and 2010 was used. Result: 403 patients had received MTX, with administration totaling 2379 person-years. 4 patients developed MTX-LPD during the observation period (2 diffuse large B-cell, 1 Hodgkin, and 1 T-cell type). The incidence of MTX-LPD was 0.00168/year. The mean MTX dose was 7.4 ± 1.9 mg/week, for a total of 1142 ± 871 mg per patient. After MTX withdrawal, spontaneous tumor regression was seen in one patient, and transient regression and relapse in another, with the latter requiring chemotherapy. The incidence of lymphoma in RA patients who received MTX was 9.9 times higher than that in the general population.

W59-5

Safety of high dose MTX 10mg-32mg/w for Japanese RA patients

Fujio Amamoto¹, Yasuhito Takita²

¹Jiyugaoka Orthopedics, ²Shonan Kamakura Joint Reconstruction Center

To investigate the safety of high dose MTX (10mg-32mg/w) for Japanese patients, we conducted a retrospective chart review study of 1084 RA patients on MTX (median age 54 [18-90]).

Distribution of MTX dose were ≤ 8 mg/wk (Gr A) 17%, 10-16mg/wk 70% (Gr B), and >17.5 mg/wk 13% (Gr C).

36 % had dose reduction due to remission or improve 15%, adverse events 16%:(liver dysfunction 7%,gastrointestinal tract disorder 3%, malaise 2%, stomatitis 1%, hair loss 1% others 1%) and others 5%.

In Gr B+C, frequency of liver dysfunction was relatively high, however, most were manageable with dose reduction. 56 % were given in combination with biological agent. Clinical remission was seen in 52% (Gr A: 45%, B 54%, C 48%).

High dose MTX for Japanese RA patients was safe and effective in our clinic.

W60-1

Utility of tacrolimus serum concentration in rheumatoid arthritis

Hajime Owaki¹, Masataka Nishikawa², Takeshi Fuji²

¹Department of Rheumatic Diseases, Osaka Koseinenkin Hospital, Osaka, Japan, ²Department of Orthopaedics, Osaka Koseinenkin Hospital, Osaka, Japan

Purpose: To investigate the relationship of tacrolimus (TAC) serum concentration and its effectiveness in rheumatoid arthritis (RA). Method: 457 RA cases given TAC for more than 24 weeks were tested. Until 52 weeks from the beginning of TAC, the cases have more than 24 weeks of consistent TAC dosage were selected. Consistent dosage of 1mg TAC was given in 60 cases, and 50 cases for 1.5mg. Ratio of serum MMP-3 at TAC start and after 24 weeks consistent dosage given was calculated and simple regression analysis was done with TAC serum concentration. Result: P-value of the analysis was 0.013. Conclusion: TAC serum concentration was seemed to be important for the clinical use.

W60-2

Radiographic efficacy of tacrolimus for patients with rheumatoid arthritis

Hiraku Motomura, Isao Matsushita, Eiko Seki, Tomoatsu Kimura
Department of Orthopaedic Surgery, Faculty of Medicine, University of Toyama

Objective: To assess the radiographic efficacy of tacrolimus for patients with rheumatoid arthritis (RA). Methods: We enrolled 23 patients with RA who showed an insufficient response to other DMARDs. Joint destruction was assessed using the modified total sharp score (mTSS) at baseline and at 1 year of tacrolimus therapy. Clinical response were evaluated by EULAR criteria. Results: Nineteen patients (82.6 %) were evaluated as having a moderate or good response at 1 year after tacrolimus therapy. The mean value of the estimated yearly progression rate of mTSS at baseline was 11.8, while the mean value of Δ mTSS was 2.6 at 1 year of tacrolimus therapy. Conclusion: Our results suggest that tacrolimus therapy appears to be efficacious in suppressing the progression of joint damage.

W60-3

The long-term efficacy and safety of tacrolimus therapy in patients with RA

Syota Sakaguchi, Kazuyoshi Kubo, Toshihiko Hidaka, Hiroshi Kuroda

Institution of Rheumatology, Zenjinkai Shimin-no-Mori Hospital

We assessed the long-term efficacy and safety of tacrolimus in patients with rheumatoid arthritis. One hundred and twenty drug-resistant RA patients were administered tacrolimus. Over the 24 and 52-week treatment period using LOCF method, we evaluated responses to tacrolimus therapy based on disease activity score (DAS) 28. The mean levels of DAS28 decreased from 5.42 to 4.41 (24 weeks, $p < 0.001$) and 3.71 (52 weeks, $p < 0.001$). Based on the EULAR response criteria, 69% and 82% of patients exhibited better than a moderate response to therapy after 24 and 52 weeks, respectively. Although mild adverse were encountered in 59 of 120 patients (49%), no severe adverse reactions were reported. These data indicate that long-term tacrolimus therapy is safe and clinically effective for RA.

W60-4

Tacrolimus in NinJa 2009

Toshihiro Matsui^{1,3}, Shigeto Tohma^{2,3}

¹Department of Rheumatology, Sagami National Hospital, National Hospital Organization, Kanagawa, Japan, ²Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami National Hospital, National Hospital Organization, Kanagawa, Japan, ³iR-net

[Aim & Methods]Using data of NinJa 2009, we evaluated the use of Tacrolimus (TAC) in patients with RA. [Results] Among 7085 patients, 517 patients (7.3%) were under the treatment with TAC. Among them, 304 patients (58.8%) were treated with TAC in combination with other DMARDs including biologics (TAC-comb group). MTX were used most frequently as a DMARD in combination with TAC (41.8%) following biologics 16.4% (ETN 68.2%, IFX 2.4%, ADA 9.4%, TCZ 20.0%), SASP 9.5%, and BUC 4.3%. Mean dosage of TAC was 2.03mg/d in TAC-mono group and 1.66mg/d in TAC-comb group, respectively. Mean value of DAS28-ESR was comparable between the two groups (mono 3.90 vs comb

3.86). Mean dosage of TAC (1.34mg/d) in patients taking MTX (>8mg/w) was significantly lower than in those (1.69mg/d) taking MTX (\leq 8mg/w).

W61-1

Remission maintenance in RA patients treated with ETN, focusing on cost

Makoto Nishinarita

Nishinarita Clinic, Ibaraki, Japan

Subjects 26 etanercept (ETN) treated RA pts w/ moderate to high disease activity (DA), who met remission criteria (DAS28/ESR <2.6), & were able to maintain \leq low DA. **Pts' Background** 24 women & 2 men w/ mean age of 51.7 yo; mean RA duration 80.0 mths; 20 pts in Stage I/II & 6 pts in III/IV. **Results** 1) Mean observation period before remission was 67.2 wks. Mean weekly ETN dose 45.9 mg changed to 38.8 mg after remission; cost cut of 4,347 yen/w. 2) 15 pts (57.7%) maintained remission w/ mean reduced dose of 33.1 mg/w; cost cut of about 10000 yen/w vs. full dose. 3) Remission maintenance cost was cut by about 7,000 yen/w compared to mean cost before reaching remission. 4) 11 pts on unchanged ETN doses after remission tended to have lower baseline serum MMP3 compared to pts on reduced ETN doses.

W61-2

One-year outcome in patients who achieved etanercept (ETN)-free remission

Yukitomo Urata¹, Ryoko Uesato¹, Dai Tanaka¹, Kenji Kowatari¹, Yoshihide Nakamura², Taisuke Nitobe¹

¹Seihoku Chuo Hospital, Aomori, Japan, ²Department of Rehabilitation, Hirosaki University Hospital

Objective We examined 1-year outcome of RA pts achieving clinical remission via ETN & discontinuing thereafter. **Methods** Calculated 1-yr data: relapse rate; total sharp score w/ modified van der heijde, mHAQ, structural (DTSS \leq 0.5) & functional (mHAQ <0.5) remission rate in maintained remission vs. relapsed; ETN-resumed pts were included as relapsed. **Results** 14 ETN-free pts & 5 (35.7%) post 1-yr relapsed pts. Mean DAS, mHAQ & TSS at 1-yr in maintained remission vs. relapsed were 2.02, 0.08, -2.40 vs. 3.51, 0.41, 0.86; structural & functional remission, 88.8%, 66.7% vs. 40%, 40%, respectively. **Conclusion** Some pts maintained clinical, structural & functional remission even after ETN discontinuation. Even if relapsed, remission recurred w/ DA monitoring, adequate treatment after discontinuation.

W61-3

Four ETN-tightly controlled cases with ETN-free remission for more than 6 months

Keio Ayabe, Takumi Wakisaka, Muneo Aoyagi, Sachiko Itoi, Hiromi Kameda, Keiko Sonobe

keiyu Orthopedic Hospital, Gunma, Japan

Since introduction of biologics, the goal for practical RA treatment is to achieve remission by tight control & nowadays bio-free remission is being drawn attention. We report on 4 pts maintaining remission after etanercept (ETN) discontinuation that suggest importance of tight control, & also on the ETN usage in our site. Although no consensus is reached on what is correlated w/ bio-free remission, we define ETN discontinuation criteria as having not exceeding normal CRP, ESR & MMP-3 ranges for \geq 0.5 year & normal RAHA. 4 pts met this criteria and achieved clinical remission

(DAS28CRP <2.32), discontinued ETN, & currently maintain remission with ETN-free status continuing for 6 mths to 1y + 10 mths.

Discussion Data suggests that ETN-free remission is possible by maintaining tight control.

W61-4

Remission maintenance and bio-free status by tapering ETN dose (Update report)

Hiroshi Yokoyama

Yokoyama orthopedics department

Objective We examined the possibility of remission maintenance and bio-free status by tapering etanercept (ETN) in ETN-responsive patients (pts). **Methods** 21 pts who started ETN at 50 mg/w; those at DAS28 improvement, absence of joint swelling & X-ray finding of no progressive joint destruction had ETN tapered to 25 mg/w, then 25 mg/2 wks. ETN was further tapered in pts in whom clinical remission maintained for about half year with 25 mg/2 wks and synovitis nearly resolved on contrast MRI. Pts w/out relapse of joint swelling/pain with 25 mg/4 wks were considered ETN-free. **Results** ETN was tapered in 16 of 21 pts; bio-free status was achieved in 2 and under consideration in 1. **Discussion** Some ETN-responsive pts could maintain remission after tapering ETN, suggesting the possibility of bio-free

W61-5

Study of RA patients' background that affect ETN treatment remission rate (RR)

Toshihiko Hidaka¹, Kazuyoshi Kubo¹, Shota Sakaguchi¹, Hiroshi Kuroda¹, Kunihiro Umekita², Akihiko Okayama²

¹Institution of Rheumatology, Zenjinkai Shimin-no-Mori Hospital, ²Internal Medicine, Department of Rheumatology, Infectious diseases and Laboratory medicine, University of Miyazaki

Objective We examined whether RR of etanercept (ETN) treatment have correlation with patients' (pts') background or not. **Subjects and Methods** Our 108 RA pts (19 men, 87 women) receiving ETN; rate of pts with DAS28ESR <2.6 (RR) at 1 year (y) treatment, using LOCF method was compared by background: 1) with/without concomitant MTX, 2) stage, 3) RA duration, 4) age and 5) HAQ. **Results** DAS28ESR significantly improved from 5.64 ± 1.23 baseline to 3.55 ± 1.27 at 1 y ($p < 0.001$) with RR of 28%. RR by background: 1) with MTX 43%, without MTX 16% ($p < 0.01$); 2) stage I/II 38%, III/IV 21% ($p < 0.1$); 3) RA <5 ys 40%, \geq ys 21% ($p < 0.1$); 4) <65 yo 36%, \geq 65 yo 18% ($p < 0.1$); 5) HAQ ≤ 0.5 56%, ≥ 0.5 15% ($p < 0.001$). **Conclusion** Initiation of concomitant MTX with ETN while pts having low HAQ can lead to increase in RR.

W62-1

Analysis of serum MMP-3 in rheumatoid arthritis treated by etanercept therapy.

Yuji Yamanishi¹, Masanori Kawashima²

¹Hiroshima Rheumatology Clinic, ²Department of Rheumatology, Hiroshima City Hospital, Hiroshima, Japan

Objective: To analyze relationships between serum MMP-3 and disease activity, and predict clinical response to etanercept (ETN) in patients with rheumatoid arthritis (RA). **Methods:** Serum MMP-3 and disease activity score (DAS28-ESR) were evaluated in 117 females with RA treated by ETN. **Results:** Pretreatment MMP-3 levels were elevated in approximately 90% of patients. Most patients with

high MMP-3 levels ($300 \leq \text{ng/ml}$) were defined as having high disease activity. Patients with normal MMP-3 showed moderate or high disease activity and demonstrated not only small but also large joint arthritis. Low levels of MMP-3 before treatment predicted a higher remission rate at week 24. Conclusion: MMP-3 is useful to evaluate disease activity and roughly predict induction of remission in RA.

W62-2

Efficacy of Etanercept therapy in rheumatoid arthritis patients

Naooki Katsuyama¹, Takahito Kimata¹, Masaomi Yamasaki¹, Shoichi Ozaki²

¹Division of Rheumatology, Yokohama City Seibu Hospital, St.Marianna University School of Medicine, ²Division of Rheumatology and allergy, St.Marianna University School of Medicine

Objective: We analyzed whether low dose Etanercept therapy (ETA) respond to RA patients. We defined low dose ETA therapy that administrated less than 25mg/week. **Method:** 35 (5men, 30women) of RA patients treated with ETA at our clinics. 32 patients treated with low dose ETA. 2 patients treated with regular dose, more than 25mg/week of ETN. 26 patients were treated with MTX. We evaluated efficacy with DAS28 CRP. **Result:** The continuance rate was 80.0%. 18 patients (51.4%) achieved remission. 17 of the 18 patients treated with low dose ETA. There is no difference between low dose and regular dose of ETN. 7 patients discontinued the treatment, because of 3 interstitial pneumonia, 1 infection and ineffectiveness of ETN in 3 patients. **Conclusion:** Low dose ETA therapy was effective of RA patients.

W62-3

Early-stage efficacy of etanercept may predict mid-stage therapeutic outcomes

Yuji Kishimoto¹, Toshiyuki Dokai¹, Yoshihiro Kato¹, Toru Okano¹, Hiroshi Hagino², Ryota Teshima¹

¹Department of Orthopaedic Surgery, Faculty of Medicine, Tottori University, Tottori, Japan, ²Faculty of Health Science, Tottori University, Tottori, Japan

[Objective] To evaluate the utility of early-stage outcomes of etanercept to predict mid-stage efficacy in RA. **[Methods]** Efficacy at 1, 3 and 12 months (Mo) was evaluated in 56 patients with RA. We calculated the Odds ratios (ORs) and compared outcomes at early-stage (1, 3 Mo) and mid-stage (12 Mo) in "ineffective (IE)" and "effective (E)" groups, and in "good response (GR)" and "incomplete response (IR)" groups. **[Results]** When IE at 12 Mo was set as the outcome, ORs for IE vs. E at 1 Mo and 3 Mo were 17.0 (95% CI: 3.2–90.6) and 23.4 (4.7–116.4), respectively. IE at both 1 and 3 Mo was 15.2 (2.69–57.1). When GR at 12 Mo was set as the outcome, OR for GR vs. IR at 3 Mo was 10.6 (2.3–48.5). **[Discussion]** The early-stage response may predict the mid-stage treatment efficacy.

W62-4

Efficacy and remission rate of etanercept therapy in patients with RA

Tadamasa Hanyu¹, Takako Saeki², Tomoyuki Ito², Hiroshige Sano¹

¹Japanese Red Cross Nagaoka Hospital, Nagaoka, Japan, ²Department of Nephrology and Collagen Disease, Japanese Red Cross Hospital, Nagaoka, Japan

Objective & Methods: Efficacy, safety profiles, continuance and remission rate of etanercept (ETN) were assessed, in 80 RA patients

(female 73%, mean age 53 y.o., duration 7 years, baseline DAS28ESR 5.4, switching from infliximab 4 cases, PSL user 49 cases, MTX user 69 cases), introduced before September 2008. **Results:** The main causes for withdrawal of ETN (n=13) were inefficacy and adverse events. Survival rate of ETN was 74% in 5 years. PSL doses could decrease in 37 cases (75%), and discontinue in 12 cases. Remission cases, defined as DAS28ESR <2.6, were 34, and mean remission rates of each year were about 30%. For the present, flare-up case was only 1, but drug-off case was nothing. **Conclusion:** ETN therapy was effective for a long-term period, but complete remission was difficult.

W63-1

Two RA cases wishing to conceive chose etanercept (ETN) therapy and gave birth

Yoshiko Sato

Yokkaichi.Social Insurance Hospital

Case 1 A 36-yo woman developed RA Aug. 2006, received MTX 6 mg + ETN treatment. Due to high disease activity (DA), MTX increased to 13 mg. DA relieved; MTX decreased. Feb. 2009 switched to ETN alone to conceive and discontinued ETN after gestation. DA re-increased and ETN resumed at gestation week 17. Jun. 2010 she delivered w/ good progress. **Case 2** A 29-yo woman developed RA Mar. 2008, received MTX 6 mg treatment. Jul. 2008 switched to ETN alone to conceive, despite low DA. Remission was achieved and ETN was discontinued, followed by gestation. Jul. 2010, she delivered w/ good progress. **Discussion** Many RA pts wish to conceive. MTX, anchor drug, is often difficult to control DA in such pts due to its teratogenic feature. ETN can be a promising drug for young RA pts who wish to bear a child.

W63-2

Successful pregnancy in three cases treated with etanercept

Noriyuki Takasu

Takasu Clinic

We report 3 cases with rheumatoid arthritis (RA) who successfully gave birth just after etanercept (ETN) was introduced for the treatment of RA. **[case1]** 41 year-old (Stage4, Class2). **[case2]** 36year-old (Stage1, Class1). **[case3]** 33 year-old (Stage4, Class1). All of them stopped ETN owing to the fear of side effects during pregnancy. The activity of RA was controlled with prednisolone before birth. And the newborns have no abnormal incidences. We think that ETN may be a suitable drug for patients with RA who desire to become pregnant.

W63-3

Pregnancy in women with rheumatoid arthritis receiving biological agents

Hisato Ishikawa¹, Toshihisa Kanamono¹, Toshihisa Kojima², Atsushi Kaneko³, Naoki Ishiguro²

¹Department of Orthopedics, Nagano Red Cross Hospital, ²Department of Orthopaedic, Nagoya University School of Medicine, ³Department of Orthopedics, Nagoya Medical Center

RA is one of the autoimmune disease, often generated in a middle-aged woman and the patient of reproductive age is not few either. The evidence of treatment with Disease Modifying Anti Rheumatic Drugs (DMARDs) for the pregnant RA patient is limited. It is very difficult to give what kind of medication for them because of a possibility of the pregnancy. The aim of this study is to investigate

how the pregnant patients in TBC (Tsurumi Biologics Communication) registry were treated with biologics. In TBC registry, 20 patients (14 with ETA exposure, 3 with INF exposure and 3 with TCZ exposure) got pregnant after treatment with the biological agent and they all delivered healthy infants.

W63-4

Efficacy of biologics for elderly patients with rheumatoid arthritis

Naofumi Yamauchi¹, Koji Ihara², Takuji Nishisato²

¹Department of Rheumatology, Kiyota Hospital, Sapporo, Japan,

²Department of Internal Medicine, Kiyota Hospital, Sapporo, Japan,

³Department of Internal Medicine, Sapporo Medical University, Sapporo, Japan

Objective: We investigated the efficacy of biologics in elderly patients with rheumatoid arthritis (RA). **Methods:** 23 RA patients (6 male, 17 female) with mean age of 72 (range 65-81) years were administered biologics. The mean disease duration was 14 years. 9 patients were elderly-onset RA (EORA). Effectiveness was assessed by DAS28(CRP). **Results:** Infliximab was administered to 7 cases, etanercept to 9, adalimumab to 5 and tocilizumab to 2. 16 cases (70%) were good response (remission 26%) and 3 cases (13%) were no response. 78% of EORA patients achieved a good response (remission 33%). Adverse events that required hospitalization were 3 pneumonia, 1 herpes zoster and 1 phlegmone. **Conclusion:** Biologics were effective for elderly RA patients and it is necessary to note serious infections.

W64-1

The situation of Rheumatology in Nepal and the international cooperation

Ryukichi Ishida

Ueda-shimotanabe Hospital

Nepal is the poorest country in Asia. After retirement from 30 years long Rheumatology practice in Japan, author is engaging in the research and volunteer in Nepal. WHO ILAR and BJD (Bone and Joint Decade) were expected their role in the developing country, but both were not tackled here. Nepal is not yet accepted as a member country of APLAR. ILAR COPCORD (Community Oriented Program for Control of Rheumatic Diseases) needs too much staffs and budget, so it is impossible now. MTX treatment for RA is not yet common, and steroids are over-used. The Biologics are not yet approved by the government. As the future theme, the clinical guideline suitable for the local reality (How to use MTX safely etc), working force education, COPCORD study are under discussion with the local doctors.

W64-2

Investigation about medical care for rheumatoid arthritis in Do-to area

Shin Furukawa¹, Kenji Oku¹, Hirohiko Kitakawa¹, Takeshi Yoshioka³, Takashi Abe²

¹Kushiro red cross hospital, ²Kushiro city general hospital, ³Kushiro kin-i-kyou hospital

Introduction: Rheumatoid arthritis (RA) treatment accomplished a change by biological drugs dramatically, and RA treatment objective changed. However, we can't achieve the treatment objective enough in this area. **Contents:** We performed a civic open lecture twice. All the local RA specialists participated not only a medical

specialist of a university by a lecture especially and performed Q and A session. A local patient representative gave a presentation, too. We investigated needs about RA medical care by a questionnaire. **Results:** About 150 participants. The questionnaire results: RA complications 16%/Latest treatment 14%/Costs 14%/Collagen disease except RA 12%/RA&life 11%/Rehabilitation 8%/Folk medicine 8%. **Discussion:** The patient needs for RA medical care was diverse as well as the latest treatment.

W64-3

Mentoring to family doctor and patient with RA in isolated island in Yamaguchi

Hiroshi Nakamura¹, Seiko Fukuta², Makoto Kubo²

¹Department of Community Health and Medicine, Yamaguchi University School of Medicine, ²Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine

The detached island in about 8km of the northern Yamaguchi seashore offings was selected, the detached island clinical practice guideline was created with the volunteer of a clinic doctor (non-rheumatism medical specialist) and a medical department student, and instruction of rheumatism medical examination and medical education was started. MTX (6 mg/week) was started from July, 2009 to one person by whom consent was got. Telemedicine was carried out for cooperation of a clinic doctor and a rheumatism advising doctor. Improving the vicious cycle of the medical gap which surround a sufferer from rheumatism, or local environment, and developing rheumatism medical treatment safely and effectively has high social contribution, and it is expected that educational motivation will also improve.

W64-4

Questionnaire about cooperation between rheumatologists and general physicians.

Shinichi Mizuki, Fumihiko Konishi, Naoko Ueki, Kazuo Kamada, Kensuke Oryoji, Eisuke Yokota

Matsuyama Red Cross Hospital, The Centre for Rheumatic Diseases

We performed questionnaire to 15 specialized rheumatologists and 28 primary care physicians. Primary care physicians were less aware of complications of rheumatoid arthritis and side effects of rheumatic DMARDs. Specialized rheumatologists should conduct education to not only primary care physicians but also specialized nurses, physical and occupational therapists and social workers in rheumatic diseases.

W65-1

AA amyloidosis secondary to RA: SAA1.3 allele genotype and treatments

Tadashi Nakamura¹, Syu-ichi Higashi¹, Kunihiko Tomoda¹, Michishi Tsukano¹

¹Kumamoto Center for Arthritis and Rheumatology, ²Yuge Hospital, Kumamoto, Japan

To compare the efficacy of cyclophosphamide (CYC) with that of etanercept (ETN) on treatment for patients with amyloid A (AA) amyloidosis secondary to rheumatoid arthritis (RA), CYC and ETN were administered to 62 and 14 RA patients, respectively, carrying the SAA1.3 allele. ETN demonstrated a greater efficacy than CYC, showing amelioration in CRP and serum albumin (Alb) ($P < 0.01$). Administration of ETN improved CRP, Alb and estimated glomerular filtration rate (eGFR) ($P < 0.01$, $P < 0.01$, and $P = 0.032$, respective-

ly). The SAA1.3 allele did not affect the susceptibility of these medications. Administration of ETN was more effective than CYC on treatment for AA amyloidosis secondary to RA, and CRP, Alb, and eGFR could be surrogate markers for efficacy.

W65-2

Association between renal function and amyloid deposition in renal biopsy in RA

Takeshi Kuroda^{1,2}, Daisuke Kobayashi², Yoko Wada², Shuichi Murakami², Masaaki Nakano³, Ichiei Narita²

¹Niigata University Health Administration Center, ²Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, ³Department of Medical Technology, School of Health Sciences, Faculty of Medicine, Niigata University

To clarify the association between various factors including renal function and the area of amyloid deposition in reactive amyloidosis associated with rheumatoid arthritis (RA), 58 patients with an established diagnosis of reactive AA amyloidosis were studied. For statistical analyses, the percentage of the area occupied by amyloid was found to be correlated with age, creatinine (Cr) level, creatinine clearance (Ccr), blood urea nitrogen (BUN) level, and the estimated glomerular filtration rate (eGFR). However, the levels of uric acid (UA) and urinary protein were not correlated. Recently, therapies with biologic agents such as anti-TNF and anti-IL-6 have become standard for DMARD-resistant RA patients, and might also become a routine strategy for amyloidosis patients with RA.

W65-3

Cardiac involvements in patients with AA amyloidosis due to rheumatoid arthritis

Daisuke Kobayashi¹, Yoko Wada¹, Shuichi Murakami¹, Takeshi Kuroda², Masaaki Nakano³, Ichiei Narita¹

¹Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, ²Health administration center of Niigata University, Niigata, Japan, ³Department of Medical Technology, School of Health Science, Faculty of Medicine, Niigata University, Niigata, Japan

Purpose; To examine the cardiac features of patients with rheumatoid arthritis (RA) associated with AA amyloidosis. **Methods;** Twenty-one RA patients with AA amyloidosis were enrolled. Patients' background data and echocardiographic features were analyzed retrospectively. **Results;** The echocardiographic findings showed left ventricular hypertrophy (LVH), low E/A ratio, and normal ejection fraction. Fourteen patients with LVH (LV wall >12mm) had longer history of RA, impaired renal function, and high frequency of proteinuria, compared with those of patients without LVH. We found a negative correlation between eGFR and LV wall thickness. **Conclusion;** Whereas cardiac involvement is believed as a late complication, subclinical LV dysfunction may progress in early asymptomatic phase.

W65-4

Changes of clinical features and improving prognosis in RA with AA amyloidosis

Yasuaki Okuda, Makoto Onishi, Kenichiro Matoba, Kazuo Jouyama, Akihiro Yamada, Masashi Takebayashi, Naoya Sawada, Sho Mokuda, Kiyoshi Takasugi

Center for Rheumatic Diseases, Dohgo Spa Hospital

Aim: To clarify the changes of clinical characteristics and improving prognosis in rheumatoid arthritis (RA) complicating AA amyloidosis. **Methods:** We compared the clinical characteristics and the prognosis of 405 RA cases complicating AA amyloidosis among three decades of the AA amyloidosis onset (1980-1889, 1990-1999 and 2000-2009). **Results :** Older onset of AA amyloidosis, lower values of inflammatory marker and lower incidence of AA amyloidosis were significantly observed as time progresses. Survival rates of RA complicating AA amyloidosis significantly improved as time advances ($p < 0.001$). **Conclusion :** The changes of clinical characteristics and improving prognosis in RA complicating AA amyloidosis were demonstrated.

W66-1

Fact of pregnancy and delivery with connective tissue disease in our hospital

Hiromi Kizu, Kentaro Susaki, Tomohiro Kameda, Miharuru Izumikawa, Yohei Takeuchi, Shusaku Nakashima, Hiroaki Dobashi
Division of Endocrinology and Metabolism, Hematology, Rheumatology and Respiratory Medicine, Department of Internal Medicine, Faculty of Medicine, Kagawa University,

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. We investigated dose of corticosteroid, pregnancy course, mode of delivery, and complication in our hospital. Study patients had systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease. 23 patients continued treatment with corticosteroid during pregnancy. In 3 severe cases, steroid pulse therapy was needed because primary disease became worse. Most patients had vaginal or cesarean delivery, although some cases complicated amniorrhexis or preterm birth. We suggest that it is possible to manage pregnancy safely with the control of disease activity.

W66-2

Nationwide Survey of Pregnant Cases with Anti-SS-A antibodies (Second Report)

Atsuko Murashima¹, Koshi Yamaguchi¹, Masako Waguri², Ran Matsudaira³, Yoshinari Takasaki³, Hiroto Tsuboi⁴, Takayuki Sumida⁴, Mitsumasa Kishimoto⁵

¹Department of Women's Health, National Center for Child Health and Development, ²Department of Maternal Medicine, Osaka Medical Center and Research Institute for Maternal and Child Health, ³Department of Internal Medicine and Rheumatology, Juntendo University, School of Medicine, ⁴Division of Clinical Immunology, Doctoral Program in Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, ⁵Section of Allergy and Rheumatology

We have been conducting multicenter investigations to identify risk factors for neonatal lupus (particularly for congenital heart block; CHB) and to evaluate the usefulness of therapeutic intervention. At the last meeting, we presented the distribution state of these cases managed at nationwide medical facilities and the results of analysis of 192 cases, demonstrating that the mothers of neonates developing CHB tended to be young, to have received no diagnosis of rheumatic disease, to have a history of meningitis, and with some exceptions, to have high titers of these antibodies developing CHB. The results from analysis of a larger number of cases will be presented.

ted concerning the correlation between drug therapy and the onset of neonatal lupus will be discussed.

W66-3

Pregnancy and delivery in patients with rheumatoid arthritis

Eri Sato, Daisuke Hoshi, Kumi Shidara, Naoki Sugimoto, Eisuke Inoue, Yohei Seto, Toru Yamada, Eiichi Tanaka, Ayako Nakajima, Atsuo Taniguchi, Shigeki Momohara, Hisashi Yamanaka
Institute of rheumatology, Tokyo women's medical university

Purpose:To investigate pregnancy of RA patients.**Methods:**Queries about pregnancy was performed to 77 patients between 2005 and 2007 in IORRA cohort.**Results:** 62 (81%) RA patients responded to the queries and reported 64 pregnancies and 57 deliveries. 24 cases (38%) spent more than 1 year to get pregnant after they planned. 27 cases (42%) were treated for their infertility. Preterm, full term, postmature delivery were 10(18%), 46(81%) and 1(2%), respectively. 11 infants (19%) were born by Caesarean section. Patients spent more than 1 year to get pregnant had longer disease duration (9.0 ± 4.1 vs 5.7 ± 4.8 years), more steroid use (6.1 ± 2.2 vs 3.4 ± 6.2 mg/day), less DMARDs use (7.1% vs 47.8%) ($p < 0.05$) compared with patients spent less than 1 year.**Conclusion:** We showed the states of pregnancy of RA women.

W66-4

Takayasu's arteritis (TA) in pregnancy: two serious revival cases

Maki Kagitani, Takuro Ozaki, Yuko Kimura, Nao Tatsukawa, Takaaki Ishida, Daisuke Wakura, Koji Nagai, Kenichiro Hata, Shuzo Yoshida, Takuya Kotani, Tohru Takeuchi, Shigeki Makino, Toshiaki Hanafusa
1st department of Internal medicine, Osaka Medical College, Osaka, Japan

We report two cases with TA in a stable condition at the permission of pregnancy. They underwent caesarean section with successful delivery in the third trimester. *Case 1:* A 34-year-old primigravida controlled 5mg of PSL presented complaining of headache at 4 days after delivery. Cerebral hemorrhage was happened by the revival of TA although the dosage of PSL was 30mg at the operation day. She has been suffered from hydrocephalus and aphasia. *Case 2:* 32-year-old primigravida was controlled 14mg of PSL. She underwent the delivery with a steroid cover of 40mg. She presented no complaining except headache. The blood pressure with both two cases were controlled well through the progress, but examined a symptom to suggest revival of TA. In the delivery with TA, enough attention was necessary.

W66-5

A 35-year-old Woman who Developed Eosinophilic Panniculitis after Delivery

Yumi Terai, Kazuyoshi Ishigaki, Hirofumi Shoda, Akiko Okamoto, Kazuhiko Yamamoto
Dept. of Allergy and Rheumatology, Graduate School of Medicine, the Univ. of Tokyo, Tokyo, Japan

A 35-year-old woman with a history of Basedow's disease was admitted to our department due to fever, erythema and polyarthralgia. Four months after delivery of her first child, edema developed in both legs. She was diagnosed as hypothyroidism and started taking levothyroxin. From the next day, fever, erythema and arthralgia developed, and she was admitted to our department. A skin biopsy

revealed septal panniculitis with massive infiltration of eosinophils, and histological diagnosis was eosinophilic panniculitis. There was no evidence of co-existing malignancy, infection or collagen vascular diseases. Prednisolone 30mg daily was started, and symptoms disappeared in two weeks. We report this rare case with a brief review of the literature.

W67-1

Risks for falls in patients with rheumatoid arthritis after lower limb surgery.

Kengo Harigane¹, Yuichi Mochida¹, Katsushi Ishii¹, Naoto Mitsugi², Naoya Taki², Yasushi Akamatsu², Tomoyuki Saito³

¹Center for Rheumatic Diseases, Yokohama City University Medical Center, Yokohama, Japan, ²Department of Orthopaedic Surgery, Yokohama City University Medical Center, Yokohama, Japan, ³Department of Orthopaedic Surgery, Yokohama City University School of Medicine, Yokohama, Japan

Backgrounds: The aim of current study was to analyze the incidence of falls in patients with rheumatoid arthritis (RA) in association with lower limb surgeries. **Methods:** Self-reported questionnaires were performed for 100 patients who visited our hospital from July to September in 2010. **Results:** The incidence of falls in patients who underwent lower limb surgery was significantly fewer when compared to patients who have no history of surgery (12.3% vs. 31.4%, $p = 0.03$). **Discussion:** It was supposed that walking ability and stability might improve after surgery, which resulted in decreased incidence of falls.

W67-2

Post-operative walking ability of the proximal femoral fractures in RA patients

Akihiro Nakazawa, Izumi Saito
Department of Orthopaedic Surgery, Yokohama Municipal Citizen's Hospital

(Objectives) To compare the post-operative walking ability of the proximal femoral fractures in RA patients and non-RA patients. (Patients) Twenty-four proximal femoral fractures with RA patients were treated between April, 2004 and March, 2009. Control group were 113 proximal femoral fractures with non-RA patients who treated between April, 2008 and March, 2009. (Results) 74% of RA patients were able to walk without support at last follow-up (mean 12months after operation) but 62% of non-RA patients. (Discussion) The young average age and the low rate of dementia and obesity in RA patients were causes of good post-operative walking ability. (Conclusions) The post-operative walking ability of proximal femoral fractures in RA patients was significantly better than non-RA patients

W67-3

3D operation planning for Protrusio Acetabuli of RA cases

Nobuyuki Watanabe¹, Hirotaka Iguchi¹, Masaaki Kobayashi², Yuko Nagaya², Hideyuki Goto², Masahiro Nozaki², Takanobu Otsuka²

¹Department of Arthroplastic Medicine, Nagoya City University Graduate School of Medical Sciences and Medical School, ²Department of Orthopedics, Nagoya City University Graduate School of Medical Sciences and Medical School

However arthroplastic operation would be decreased with RA patients, severe dysplastic cases were observed. We performed total hip arthroplasty in protrusio acetabuli cases using 3D pre-operative

planning. There were three cases, two males and one female. Average age was 68y.o.. Their average standing RA was 18years. Steroids were prescribing for two cases (5mg/day and 7.5mg/day). With Sotelo-Garaza Grading of protrusio acetabuli, there was one Grade 1 case and two Grade 2 cases. We performed 3D templating for these operations with patient's CT DICOM data. Total hip arthroplasty with cementless big cup (average 56mm) were performed for all cases without cup supporters using allograft. Excellent short-term results were observed. We will present these cases.

W67-4

Short term results of TNH Total Hip Arthroplasty for RA

Sei Mori, Shu Saito, Takao Ishii, Takanobu Sumino, Kunihiro Hosaka, Keinosuke Ryu, Hitoshi Ishigami, Junnosuke Ryu
Department of Orthopaedic Surgery, Nihon University School of Medicine, Tokyo, Japan

[Purpose] We report on the short term results of the TNH type cementless total hip arthroplasty for RA. **[Material and method]** Between January 2004 and November 2009, 27 primary THA were performed in 24 patients at our institution using the TNH type cementless THA for RA. There were 1 male and 26 females with an average age of 64.6 years (range, 53-80 years). The average follow-up was 48.6 months (range, 12-74 months). We examined clinical results (JOA score), evaluation of the X-rays studies, a complication. **[Result]** The JOA score improved all cases, and there was no polyethylene liner wear, no unstable implants of shell cups and stems in X-rays. The short-term results of the TNH type cementless total hip arthroplasty for RA were good.

W67-5

Complications after cementless total hip replacement for rheumatoid arthritis

Tetsuya Jinno¹, Daisuke Koga¹, Yuki Yamauchi¹, Naofumi Taniguchi¹, Atsushi Okawa¹
¹Department of Orthopaedic Surgery, Tokyo Medical and Dental University, Tokyo, Japan, ²Department of Rehabilitation Medicine, Tokyo Medical and Dental University, Tokyo, Japan

We reviewed the recent results of 38 cementless THAs for RA, age 46-77, followed for 3.4 (0.5-8) years. All implants were cementless except 3 cups with KT plates. 30% had received biologics. At the final follow-up, all implants were bony stable. Deep infection and symptomatic venous thromboembolism was not seen. One patient died after 6 months due to sepsis and myocardial infarction unrelated to the surgery. Dislocation occurred in 4 hips using 26mm head and posterolateral approach, and intraoperative femoral crack occurred in 3. Postoperative non-traumatic fracture occurred in 4 including 2 insufficient pelvic fractures unrelated to the implant insertion, suggesting the need for perioperative management against bone atrophy.

W68-1

The present situation of RA patients over 10 years follow up after TKA

Masataka Nishikawa¹, Hajime Owaki², Takeshi Fuji¹
¹Department of Orthopaedic Surgery, Osaka Koseinenkin Hospital, Osaka, Japan, ²Department of Rheumatology, Osaka Koseinenkin Hospital, Osaka, Japan

Purpose. To evaluate the present situation of RA patients followed up over 10 years after TKA. **Method.** Forty-two knees operat-

ed from 1993 to 2000 were studied. The average age and followed up periods were 71.1 and 142 months. The current medication, CRP, MMP-3, ROM, Knee Score (KS), Function Score (FS) and FTA were evaluated. Results. PSL(ave.3.5mg)/ MTX/ DMARDs combination/ biologics were administrated to 23 knees/ 27 knees/ 23 knees/ 7 knees, respectively. CRP and MMP-3 were well controlled (0.5 and 114.9). The average ROM/ KS/ FTA were 1.3-122.1°/ 91 / 175° and knee functions were good. But average FS was low (55) and severe gait disturbance (FS<40) were seen in 11 knees. Conclusion. Although RA control and knee function were good, gait function was low for multi-joint deformities.

W68-2

Long term results of the Advantim total knee for RA patients

Arata Nakajima¹, Koichi Nakagawa¹, Masato Sonobe¹, Yoshifumi Shibata¹, Yasuchika Aoki¹, Shintaro Tsuge¹, Yu Sasaki¹, Manabu Fujino¹, Teruo Furufu¹, Toru Suguro²
¹Department of Orthopedic Surgery, Toho University Sakura Medical Center, ²Department of Orthopedic Surgery, Toho University Omori Medical Center

[Objective] Investigation of long term results of the Advantim total knee for RA patients. **[Patients and Methods]** We investigated 25 knees in 19 RA patients who underwent TKAs with the Advantim total knee at our hospital between Oct 1991 and Aug 2000. They included 13 cemented- and 12 cementless-TKAs. Postoperative implant loosening and complications were investigated. **[Results]** We found evident loosening of the implants neither in cemented- nor cementless-TKAs. Complications included late infection, PCL tear, femoral suprachondylar fracture, and combination of patellar fracture and patellar tendon tear. **[Discussion]** The results showed not only good long term results of the Advantim total knee but also relatively high incidence of postoperative complications that are attributed to RA.

W68-3

Mid- term Results of Scorpio Mobile Bearing Total Knee Arthroplasty (Stryker®)

Hideo Kobayashi¹, Naoto Mitsugi¹, Yuichi Mochida², Naoya Taki¹, Junichiro Nakamura¹, Yasushi Akamatsu¹, Katsushi Ishii², Kengo Harigane², Tomoyuki Saito³
¹Department of Orthopaedic Surgery, Yokohama City University Medical Center, Yokohama, Japan, ²Center for Rheumatic Diseases, Yokohama City University Medical Center, Yokohama, Japan, ³Department of Orthopaedic Surgery, Yokohama City University Graduate School of Medicine

Purpose: To investigate the mid-term results of 36 knees in 31 patients undergoing TKA using Scorpio Plus Mobile Bearing Knee System (Stryker), and compare the outcomes between patients with Group A (OA:23, ON:1) and patients with Group B (RA:12).

Methods: The clinical results and radiographic results were evaluated.

Results: JOA score improved in both groups. There were no significant differences between the groups with regard to ROM, FTA, and the Knee Society radiographic evaluation. Spontaneous dislocation of an insert occurred in two patients.

Discussion: With regard to the clinical and the radiographic results, there were no significant differences between two groups. In our case, failure of the locking ring was the most likely cause for the polyethylene insert dislocation.

W68-4

Mid-term results of FNK type total knee arthroplasty for rheumatoid arthritis

Takao Ishii, Shu Saito, Sei Mori, Takanobu Sumino, Kunihiro Hosaka, Keinosuke Ryu, Hitoshi Ishigami, Junnosuke Ryu
Department of Orthopaedic Surgery, Nihon University School of Medicine, Tokyo, Japan

We reviewed mid-term results of FNK type total knee arthroplasty for RA over 5 years. Between 1995 and 2005, 198 patients (340 knees) were performed TKA with FNK. There were 24 males and 198 females. The average age at the operation was 62.6 years and the average follow-up period was 7.6 years. We examined ROM and JOA score to compare in pre-operation and in final assessment, and complication. JOA score changed 45.5 to 85.1. Average ROM changed 100.2 degree to 111.0 degree. Complications were revision (3 knees), peri-prosthesis fracture (1 knee), polyethylene dislocation (1 knee), idiopathic hematoma (1 knee).

W68-5

Minimum 10-year follow-up results of Hi-tech knee total arthroplasty in patients with rheumatoid arthritis

Tatsuya Kobayashi¹, Masahiko Suzuki¹, Takahisa Sasho¹, Tae Hyun Lee², Tadashi Tsukeoka², Taisei Kawamoto³, Hajime Yamanaka⁴, Koichi Nakagawa⁵, Toyomi Tsuchida⁶

¹Dept. of Orthop. Surg., Graduate School of Medicine, Chiba Univ, Chiba, Japan, ²Dept. of Orthop. Surg., Chiba Rehabilitation Center, Chiba, Japan, ³Dept. of Orthop. Surg., Matsudo City Hospital, Chiba, Japan, ⁴Dept. of Orthop. Surg., Shimoshizu Nation Hospital, Chiba, Japan, ⁵Dept. of Orthop. Surg., Toho Univ. Graduate School of Medicine, Sakura Hospital, Chiba, Japan, ⁶Tsuchida Clinic, Chiba, Japan

Forty-six total knee arthroplasties in 61 patients (9 men and 37 women) with rheumatoid arthritis were reviewed. Average patient age at surgery was 54.1±8.5 years. Average follow-up was 13.6±1.5 years. Hi-tech knee II cruciate-retaining type has a flat-on-flat surface, and all prostheses were fixed without cement. The average clinical score of the Japanese Orthopedic Association was 76.7 at follow-up. There were three complications (1 patella fracture and 2 subsidence). Survivorship analysis showed that average implant survival for all revisions was 100% at 10 years. Long-term results of cementless, PCL-retaining total knee arthroplasty for rheumatoid arthritis are excellent in terms of improved clinical function and pain relief.

W69-1

The disorders of the foot and radiological evaluation in patients with RA

Kiyoshi Nakazono, Akira Murasawa, Hajime Ishikawa, Satoshi Ito, Asami Abe, Hiroshi Otani, Hiroe Sato, Yoichi Toyoshima
Niigata Rheumatic Center, Shibata, Japan

To investigate the association between the disorders of the foot and the radiological evaluation in patients with rheumatoid arthritis (RA). The subjects were 460 feet of 230 RA patients (43 men and 187 women) aged mean 64 years. We measured the foot length, foot width, foot girth, HVA, DMVA, MTR, MTA and HV, M1M2, M1M5, CP in AP and lateral radiographs. The aggration of the M1M2 was seen with a rise of stage. The HV was 49.1%, the DMV was 22.7% and the flat foot was 29.8%. HVA, M1M2 and DMVA were significantly high in the right but CP

was in the left.

It seemed that examination such as the shoes was necessary by the total evaluation by the condition and X-rays of the foot with RA patients.

W69-2

Total ankle arthroplasty using 3D custom-made surgical guide in RA cases

Makoto Hirao¹, Kunihiro Oka², Akihide Nampei⁴, Hideki Tsuboi⁵, Kenrin Shi¹, Tsuyoshi Murase¹, Kazuomi Sugamoto³, Hideki Yoshikawa¹, Jun Hashimoto¹

¹Department of Orthopaedics, Osaka University Graduate School of Medicine, ²Dept. of Orthopaedics, Bell Land General Hospital, ³Department of Orthopaedic Material Science, Osaka University Graduate School of Medicine, ⁴Dept. of Orthopaedics, Osaka Rosai Hospital, ⁵Dept. of Orthopaedics, National Hospital Organization Osaka Minami Medical Center

We performed total ankle arthroplasty (TAA) using 3D custom-made surgical guide system for more accurate bone cutting in 15 RA cases. The utility was evaluated as compared with 14 cases using conventional guide. From CT data, 3D model bone was constructed to make custom-made surgical guide involving cutting planes. Angles between cutting plane and axis of tibia according to X-ray picture was 90.1±1.62 degrees (mean±SD) in custom-made group, the angle in conventional group was 90.6±2.44 degrees, suggesting smaller variability using custom-made guide. Frequency that outlier was more than ±1.5 degrees were 5/15 in custom-made guide group, and 10/14 in conventional one. Additionally, this system is useful for simulation for the surgery and understanding appropriate place of implantation.

W69-3

Clinical short term results of total ankle arthroplasty using FINE TAS

Masahiro Tada¹, Tadashi Okano¹, Yuko Sugioka¹, Shigeyuki Wakitani¹, Tatsuya Koike²

¹Department of Orthopaedic Surgery, Osaka City University Medical School, Osaka, Japan, ²Department of Rheumatology, Osaka City University Medical School, Osaka, Japan

Background: TAA was performed for ankle disorders by RA or OA. We report clinical results of mobile bearing TAA. **Methods:** Twenty TAA were performed in patients with RA (n=14) or OA (n=6) in 19 patients. We used FINE TAS that is mobile bearing system. Patients were assessed for AOFAS score, ROM, radiolucent line (RLL) and sinking. **Results:** The mean age was 64.1 years old. The mean follow-up period was 34.0 months. We found improvement of AOFAS score and ROM. Five ankles showed RLL or sinking. Three ankles were performed reoperation. **Discussion:** RLL or sinking occurred at high frequency (25%). But, only two ankles (10%) were had to reoperation. We take account of the fact that the symptom was lack in spite of radiological changes. Good clinical results could be achieved with FINE TAS.

W69-4

Mid-term results of FINE total ankle replacement with subtalar arthrodesis in RA

Kenrin Shi¹, Makoto Hirao¹, Akihide Nampei², Hideki Tsuboi², Hideki Yoshikawa¹, Jun Hashimoto¹

¹Department of Orthopaedic Surgery, Osaka University Graduate School of Medicine, ²Department of Orthopaedic Surgery, Osaka Rosai Hospital

Mid-term clinical results of FINE total ankle replacement (TAR) with corrective subtalar arthrodesis for RA were studied. Standing radiographs (AP, lateral and subtalar view) and AOFAS scale were evaluated in 15 feet of 13 RA patients (mean age, 60.5 yrs; mean follow-up, 50.9 mts). No signs of loosening were recognized except one with revision TAR after subsidence of talar component, which was thought due to undersize of the component. On radiographs at the final follow-up, however, clear zone was observed around tibial and talar component in 7 and 6 feet, respectively. Hindfoot was kept well-aligned with mean tibio-calcaneal angle on subtalar view of 0.7 degree valgus at the final follow-up. Mean AOFAS scale significantly improved from 34.9 preoperatively to 75.8 at the final follow-up.

W70-1

Problems and solutions in biologic medication from viewpoint of nursing

Sanae Ishii¹, Masamitsu Natsumeda², Ryutaro Yamanaka², Misuzu Yamashita², Koji Takasugi², Kayo Ezawa², Kazuhiko Ezawa², Yoshihisa Nasu³

¹Department of Nursing, Kurashiki Kosai Hospital, Kurashiki, Japan, ²Department of Internal Medicine, Kurashiki Kosai Hospital, Kurashiki, Japan, ³Department of Orthopaedic Surgery, Kurashiki Kosai Hospital, Kurashiki, Japan

Objective: There are many problems for RA patients and medical staffs on biologic medications in our hospital. We consider the problems and solutions from viewpoint of nursing. **Problems:** Patients feel uncertain about financial burden, self-injection, side effects or their future. Medical staffs have problems on ensuring infusion rooms, waiting hours or instruction skills differing by nurses. **Solutions:** 1)Provide cost consultations with MSW 2)Prepare form on cautions at home, next plan and hotline 3)Prepare form on critical path of self-injection 4)Monitor patients during drip infusion based on vital sign checklist. **Conclusion:** Usage of forms enabled consistent instructions, providing relief to patients in their treatment. Building trustful relationships with patients is most important.

W70-2

Psychological insecurity of patients who receive infliximab therapy

Kanako Hirai¹, Tomoko Kawakami¹, Yuki Tanaka¹, Makoto Onishi²

¹Nursing Department, Center for Rheumatic Disease, Dogo Spa Hospital, ²Center for Rheumatic Disease, Dohgo Spa Hospital

Purpose: Research of insecurity of patients in infliximab (IFX) therapy and discussion of measures against it. **Subjects:** 26 patients before or in IFX therapy. **Method:** Before and after informed consent, and after IFX use, questionnaire survey and psychological analysis were conducted. For evaluation of insecurity, VAS was used. **Results:** Before IFX use, 86% of subjects could understand explanation. Insecurity was observed in 81%, 57% and 52% of subjects before and after explanation and after IFX use, respectively. Insecurities comprised continual efficacy, relapse, drug change, etc. **Conclusion:** While IFX could be understood to some extent before use, insecurity varied before and after IFX use. We could not cope

with it properly and we think finely-tuned measures against it are necessary.

W70-3

The sense of difficulties in patients with self-injection of biological products

Kumiko Yamada¹, Kanako Orii¹, Chikage Kawabata¹, Emi Motoki²

¹Konan Hospital Foundation Kakogawa Hospital, ²Konan Hospital Foundation Kakogawa Hospital nursing support center

The purpose of this study is to clarify the sense of self-injection difficulties in patients with rheumatoid arthritis to have been shifted to self-injection treatment. Semi-structured interviews were conducted approximately 30 minute for 20 patients who had been diagnosed with rheumatoid arthritis and have been shifted to self-injection treatment with adalimumab. Transcripts were created from the data obtained and were analyzed qualitatively. The sense of difficulties in the extracted related to the injection procedure was reduced to a single program it. But patients with rheumatoid arthritis need time to consult a nurse about daily. In this institution, we considered the system to support continuous patient as the support to patients after transition to self-injection.

W70-4

Involvement of nurses in etanercept (ETN) therapy

Sari Takahashi, Masataka Komagamine
Komagamine Rheumatoid Orthopaedic Clinic

Purpose For patient education (PE) at ETN therapy initiation, our patients (pts) by ETN dose were analyzed; disease duration and stage etc., and the patient factors for remission were studied.

Subjects ETN-treated pts (n = 36; 54% with ETN use ≥ 2 year)

Results As treatment results, 43% pts “very satisfied”; 36% “satisfied”; 21% “slightly dissatisfied.” Further, 53% cited “decrease/discontinuation of steroids or NSAIDs” as merit of ETN therapy, & 16% “high drug cost” as demerit. Comparison among survey items showed satisfaction levels were not correlated with DAS scores or test results in some pts.

Discussion In daily busy outpatient practice, PE not only by doctors but also by nurses is important as index for determining treatment strategy, ETN therapy initiation & RA patient follow up.

W70-5

Efforts by nurses to increase etanercept (ETN) dose from 25 mg/w to 50 mg ×1

Naoko Tabata
Kushiro Sanjikai Hospital, Hokkaido, Japan

Background ETN has great clinical efficacy but many pts actually experience lack of efficacy (LOE) because various factors prevent 50 mg/w dose. We report our nurses' efforts on ETN increase. **Subjects** 12 pts on ETN 25 mg/w **Methods & Results** Our nurses measure DAS28 to determine reduced efficacy & switch timing to other drugs in ETN treated pts. Since Oct. 2010 introduction of ETN 50 mg syringe, our staff as a whole began explaining to LOE pts w/ 25 mg/w about the importance of 50 mg/w (e.g. joint destruction inhibitory effect) in addition to DAS28 measurement under doctor's order. As of 10/Nov/2010, 4 pts increased to 50 mg ×1/w & other LOE pts generally gave consent. **Discussion** Nurses' sys-

tematic involvement in ETN treatment enabled detection of LOE pts w/ 25 mg/w & increase to 50 mg \times 1/w.

W71-1

The Questionnaire Survey On Rheumatoid Arthritis Treatment

Katsuaki Shiroto, Sugii Shoji, Naoto Yokogawa, Takahiro Nunokawa, Yoshiki Nagai, Naofumi Chinen, Kota Shimada, Satoshi Watanuki, Mutsuhito Ui, Shinichi Inada

Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center

Introduction: To understand what patients are hoping on treatment in order to enhance patient satisfaction and make outpatient care go on smoothly.

Method: We conducted a questionnaire to patients on what they have placed great importance on outpatient care by pointing out a maximum of 3 things.

Result: A total of 71 patients (10 male, 61 female) gave 172 answers. The most answers making up 16 % are regarding “symptoms”. Then, 15% of the answers mentions “medicine”: 10% is about “communication”; “waiting time” accounts for approximately 5%; and only 1.7% answers describe refer to physician’s personality.

Conclusion: A lot of answers mention patient’s condition or prognosis. Answers regarding ambulatory setting are minor contrary to our expectations.

W71-2

Investigation of the problems of daily life in RA patients.

Chiaki Kita¹, Kifumi Suga¹, Yasunori Kobata², Ryota Hara², Yasuhito Tanaka², Takashi Fujimoto³, Yasuhiro Akai⁴

¹Nara Medical University Hospital, Kashihara, Japan., ²Department of Orthopaedic Surgery, Nara Medical University, Kashihara, Japan., ³Department of General Medicine, Nara Medical University, Kashihara, Japan., ⁴Center for Postgraduate Training, Nara Medical University, Kashihara, Japan.

Seventeen outpatients with rheumatoid arthritis (RA) were interviewed by a rheumatology nurse for clarifying the patient’s physical, mental and social problems. From our results, the problems of RA patients can be grouped into six categories; problems related to activity of daily living (35%), problems in social life (22%), concern about medical treatment (18%), anxiety for future (12%), mental instability (8%), family-finance issue (6%). Problems on activity of daily living and in social life revealed more serious in RA patients, therefore rheumatology nurse specialists should intervene aggressively in RA patients and play important roles to solve especially in these problems.

W71-3

Pamphlet for RA patients that aimed to improve their self-management ability

Yumiko Hisaoka¹, Akemi Nakashima¹, Rieko Iida¹, Kuniko Kubo¹, Kyoko Horii¹, Sachiko Mitsuki²

¹University Hospital, Kyoto Prefectural University of Medicine, ²Kyoto Prefectural University of Medicine School of Nursing

Background: Nurses lacked a guidance tool for nursing intervention with RA patients in our ward.

Method: We collected existing documents and pamphlets, and examined them with a medical team that consisted of doctors, nurses, and therapist, all of whom work with RA patients.

We gave priority to information on the rehabilitation and the social resource connected with RA patient’s daily life. We noted that the pamphlet became easy to understand, with the use of pictures and illustrations.

Result: We created our pamphlet titled “Living with the Rheumatism”, contain latest topics rheumatic therapy and care.

Conclusion: It became a good chance to form a common recognition between the medical team. We stepped forward to care for RA patients.

W71-4

Thoughts on steroid therapy in adolescent female patients with rheumatic disease

Sayaka Matsuzaki¹, Yumi Kawakami¹, Narumi Hamaguchi¹, Taiichiro Miyashita², Yasumori Izumi², Kiyoshi Migita³, Emi Matsuura⁴, Kana Takesue⁴

¹Nursing department, NHO Nagasaki Medical Center, Omura, Japan, ²Rheumatology and General Internal Medicine, NHO Nagasaki Medical Center, Omura, Japan, ³Clinical Research Center, NHO Nagasaki Medical Center, Omura, Japan, ⁴The Department of Nursing School, Kwassui Women’s university

Objective: To recognize what adolescent females are feeling about oral corticosteroid treatment, and to clarify its uniqueness. **Patients and methods:** 12 adolescent female patients with rheumatic diseases receiving oral corticosteroids had semi-structured interviews respectively, and hearing transcripts were created, then inductively analyzed by Grounded Theory method. **Results:** [live with hope for the future while accepting the disease and medication adverse effects] was isolated as a core category. As a category of adolescent women, [body image changes caused by disease or drugs] and [marriage, childbirth, the impact on employment] were observed. **Conclusion:** A characteristic feeling unique to adolescent females including the concept of conflict was found.

W71-5

Intake of n-6/n-3 fatty acids may participate in pathogenesis and activity of RA

Ai Sasaguri¹, Harumi Hata¹, Ayumi Uchino², Kae Tsuruoka², Toshiyuki Ota³, Yoshinobu Koyama²

¹Division of Dietetics, Iizuka Hospital, Fukuoka, Japan, ²Center for Rheumatology, Iizuka Hospital, Fukuoka, Japan, ³Department of Laboratory and Transfusion Medicine, University of Occupational and Environmental Health, Fukuoka, Japan

[Purpose] To investigate the relationship between the intake of n-6/n-3 fatty acids in RA patients and the disease activity.

[Method] The intake of n-6/n-3 fatty acids ratio (6/3-ratio) was investigated in newly diagnosed RA patients (n=24). The relationship between the 6/3 ratio and disease activity of RA was also analyzed.

[Result] The 6/3-ratio in newly diagnosed RA patients was high (4.31 \pm 0.79) as compared with the average value of Japanese people (3.7). The significant high DAS value was detected in the high 6/3-ratio group (\geq 4.2) compared with the low 6/3-ratio group (\leq 3.2).

[Discussion] The 6/3-ratio might be implicated in the pathogenesis or disease activity of RA. A dietary management which correct the high 6/3 ratio is possible to be a candidate for adjunctive treatment for RA.

W72-1

Correlation between radiographic changes and CRP in psoriatic arthritis.

Naomi Ichikawa¹, Atsuo Taniguchi¹, Midori Akatsu¹, Satomi Kobayashi², Tsuyoshi Kobashigawa¹, Toru Yago¹, Yuki Nanke¹, Shigeru Kotake¹, Hisashi Yamanaka¹

¹Institute of Rheumatology, Tokyo Women's Medical University,

²Department of Dermatology, Tokyo Women's Medical University

Aim: To investigate whether CRP was correlated with radiographic changes in psoriatic arthritis (PsA). **Method:** Two sets of films of hands and toes with various intervals were evaluated by Sharp/van der Heijde score (SHS) in 15 PsA patients. Controls were RA patients matched on the basis of intervals of two sets of radiographic exam. The correlation between the SHS and time-integrated CRP (Σ CRP) were examined. **Results:** Mean changes in joint space narrowing (JSN) score, erosion score and total score significantly correlated with Σ CRP in RA. In PsA, Σ CRP significantly correlated with mean changes in JSN and total score but did not significantly correlate with erosion score. **Conclusion:** It was suggested that CRP as a marker of radiographic joint destruction is not performed as well in RA.

W72-2

A radiological study of spinal involvement in patients with psoriatic arthritis

Midori Akatsu¹, Naomi Ichikawa¹, Satomi Kobayashi², Atsuo Taniguchi¹, Hisashi Yamanaka¹

¹Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, ²Institute of Dermatology, Tokyo women's Medical University, Tokyo, Japan

Aim: To investigate radiographic findings of spinal and sacroiliac joints (SIJ) in patients with psoriatic arthritis (PsA). **Method:** Radiographs of cervical, thoracic, lumbar spine and SIJ of 70 PsA patients were evaluated. **Results:** Age/duration of skin disease/ duration of arthritis were 52.3/14.6/8.0 years, respectively. 50% of patients had at least one of spinal involvements caused by PsA. The proportion of patients with marginal syndesmophyte/ non-marginal syndesmophyte/ ossification of supraspinous ligament were 11.4/35.7/12.8%, respectively. SIJ involvement was observed in 17 patients and 65% of SIJ involvement were bilateral. Patients with SIJ involvement had longer duration of arthritis. **Conclusion:** This study revealed the characteristics of spinal involvement in Japanese PsA patients.

W72-3

Efficacy and safety of adalimumab in patients with psoriatic arthritis.

Shigeyoshi Tsuji¹, Tetsuya Tomita⁴, Yasuo Kunugiza⁴, Hideki Yoshikawa⁴

¹Department of Orthopaedic surgery, Hoshigaoka Koseinenkin Hospital, ²Dept. of dermatology, Nissay Hospital, ³Dept. of Orthopaedic surgery, Nissay hospital, ⁴Orthopaedics, Osaka university graduate school of medicine

We investigated the clinical effects of Adalimumab (ADA) in psoriatic arthritis (PsA) patients. 10 patients were eligible for the study (all males), and the average age, psoriasis and PsA affected period were 46.2, 17.7 and 9.0 years, respectively. The most prevalently-used medicine was Methotrexate (8 cases). Average follow up periods was 4.4 months. Clinical results was evaluated according to

the DAS28 (CRP4) and BASDAI. Clinical results were evaluated before and at 4/12/24 weeks after treatment to ADA. **Results:** DAS28 (CRP4) were before/4/12/24 weeks, for 3.17 / 1.85 / 2.11 / 1.57, respectively. BASDAI were before/4/12/24 weeks, for 4.03 / 2.97 / 2.94 / 1.51 respectively. At 4/12/24 weeks, DAS28 (CRP4) and BASDAI were significantly improved, compared with pre-treatment value ($p < 0.01$).

W72-4

The treatment of psoriatic arthritis (PsA) in 18 cases

Keiki Miura¹, Ken Ogura¹, Hiroshi Okuno¹, Eiji Itoi¹, Ryuhei Okuyama²

¹Department of Orthopaedic Surgery Tohoku University School of Medicine, Sendai, Japan, ²Department of Dermatology Shinsyu University School of Medicine, Matsumoto, Japan

【Purpose】 PsA destroys various joints as well as RA. We administer SASP, MTX and biologics based on RA to treat PsA and CyA is used according to the cases. We investigated the treatment of PsA retrospectively. **【Materials and Methods】** Objectives were 18 cases of PsA (14 males and 4 females). The average age is 51.4(30-86). The mean duration of therapy was 2.6(0.2-7.9) years. **【Results】** We experienced 6 biological cases (5 cases with MTX, 2 case with CyA). Seven cases were chiefly treated with MTX (1 case with CyA). Three cases were treated with SASP. There was no case treating with CyA chiefly. Average DAS28 ESR at the last observation was 2.13(0.78-3.93). Remission (< 2.6) was 10 cases, low disease activity (2.6-3.2) was 3 cases, and moderate disease activity (3.2-5.1) was 4 cases.

W72-5

The efficacy of Tocilizumab therapy in Psoriatic arthritis

Miho Karube, Yoshinori Komagata, Shinya Kaname, Yoshihiro Arimura, Akira Yamada

First Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan

Objective: To evaluate therapeutic efficacy of Tocilizumab (TCZ) in Psoriatic arthritis. The case is 65-year-old man with Psoriatic arthritis. Although he was treated with infliximab (INF) therapy in August 2007, the therapy was discontinued due to infusion reaction, and was changed to TCZ. We evaluated response to TCZ based on disease activity score (DAS) 28-ESR, and EULAR response criteria. The value of DAS-28-ESR at pre, after 1, 3, 6, 12, 18, 24 month were 4.74, 4.26, 3.83, 2.47, 2.44, 2.61, 1.52 respectively, and disease activation was gradually improved. The response was good according to EULAR response criteria. And we obtained same efficacy compared to 2 patients (75-year-old woman and 33 year-old man) with INF therapy. TCZ was effective treatment for the Psoriatic arthritis.

W73-1

Clinical study of giant cell arteritis

Eiichi Suematsu, Tomoya Miyamura, Yoshiro Horai, Karin Shimada, Motoko Ishida, Soichiro Takahama, Rumi Minami, Masahiro Yamamoto

Department of Internal Medicine and Rheumatology, Clinical Research Center, National Hospital Organization, Kyushu Medical Center, Fukuoka, Japan

To investigate the clinical and laboratory features of giant cell arteritis (GCA). Twelve patients (1 male and 11 females) were inclu-

ded this study. Mean age was 67.7 years old. Mean level of serum CRP was 7.07mg/dl. Swelling and tender of temporal arteries were recognized in 6 cases, 4 of them revealed the histopathological findings of arteritis including giant cells. Six cases were positive for antiphospholipid antibodies (6 for anticardiolipin antibody IgG, 6 for anticardiolipin β 2GPI antibody, 0 for lupus anticoagulant). Poly-myalgia rheumatica was complicated with 2 cases. Our study demonstrates that high prevalence of antiphospholipid antibodies in GCA, although obvious thrombotic events related to GCA were not observed, suggesting reactive antibodies in relation to inflammation.

W73-2

Clinical features of eight patients with elderly onset large vessel vasculitis

Hisae Ichida, Yasushi Kawaguchi, Kae Takagi, Yasuhiro Katsumata, Takahisa Gono, Akiko Tochimoto, Hisashi Yamanaka
Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Large vessel vasculitis (LVV) encompasses the spectrum of vasculitis of the aorta and its major branches, including Takayasu arteritis (TA) and giant cell arteritis (GCA). Most patients with TA are under 40 years at the onset, and patients with GCA have temporal arteritis. In this study we examined clinical features of patients with elderly-onset LVV (eoLVV). We defined the patients with LVV over 50 year-old at the onset as eoLVV. Eight patients with eoLVV were enrolled. The frequencies of arthritis and hyperlipidemia were significantly higher in patients with eoLVV than those in TA. Fever and lymphadenopathy were seen more frequently in patients with TA than those in eoLVV. Our observations suggest a novel clinical entity in LVV that has different clinical features from TA and GCA.

W73-3

Evaluation of IMT using IMT measurement software in Takayasu arteritis

Noriko Fukuzumi¹, Hirotohi Hamaguchi², Nobuhide Hayashi¹, Akio Morinobu³, Seiji Kawano¹

¹Department of Clinical Laboratory, Kobe University Hospital, Kobe, Japan, ²Department of Neurology, Kobe University Hospital, Kobe, Japan, ³Department of Clinical Pathology and Immunology, Kobe University, Graduate School of Medicine, Kobe, Japan

Purpose:An accurate evaluation of arterial hyperplasia is important to examine the efficacy of therapy in Takayasu arteritis(TA). Our aim was to measure accurately intima-media thickness(IMT) by using IMT measurement software for ultrasonography(US). **Methods:**IMT on the far wall of CCA from 28 TA patients were measured. Max IMT and mean IMT was determined with the following measurement procedures: (Method 1) manual measurement, (Method 2) automatic software measurement, and (Method 3) manual correction after automatic software measurement. **Results:**There were no correlations between Method 1 and 2, but there were high correlations between Method 1 and 3 (correlation coefficients: max IMT 0.867, mean IMT 0.944). **Conclusions:**Automatic measurement software was useful for IMT evaluation in TA.

W73-4

Japanese patients with biopsy proven giant cell arteritis: report of 8 cases

Akio Morinobu¹, Seiji Kawano^{1,2}, Yoshinori Kogata¹, Takashi Nakazawa¹, Goh Tsuji¹, Shunichi Kumagai^{1,3}

¹Clinical Pathology and Immunology, Kobe University Graduate School of Medicine, ²Clinical Laboratory, Kobe University Hospital, ³Evidence-based Laboratory Medicine, Kobe University Graduate School of Medicine

To clarify the characteristics and imaging results of Japanese patients with giant cell arteritis (GCA), the clinical data and imaging results of 8 patients with biopsy proven GCA were examined from their medical records. Although the clinical manifestations are similar to those previously reported, none of eight patients presented ocular symptoms, and five of them had aortitis. US of temporal artery showed the halo sign in all the patients. FDG-PET was performed in four patients and indicated the presence of aortitis of the patients. US is a quick and non-invasive test to detect the inflammation of temporal artery and FDG-PET is very helpful for the early diagnosis of aortitis in GCA. Awareness of the disease and appropriate imaging tests will result in a diagnosis of GCA.

W73-5

Two cases of intractable Takayasu arteritis in remission with infliximab

Gakuro Abe, Seiichi Ono, Sadahiro Suzuki, Fusazo Urano
Nagano Prefectural Federation of Agricultural Cooperatives for Health and Welfare shinonoi general hospital

Case1: 24-year-old female was treated for diagnosis of spondylarthritis at hospital A in 2005. because of high CRP, she was consulted to our hospital in '06 and was diagnosed with Takayasu arteritis (TA). She was treated with prednisolone (PSL) and Methotrexate (MTX), however, the efficacy was insufficient. Case 2 : 22-year-old female admitted to the University Hospital B in '07 and was diagnosed TA and treated with PSL and CPA or PSL and MTX. However, there was no effect. She visited to our hospital since '08. Infliximab was given to the above two cases. Inflammatory data markedly decreased and we could discontinue PSL. TNF blockers are reported the effectiveness to TA. We have experienced such cases with TA having excellent outcomes with biologics.

W74-1

PR-3 ANCA Affinity of Wegener's Granulomatosis and Anatomic Types

Mariko Sasaki, Masaharu Yoshida
Renal unit of Internal Medicine, Hachioji Medical Center, Tokyo Medical University

We tested PR-3 ANCA affinity in sera from Wegener's granulomatosis (WG) and studied the correlation between the affinity and their anatomic types. Blood samples were collected from 18 WG PR-3 ANCA positive patients. We examined PR-3 ANCA titer and its affinity using a competitive inhibition test of PR-3 ANCA ELISA. We evaluated ELK anatomic classification and BVAS score from WG patients' clinical cases. The PR-3 ANCA affinity could be classified into two groups: One group has a limited type (E); another group has the RPGN type (K) and a generalized type (ELK). Some ANCA IgG examined inhibited a PR-3 activity. As with MPO-ANCA affinity (Yoshida et al., CER 27 S-28, 2009), there seems to be an IC50 difference in PR-3 ANCA affinity and possibly an anatomic classification of WG.

W74-2

Difference between MPO and PR3-ANCA-positive Wegener's granulomatosis

Yoshinori Komagata, Yoshihiro Arimura, Kazufumi Nomura, Masaki Saito, Soko Kawashima, Noriko Ikegaya, Hitoshi Koji, Kazuhito Fukuoka, Miho Karube, Ken Yoshihara, Shinya Kaname, Kimimasa Nakabayashi, Akira Yamada

First Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan

We studied differences in clinical feature based on ANCA type among 19 patients diagnosed with Wegener's granulomatosis (WG) in our hospital. Methods: Patients diagnosed using the criteria of Japanese ministry of Health were enrolled. Initial symptoms, laboratory data, medication were compared by ANCA type. Results: The ratio of MPO-positive to all WG patients was 32% (6/19), and the percentage of female in MPO-positive was higher. Four of six MPO-positive patients have no sign of granuloma at the first visit and diagnosed with WG at relapse. Renal involvement was more common in patients with MPO-ANCA while Ear-Nose-Throat involvement was more prevalent in PR3-ANCA-positive. Conclusion: It is possible that MPO-ANCA-positive WG is pathologically distinct disease from PR3-ANCA-positive WG.

W74-3

Four Cases of Refractory Wegener Granulomatosis Treated with Rituximab

Noriyuki Sakurai, Mayuko Tsukida, Azusa Umemoto, Ken Kayakabe, Toru Sakairi, Hidekazu Ikeuchi, Akito Maeshima, Takashi Kuroiwa, Keiju Hiromura, Yoshihisa Nojima

Department of Medicine and Clinical Science, Gunma University Graduate School of Medicine, Maebashi, Japan

We report on four patients with Wegener granulomatosis (WG) who were treated with rituximab (RTX) in our hospital between 2008 and 2010. The mean patient age was 53 years. (male:2, female:2). These patients were all refractory to standard medication with steroid, cyclophosphamide, azathioprine, and methotrexate, and had limited type WG without renal impairment. Affected lesions were hypertrophic pachymeningitis (1), intraorbital tumor (2), sinusitis (3), bronchial stenosis (1), and lung nodules (4). After RTX treatment, intraorbital tumor (1) and lung nodules (2) were improved. However, remaining 1 patient showed no improvement in lung nodules and accompanied with infection. We should take care of indication of RTX in treating refractory WG, because of a growing risk of infection.

W74-4

Clinical analysis of Wegener's granulomatosis: a retrospective study

Hiromasa Nakano¹, Seido Ooka¹, Tomohiko Shibata¹, Hitoshi Ogawa¹, Yukiko Takakuwa¹, Kohei Azuma¹, Kumiko Tonooka¹, Yoshioki Yamasaki¹, Hiroko Nagafuchi¹, Takahiro Okazaki¹, Hidehiro Yamada¹, Shoichi Ozaki¹, Masaomi Yamasaki²

¹Division of Rheumatology and Allergy, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan, ²Division of Rheumatology, St. Marianna University Yokohama seibu hospital, Yokohama, Japan

We investigated the clinical manifestations of patients with Wegener's granulomatosis (WG) admitted to our hospital from April 2005 to July 2010. Fifteen patients (11 males, 4 females) were included.

Six patients were hospitalized after initial presentations, and the remaining 9 were due to relapse. The involvement of the upper respiratory tract, the lung, and the kidney was observed in 93%, 80% and 46%, respectively. Refractory cranial granulomas, including retrolbulbar granulomas, were found in 33%. Positive PR3-ANCA, MPO-ANCA, C-ANCA and P-ANCA were noticed in 67%, 13%, 40% and 0%, respectively. Since 60% of the patients analyzed were hospitalized after relapse, the importance of the effective maintenance therapy was suggested.

W74-5

Efficacy of IVIG therapy for peripheral neuropathy in remission stage of CSS

Tomoko Matsuda, Yoshihiro Arimura, Aya Isomura, Masaki Saito, Soko Kawashima, Noriko Ikegaya, Tetsu Hayakawa, Hitoshi Koji, Kazuhito Fukuoka, Miho Karube, Ken Yoshihara, Yoshinori Komagata, Akira Yamada

First Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan

BACKGROUND: Most of the patients with Churg-Strauss syndrome (CSS) suffered from neuropathy. The neuropathy affects ADLs even in the remission stage of CSS. OBJECTIVE: Assess the efficacy of high-dose intravenous immunoglobulin therapy (IVIg) for peripheral neuropathy in remission stage of CSS. PATIENTS & METHODS: Six patients with neuropathy (duration; 3month ~ 8 years) in remission stage of CSS. IVIg was performed with a dose of 400mg/kg of immunoglobulin daily for 5 days. Neuropathy was evaluated with the manual muscle strength test (MMT) and visual analogue scale (VAS). RESULT: MMT improved in 4 patients. VAS (Numbness and neuralgia) improved in 3 patients. CONCLUSION: IVIg therapy was effective to long-lasting peripheral neuropathy in remission stage of CSS.

W75-1

Plasma exchange for alveolar hemorrhage in patients with ANCA related vasculitis

Yoshinobu Fuke, Chie Shimizu, Takayuki Fujita, Masayoshi Soma

Department of Medicine, Division of Nephrology, Hypertension and Endocrinology, Nihon University School of Medicine, Tokyo, Japan

Alveolar hemorrhage (AH) frequently is a life-threatening feature of ANCA related vasculitis. There were few studies examining plasma exchange (PEX) for AH. Five patients, who were treated with PEX for their first episode of ANCA related vasculitis with HA, were entered. Clinical parameters, such as ANCA titer, Cr, CRP and degree of HA, were periodically evaluated after PEX. ANCA titer was extremely high (652.6 ± 442.9 EU). After PEX, ANCA titer was remarkably decreased ($-83.1 \pm 85.3\%$) without obvious flare-up and chest X-P abnormality normalized at 24.2 ± 13.3 days. Four of them were needed dialysis on admission, but two patients could detach from dialysis soon. This study indicates that prompt initiation of PEX could speedily reduce ANCA titer, and might improve HA and RPGN.

W75-2

An autopsy case of microscopic polyangiitis

Soko Kawashima, Fumiharu Konishi, Yoshinori Komagata, Shinya Kaname, Yoshihiro Arimura, Akira Yamada

A 82-year-old man admitted with cerebral infarction. There was no progression of paralysis, but low fever, inflammation and RPGN, systemic eruption with small dermal necrotizing angitis by skin biopsy and MPO-ANCA titer 130EU were shown. Then microscopic polyangiitis (MPA) was diagnosed. Immunosuppressive therapy improved general condition, but for 6 days after treatment, sudden death caused by massive retroperitoneal hemorrhage. The results of his autopsy, necrotizing vasculitis of small vessels in the brain as well as skin, retroperitoneal and kidney were shown. MPO-positive cell infiltration and MPO deposits in the vascular walls were detected. Cerebrovascular disease with MPA are rare in comparison with renal and lung disease. Present case is unique of MPA.

W75-3

Two cases of microscopic polyangitis concurrent with gastric cancer

Kazuaki Uekubo, Eigo Kikuchi, Naoko Aoki, Akitake Suzuki, Ryuichi Yokohari, Takahiro Okai
Division of Rheumatology, Department of Internal Medicine, Kawakita General Hospital, Tokyo, Japan

Case1: A 75-year-old man with gastric cancer was admitted of fever, bloody sputum, acute renal insufficiency just before resection. Chest CT revealed pulmonary hemorrhage and renal biopsy findings showed crescentic glomerulonephritis and MPO-ANCA 181U/ml. He was diagnosed as microscopic polyangitis. Distal gastrectomy was done during remission induction with high doses of prednisone and IVCY in addition to plasmapheresis.

Case2: A 67-year-old man was admitted of mononeuritis multiplex, skin eruption and cough. Chest CT showed interstitial pneumonia with cavity formation and MPO-ANCA 12.7U/ml. He was also found to have gastric cancer. Distal gastrectomy was done during immunosuppressive treatment m-PSL and IVCY.

We report two cases of AAV concurrent with gastric cancer adding consideration.

W75-4

Treatment of Churg-Strauss syndrome with intravenous immunoglobulin.

Kazuhiro Hamasato¹, Shigekazu Takahashi¹, Yasushi Nawata¹

¹Division of Rheumatology and Clinical Immunology, Chibaken Saiseikai Narashino Hospital, Chiba, Japan, ²Department of neurology, Chibaken Saiseikai Narashino Hospital, Chiba, Japan

BACKGROUND: The effectiveness of intravenous immunoglobulin (IVIG) in patients with Churg-Strauss syndrome (CSS) who are un-responsive to conventional treatment with corticosteroids with or without cyclophosphamide is known.

PURPOSE: To examine the effects of IVIG in patients with CSS.

METHODS: We investigated 12 patients with CSS admitted in our hospital during April 2001 to September 2010, retrospectively. 5 patients received IVIG therapy. We evaluated curative effect at manual muscle strength test/sensory nerve symptoms/nerve conduction velocity.

RESULTS: All cases had sensory nerve impairment. Among 5 patients who received IVIG therapy, 4 patients got some kind of improvement.

CONCLUSION: We can expect the curative effect of IVIG therapy regardless of activity and duration of the disease.

W75-5

Fraction of exhaled NO (FeNO) is useful for monitoring disease activity of CSS.

Miki Yamamura, Tomoya Harada, Yasuyuki Hasegawa, Akira Yamasaki, Eiji Shimizu

Division of Medical Oncology and Molecular Respiriology Department of Multidisciplinary Internal Medicine Faculty of Medicine Tottori University, Tottori, Japan

FeNO is useful for monitoring eosinophilic airway inflammation observed in asthma. However, FeNO in CSS has not been estimated. We measured FeNO in two cases of CSS. Case1: A 60 years-old man was admitted to our hospital because of mononeuropathy multiplex. Laboratory data showed eosinophilia and CT showed ground-glass attenuation. FeNO on the admission was 103ppb and decreased to 19ppb after treatment. Case2: A 81 years-old woman was admitted to our hospital because of fever, eosinophilia, mononeuropathy multiplex and renal dysfunction. FeNO on the admission was 154ppb and decreased to 45ppb after treatment. In both patients, FeNO decreased in accordance with the improvement of their symptoms and laboratory data. FeNO might be useful for monitoring disease activity in CSS.

W76-1

Evaluation of anti-CCP Ab with immunochromatographic method:MEBChrom CCP test

Toshihiro Matsui¹, Akiko Komiya², Shigeto Tohma²

¹Department of Rheumatology, Sagami Hospital, Sagami Hospital Organization, Kanagawa, Japan, ²Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami Hospital, Sagami Hospital Organization, Kanagawa, Japan

[Aim] To evaluate the immunochromatographic method (ICT) for which blood, plasma, and serum are used for specimen material, to measure anti-CCP antibody (Ab). [Method] We examined 60 samples from RA patients and 20 samples from healthy individuals. Assay results of anti-CCP Ab with ELISA and those with ICT were compared. ICT value was determined by standard color samples. [Result] There was a good correlation between ICT value and ELISA value: 97.5% (whole blood), 96.3% (plasma), and 96.3% (serum). [Conclusion] This study showed that newly developed immunochromatographic method has a similar performance with conventional ELISA method to measure anti-CCP Ab. Immunochromatographic method enables easy and rapid anti-CCP Ab measurement and may help an earlier diagnosis of RA in daily practice.

W76-2

A multi-biomarker disease activity (MBDA) compared to conventional DAS in RA.

Shintaro Hirata, Kazuyoshi Saito, Yoshiya Tanaka

The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health Japan, Kitakyushu, Japan

To evaluate MBDA as a tool for management of RA, we studied clinical data and serum samples of 124 patients (180 visits, 91 at baseline and 89 at year 1) from the BeSt cohort. 12 biomarkers were measured and input to a pre-specified algorithm. MBDA and DAS

had a significant correlation, and similar distribution on cumulative plot. Groups stratified by EULAR disease activity were significantly different, and little overlap was between HDA and LDA. MBDA discriminated LDA with AUROC of 0.83 and threshold of 28 and 44 were suggested. Changes in MBDA and DAS were also correlated. These results indicate that MBDA is a useful surrogate for DAS to determine the therapeutic strategy. *This is collaborator study with Drs. L Dirven, Y Shen, M Centola, G Cavet, WF Lems, TW Huizinga, and CF Allaart.

W76-3

Harmonization of cutoff and measured values for rheumatoid factor (RF)

Shunichi Kumagai^{1,4}, Nobuhide Hayashi^{2,4}, Tsuneyo Mimori^{3,4}

¹Center for Rheumatic Diseases, Shinko Hospital, Kobe, Japan,

²Clinical Laboratory, Kobe University Hospital, Kobe, Japan, ³Rheumatology & Clinical Immunology, Kyoto University, Kyoto, Japan,

⁴Working Group for Standardization of RF, Japanese Committee for Clinical Laboratory Standard

【Object】 Cutoff (CO) value of RF kits is not systematically defined. We have been promoting the standardization of RF in cooperation with JCCLS (Japanese Committee for Clinical Laboratory Standards). To harmonize the CO value of RF and to standardize values up to 3 times of CO value. **【Results】**1) When RF values were measured by 17 different RF kits, the values was inconsistent among the kits and could not be compensated by WHO standard sera. 2) The mean value for each RF kits positive in 5 % of healthy sera was 14.8 IU/ml, and the CO value was set as 15 IU/ml at this point. 3) RF titers up to 45 IU/ml will be standardized using pooling sera from RA patients. **【Conclusions】**After approval by JCCLS, the CO value for any RF kit will be 15 IU/ml where 5% of healthy subjects are positive.

W76-4

Factors affecting the values of MMP-3 in RA patients –TOMORROW study-

Masahiro Tada¹, Tadashi Okano¹, Yuko Sugioka¹, Shigeyuki Wakitani¹, Tatsuya Koike²

¹Department of Orthopaedic Surgery, Osaka City University Medical School, Osaka, Japan, ²Department of Rheumatology, Osaka City University Medical School, Osaka, Japan

Background: MMP-3 is believed to indicate the activity of synovitis. However, MMP-3 is high in patients of kidney disease or SLE. **Objective:** We analysis of influential factor for MMP-3, using TOMORROW study, that is prospective cohort study for RA patients and healthy volunteers (HV). **Methods:** We measured BMI, bone metabolism markers, DXA, lipid metabolism markers, inflammation markers, and ACPA. We analyzed by multiple regression analysis. 349 female (177 RA, 172 HV) and 64 male (31 RA, 33 HV) were included. **Results:** In female, the serum MMP-3 of RA (98.6 ng/mL) is significantly higher than that of HV (42.8 ng/mL). That is same result in male. GFR of RA male correlated with the serum MMP-3 ($r=-0.589$, $p=0.0001$). **Discussion:** Our results suggest that kidney disease elevate the serum MMP-3.

W76-5

Platelet-derived microparticles in rheumatoid arthritis with anti-TNF treatment

Kunihiko Umekita¹, Shunichi Miyauchi¹, Shiro Ueno¹, Ichiro Takajo¹, Norio Kusumoto¹, Shota Sakaguchi², Yumi Kaneko¹, Yayoi

Hashiba¹, Motohiro Matsuda¹, Kazuyoshi Kubo², Yasuhiro Nagatomo¹, Toshihiko Hidaka², Akihiko Okayama¹

¹University of Miyazaki, Internal Medicine, Department of Rheumatology, Infectious diseases and Laboratory medicine, ²Institute of Rheumatology, Zenjinkai Shimin-no-Mori Hospital

Platelet-derived microparticles (PMP) are believed to play an important role in inflammatory diseases such as rheumatoid arthritis (RA). Therefore, we investigated their levels in the peripheral blood of patients with RA. The levels of PMP in patients with RA were higher than those in healthy subjects. The levels of PMP significantly decreased by the anti-TNF treatments in responder group, but not in non-responder group. After 12 weeks of anti-TNF treatments, the levels of PMP were correlated with disease activity markers (CRP, tender joint counts, DAS28). The levels of PMP in RA patients in responder group were still higher than those in healthy subjects. The mechanisms for high levels of PMP in RA might be different from that for other disease activity markers.

W77-1

Evaluating the Japanese version of MDHAQ in patients with rheumatoid arthritis

Naoto Yokogawa, Kota Shimada, Yoshiki Nagai, Takahiro Nunokawa, Katsuaki Shiroto, Shoji Sugii, Shinichi Inada

Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center

【Background】 In era of RA remission, RA patients may reflect a normal score in mHAQ. MDHAQ overcome the shortcoming of mHAQ and provides disease activity index without joint counts. **【Method】** Collaborating with New York University, We translated the MDHAQ into Japanese. Three rheumatologists administered Japanese MDHAQ to 116 Japanese RA patients, scored RAPID3 and compared with DAS28 and CDAI. **【Results】** All RAPID scores correlated significantly with DAS28 and CDAI ($\rho>0.65$, $p<0.0001$). RAPID3 6 or more has good sensitivity and specificity for moderate/high DAS28 and CDAI (83%/73 % and 91%/72%). Rapid 3 less than 2 has good specificity to detect remission of DAS28 and CDAI (41%/92 % and 58%/90%). **【Conclusion】** The Japanese MDHAQ is a reliable, valid tool for assessing Japanese patients.

W77-2

Modified RAPID3 (mRAPID3) score is a simple but valuable index for active RA

Kota Shimada^{1,3}, Naoto Yokogawa^{1,3}, Shoji Sugii^{1,3}, Shinichi Inada^{1,3}, Shigeto Tohma^{2,3}

¹Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center, Fuchu City, Japan, ²Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagami Hospital, Sagami City, Japan, ³NinJa (National Database of Rheumatic Disease by iR-net in Japan) Net Work

Background: It is hard to use indices including joint counts in busy clinics. RAPID3, a simple index on patient(Pt)'s self report, has been proposed.

Objectives: To investigate the utility of mRAPID3 to identify active RA.

Patients and Methods: mRAPID3 was defined as: (total mHAQ) $\times 1.25 + \text{Pt pain VAS(cm)} + \text{Pt global VAS}$. Optimal cutoff for intermediate or high activity in DAS28 (clinically active RA) were esti-

ated in 5480 *NinJa* Data with ROC analysis.

Results: Clinically active RA was detected with cutoff of 1.36 by sensitivity of 90% and specificity of 51%, and with 6.0 by 39% and 92%. Scores ≤ 1.36 was seen in 1475 (27%), and ≥ 6.0 in 1418 (26%).

Discussion: mRAPID3 score ≥ 6.0 , the cutoff between low/intermediate activity in original RAPID3, detected clinically active RA with high specificity.

W77-3

A comparison of composite measures in RA patients treated with anti-TNF agents

Yuji Hirano, Yukiyo Oishi

Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan

Although tight control is important in treatment of RA, it is unclear which composite measure is best to evaluate clinical disease activity. We compared four composite measures (DAS28-ESR, DAS28-CRP, SDAI, CDAI) in RA patients treated with anti-TNF agents to understand the character of each measure. Disease activity of each patient was evaluated using four measures at the time of starting anti-TNF therapy and the time of last evaluation. Our results suggest that (1) DAS28-CRP is most sensitive to reflect the change of disease activity, (2) that it is very difficult to achieve remission evaluated by SDAI or CDAI though it is easier to achieve low disease activity by SDAI or CDAI, and (3) that good response according to the EULAR criteria using DAS28-ESR is a beneficial target to treat RA.

W77-4

Validity of the Disease Activity Indices in RA under Tocilizumab Therapy

Yoshiyuki Arinuma¹, Toshihiro Matsui¹, Shigeto Tohma²

¹Department of Rheumatology, Sagamihara National Hospital, National Hospital Organization, Kanagawa, Japan, ²Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagamihara Hospital, National Hospital Organization, Kanagawa, Japan

[Objective] To evaluate the validity of the composite disease activity indices in patients with RA taking tocilizumab (TCZ)

[Methods] Disease activity and remission rate were compared when calculated with DAS28-ESR, DAS28-CRP, SDAI and CDAI using data of 172 RA patients taking TCZ and 859 RA patients taking TNF inhibitor (TNF-I) registered in *NinJa* 2009.

[Results] The mean value (\pm SD) of DAS28-ESR was significantly lower in TCZ group (3.05 ± 2.62) than in TNF-I group (3.45 ± 2.64), but that of CDAI was lower in TNF-I group (9.04 ± 16.06) than in TCZ group (10.33 ± 16.18). In patients with DAS28-ESR remission, the remission rate of CDAI was lower in TCZ group (36.5%) than in TNF-I group (56.0%).

[Conclusion] Evaluation of disease activity differs in the disease activity indices under TCZ therapy.

W78-1

The surgical results of Sauve-Kapandji procedure for rheumatoid wrist.

Hidehiro Horizono, Fuminori Kanaya, Chinatsu Azuma

Department of Orthopedic Surgery, University of the Ryukyus School of Medicine, Okinawa, Japan

We evaluated the results of Sauve-Kapandji (S-K) procedure for rheumatoid wrist. 15 S-K procedures were performed on 14 patients (12 females, 2 males). The mean age of the patients was 59 year-old. The mean follow-up period was 58 months. Evaluations were performed pre and post-operatively in terms of range of motion (ROM) of the wrist and forearm, carpal height ratio (CH/MC), carpal translation ratio (e/MC) and palmar carpal subluxation ratio (h/MC). Post-op forearm ROM was significantly improved (pre-op 118° to post-op 153°). The mean CH/MC was significantly decreased (pre-op 0.440 to post-op 0.408). The mean e/MC and h/MC were not significantly different. The S-K procedure did not prevent progression of carpal collapse but improved forearm rotation.

W78-2

Follow-up study of Sauvé-Kapandji (S-K) procedure for RA wrists

Tomoko Kanazawa¹, Kenzo Hashizume¹, Keiichiro Nishida^{1,2}, Ryuichi Nakahara¹, Taichi Saito¹, Toshifumi Ozaki¹

¹Department of Orthopaedic Surgery, Okayama University Medical School, ²Okayama University, Department of Human Morphology

15 RA wrists treated with S-K were assessed by clinical and X-ray evaluation (Schlthess classification, carpal height ratio, ulnar translation, radial rotation, VAS, wrist ROM). In addition, 15 wrists were classified into 2 groups (A, B) by the preoperative wrist ROM (Group A: more than 50 degree, B: less than 50 degree). VAS markedly decreased in all patients. Overall, rotation of forearm increased, whereas wrist ROM decreased. Postoperative wrist ROM in group A decreased significantly. Rotation of forearm improved in all types of Schlthess classification, but wrist ROM improved only in type II. We conclude that either of three types may apply to S-K but the indication was determined carefully in each individual.

W78-3

Clinical Results of Sauvé-Kapandji Procedure for the Rheumatoid Wrist

Takaaki Hasuo, Kunio Yamada, Masahiro Nishino, Tetsuya Takenaga

Komaki City Hospital, Aichi, Japan

Introduction: We evaluated the clinical results of the Sauvé-Kapandji procedure for the rheumatoid wrists. Materials: Eight wrists in 7 patients were treated between 2008 and 2009. There were 2 males and 5 females with an average age of 59.6 years. The mean duration of the disease before surgery was 9.4 years. The average follow-up period was 16.1 months. Results: Pain was completely resolved in 5 wrists, and 3 wrists had occasional mild pain and discomfort. The average wrist extension-flexion arc before the surgery was 61.3 degrees and became 69.4 degrees after the surgery. The mean range of forearm rotation increased from 155.0 degrees to 173.8 degrees. DASH score improved from 35.9 to 12.3 points. Conclusions: All patients were satisfied with their surgical outcomes.

W78-4

Results of Sauvé-Kapandji Procedure for Wrist Disorders in Rheumatoid Arthritis.

Yasunori Kobata¹, Ryota Hara¹, Takamasa Shimizu¹, Kenichi Nakano¹, Akira Kido¹, Yasuhito Tanaka¹, Akihiro Fukui², Takashi Fujimoto³, Yasuhiro Akai⁴

¹Department of Orthopaedic Surgery, Nara Medical University, Kashihara, Japan., ²Department of Orthopaedic Surgery, Nishinokyo Hospital., ³Department of General Medicine, Nara Medical University, Kashihara, Japan., ⁴center of resident, Nara medical University, Kashihara, Japan.

The Sauvé-Kapandji procedure was performed on 79 wrists in 66 patients with rheumatoid arthritis. There were 11 men and 55 women. Their average age was 56 years, ranging from 27 to 74 years. The average follow-up period was 68 months, ranging from 1 to 20 years. Pain and range of motion were evaluated. Radiographical measurements of carpal bones were also evaluated. Radiographical classification was made according to Steinbrocker and Larsen. Bony union was achieved in all but one patient. Pain improved in all patients after operation. Pronation and supination improved but flexion and extension deteriorated. As for the radiographic evaluations, some gradual deterioration was observed. The Sauvé-Kapandji procedure yields good results for wrist disorders in rheumatoid arthritis.

W78-5

Stabilization of ulnar stump using FCU tendon with a Darrach proc. for RA wrist.

Asami Abe, Akira Murasawa, Kiyoshi Nakazono, Hajime Ishikawa, Satoshi Ito, Hiroshi Otani, Hiroe Sato, Yoichi Toyoshima
Rheumatology, Niigata Rheumatic Center, Shibata, Niigata, Japan

Extensor tendon rupture and click at the ulnar stump sometimes occur after a Darrach procedure. 27 wrists in 25 patients with RA were treated by stabilization of the ulnar stump using a one-half slip of FCU tendon. This procedure was performed on the wrist with dorsally protruded ulnar stump, which could not be stabilized by pronator quadratus muscle. The 3D-CT images were taken before and after the operation, and the dorsal subluxation rate (DSR) of the ulnar end and the carpal supination angle (CSA) were measured. Postoperatively, pain-free wrist without click on forearm rotation was produced, and no tendon rupture occurred. DSR and CSA improved from 47% and 9° to 28% and 6° respectively. Stabilization of the ulnar stump using FCU tendon after a Darrach procedure is an effective method.

W79-1

Evaluation of IgG4+ cells in immunohistochemistry in IgG4 related diseases

Mari Ushikubo¹, Arafumi Maeshima², Hirotohi Matsumoto¹, Kazuhide Gomi¹, Taku Yabuki¹, Kumiko Akiya¹, Shigeru Kuramochi², Hisaji Ohshima¹

¹Department of Connective Tissue Diseases, Tokyo Medical Center, Tokyo, Japan, ²Department of pathology, Tokyo Medical Center, Tokyo, Japan

Background) Quantitation of IgG4 producing cell by immunohistochemistry have been difficult because of technical limitations. Purpose) To clarify technical problems in calculating quantity of IgG4 producing cells. Methods) Percentages of IgG4 producing cells were compared in different immunostainings in 9 patients with non-IgG4 related diseases (IgG4RD) and 3 with IgG4RD. Results) 1; Non-IgG4RD showed 0-75% (average 23%) as IgG4/IgG, while 0-45 (22), 0-30 (8), 0-25 (7)% when calculated with IgG1+2+3+4, CD38, CD138 as a denominator, respectively. 2; In IgG4RD, IgG4/IgG was >50%, but one case showed over 100%. Other indices described above were 17-98%. Conclusion) It was suggested that a

standard method for calculation of IgG4 producing cells might be necessary in immunohistochemistry

W79-2

IgG4+ cell ratio in histopathology for diagnosis of IgG4-related disease.

Yasufumi Masaki^{1,8}, Nozomu Kurose^{2,8}, Takako Saeki^{3,8}, Shoko Matsui^{4,8}, Mitsuhiro Kawano^{5,8}, Hiroto Tsuboi^{6,8}, Tomoki Origuchi^{7,8}, Takayuki Sumida^{6,8}, Hisanori Umehara^{1,8}

¹Hematology and Immunology, Kanazawa Medical University, ²Department of Pathology and Laboratory Medicine, Kanazawa Medical University, ³Department of Internal Medicine, Nagaoka Red-Cross Hospital, ⁴First Department of Internal Medicine, University of Toyama, ⁵Division of Rheumatology, Department of Internal Medicine, Kanazawa University, ⁶Division of Clinical Immunology, University of Tsukuba, ⁷Nagasaki Graduate School of Health Sciences, ⁸IgG4+MOLPS/Mikulicz's disease Society of Japan

We assessed histopathological findings on 36 samples of IgG4-related disease and 21 of other disorders to evaluate which cut-off levels, 40% or 50%, of IgG4+/IgG+ cells ratio is better for diagnosis of IgG4-related disease, and also examined frequencies of storiform fibrosis, obliterative phlebitis, or eosinophilic infiltration. Sensitivities and specificities are 94.4% vs 94.4%, and 85.0% vs 95.0% for cut-off level 40% or 50%, 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%. Specificities of storiform fibrosis, obliterative phlebitis, or eosinophilic infiltration are 100% but sensitivities of these factors are low. These results suggest that the cut-off level 40% is reliable for the criteria.

W79-3

Proteomics analysis in IgG4-related disease

Haruka Iwao¹, Hideyuki Tsuchida², Takanobu Takata², Yasufumi Masaki¹, Takuji Nakamura¹, Akio Nakajima¹, Miyuki Miki¹, Tomoyuki Sakai¹, Toshioki Sawaki¹, Takafumi Kawanami¹, Yoshimasa Fujita¹, Masao Tanaka¹, Toshihiro Fukushima¹, Naohisa Tomosugi², Hisanori Umehara¹

¹Department of Hematology & Immunology, Kanazawa-medical university, Ishikawa, Japan, ²Medical Research Institute, Kanazawa-medical University, Ishikawa, Japan

IgG4-related disease is a new clinical entity characterized by increased serum IgG4, infiltration of IgG4-positive plasma cells into tissue, and good response to steroid therapy. To seek the disease-related protein, we examined serum from patients with IgG4-related disease using proteomics analysis before and after steroid therapy. Serum proteins were separated by 2-DE and visualized by silver staining. We picked out the spots that had been changed by steroid therapy and extracted peptides using an in-gel digestion method. We identified the protein using a mass spectrometry device. There was an increase in IgG1, IgG4, and inflammatory proteins in serum from patients with IgG4-related disease before treatment. In addition, we performed validation of some proteins using ELISA.

W79-4

Transcriptome analysis in peripheral blood lymphocytes of IgG4-related disease.

Akio Nakajima¹, Yasufumi Masaki¹, Takuji Nakamura¹, Haruka Iwao¹, Miyuki Miki¹, Tomoyuki Sakai¹, Toshioki Sawaki¹, Takanori Kawanami¹, Yoshimasa Fujita¹, Masao Tanaka¹, Toshihiro Fukushima¹, Hisanori Umehara¹

¹Department of Hematology and Immunology, Kanazawa Medical University, Japan, ²Medical Research Institute, Kanazawa Medical University, Japan

We searched pathogenic genes of IgG4-related disease by analyzing mRNA of peripheral blood lymphocytes (PBLs) using DNA microarray. PBLs were obtained from four healthy controls and two patients with IgG4-related disease before and after steroid therapy. RNA was extracted and gene expression was examined by DNA microarray. 36 genes were extracted according to the expression change more than 3 times before and after steroid therapy. 21 genes were extracted according to 3 times change of expression compared with those from healthy control. Although the further studies are needed, these genes may be responsible for the pathogenesis of IgG4-related disease.

W79-5

Analysis of IgG4 class switch related molecules in IgG4-related disease

Hiroto Tsuboi¹, Naomi Matsuo¹, Mana Iizuka¹, Yumi Nakamura^{1,2}, Akihiko Tanaka³, Masafumi Moriyama³, Isao Matsumoto¹, Seiji Nakamura³, Takayuki Sumida¹

¹Division of Clinical Immunology, Doctoral program in Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan, ²JSPS Research Fellow, ³Kyushu University Faculty of Dental Science, Fukuoka, Japan

<Objective> To reveal the mechanism of up-regulation of IgG4 class switch in IgG4-related disease (IgG4-RD). <Methods> We extracted RNA from PBMC of patients with IgG4-RD (N=3), Sjögren's syndrome (SS) (N=3), Healthy control (HC) (N=3), and labial salivary glands (LSG) of patients with IgG4-RD (N=11) and SS (N=10). The mRNA expression levels of IgG4 specific class switch related molecules (IL-4, IL-13, IL-10, TGF β , GATA3, Foxp3) and IgG4 non-specific class switch related molecules (AID, CD40/CD154, IRF4, BAFF, APRIL) were examined by quantitative PCR. <Results> The expression of BAFF and CD40 was lower in PBMC of IgG4-RD, and that of IL-10 and AID was higher in LSG of IgG4-RD than SS. <Conclusion> These IgG4 class switch related molecules might play the pathogenic roles in IgG4-RD.

W80-1

IgG4-related disease and malignancy

Motohisa Yamamoto¹, Tetsuya Tabeya¹, Yasuyoshi Naishiro¹, Yui Shimizu¹, Hidetaka Yajima¹, Mikiko Obara¹, Chisako Suzuki¹, Hiroyuki Yamamoto¹, Toshiaki Sugaya¹, Hiroki Takahashi¹, Yasuhisa Shinomura¹, Kohzoh Imai²

¹First Department of Internal Medicine, Sapporo Medical University School of Medicine, ²Advanced Clinical Research Center, The Institute of Medical Science, The University of Tokyo

Objective: IgG4-related disease (IRD) is a systemic disease presented with various organ dysfunction. We sometimes experience the cases with malignancy at the diagnosis of IRD. So we analyzed them in our hospital. Methods: We evaluated nine cases with malignancy clinically and serologically. Results: Seven cases were men. The average age of the onset was 65.7 years old. There were three cases with hematological malignancy, and six cases with solid cancer. In two lymphoma cases, IRD had been diagnosed several years ago. In other cases, the diagnosis of IRD was same or later. It was less frequency that the organ failure was complicated. The average level of serum IgG4 was 645 mg/dl. Conclusions: We have to con-

sider the complication of lymphoma and solid cancer in diagnosing IRD.

W80-2

IgG4-related disease and malignancy

Takako Saeki¹, Nobuaki Suzuki¹, Tomoyuki Ito¹, Hajime Yamazaki¹, Yoko Wada², Ichiei Narita²

¹Department of Internal Medicine, Nagaoka Red Cross Hospital,

²Division of Nephrology and Rheumatology, Niigata University

We examined the clinical features of malignancy in 25 patients diagnosed as having IgG4-related disease. Eleven cancers were diagnosed in 9 of the 25 patients. Three cancers were diagnosed at the time of diagnosis of IgG4-related disease. Two cancers were diagnosed before, and 6 were diagnosed after the diagnosis of IgG4-related disease. The sites of cancer origin were the stomach in 4 cases, the lung in 2, the colon in 2, and the prostate, bladder and upper pharynx in one case each, respectively, being different from the organs affected by IgG4-related disease. In one patient, lung cancer was misdiagnosed as an IgG4-related lung lesion. In patients with IgG4-related disease, it is necessary to be mindful of possible malignancy at all times and in all parts of the body.

W80-3

Four cases of neoplastic lesions associated with IgG4-related disease

Taiichiro Miyashita¹, Yasumori Izumi¹, Atsushi Kawakami³, Katsumi Eguchi⁴, Kiyoshi Migita⁵

¹Rheumatology and General Internal Medicine, NHO Nagasaki Medical Center, Omura, Japan, ²Pathology, NHO Nagasaki Medical Center, Omura, Japan, ³The First Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan, ⁴Rheumatology, Sasebo Municipal Hospital, Sasebo, Japan, ⁵Clinical Research Center, NHO Nagasaki Medical Center, Omura, Japan

It is not yet clear that chronic inflammation due to persistent IgG4+ plasma cell infiltration can be a foundation for the onset of malignancy. Here we report four cases of IgG4-related disease complicated with neoplastic lesions. Neoplastic lesions complicated were prostate cancer, renal cell carcinoma, lymphomatoid papulosis, IPMN, respectively, and the mean serum level of IgG4 was 746mg/dl. Steroid therapy was performed in all four patients, showing good response to therapy. The three cases underwent surgery for neoplastic lesions, and in the cases of two, IgG4+ plasma cell infiltration was noted as a positive background in addition to the pathologic tumor cells. These cases are considered valuable for the report in considering the outcome of the disease and pathogenesis.

W80-4

Clinical significance of serum BAFF and APRIL levels in IgG4-related disease

Kazuhiro Kiyama, Daisuke Kawabata, Naoichiro Yukawa, Hajime Yoshifuji, Koichiro Ohmura, Takao Fujii, Tsuneyo Mimori

Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine

Aim; To investigate the clinical significance of BAFF and APRIL in patients with IgG4-related disease (IgG4-RD). Methods; We determined serum levels of BAFF and APRIL, and clinical association in patients with IgG4-RD. The serum levels of BAFF and APRIL were tracked following steroid treatment. Results; The serum BAFF and APRIL levels in patients were significantly higher

than those in normal controls. Although clinical parameters such as serum IgG4 and the number of affected organs were not correlated with the levels of BAFF, serum APRIL levels were inversely correlated with serum IgG4 levels. While serum BAFF levels reduced following steroid therapy, serum APRIL levels increased during follow-up. Conclusion; Elevated serum BAFF and APRIL might play a role in the pathogenesis of IgG4-RD.

W80-5

IgG4+multiorgan lymphoproliferative syndrome with allergic disease: 3 cases

Satoshi Hachisuka¹, Hidetoshi Miyakawa¹, Naoki Katsuyama¹, Takahito Kimata¹, Masaomi Yamasaki¹, Shoichi Ozaki²

¹Division of Rheumatology, Yokohama City Seibu Hospital, St. Marianna University School of Medicine, ²Division of Rheumatology and allergy, St. Marianna University School of Medicine

OBJECTIVE: To report 3 cases of IgG4+multiorgan lymphoproliferative syndrome (IgG4+MOLPS) with allergic disease. **METHODS:** Retrospective study of 1 woman and 2 men of IgG4+MOLPS with allergic disease. **RESULTS:** All patients showed high titer of IgG4 levels (ave. 874.8 mg/dl) and infiltration of IgG4+plasma cells in the tissues. All patients had swelling of salivary gland, although no patient had xerostomia and xerophthalmia. Two had a severe bronchial asthma and two had allergic rhinitis. Two had eosinophilia and high IgE levels (ave. 910 IU/ml). All patients were successfully treated with glucocorticoids (mean initial dose, 35mg of prednisone) and showed marked clinical improvement. **CONCLUSION:** There is a possibility that allergic condition is one of the features of IgG4+MOLPS.

W81-1

Institutional patient instruction of Hydroxychloroquine

Naoto Yokogawa^{1,2}, Shoji Sugii^{1,2}, Tsuyoshi Odai^{1,2}, Shinichi Inada^{1,2}

¹Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center, ²Japanese Hydroxychloroquine Study Group

[Background] Hydroxychloroquine is a standard therapy for SLE/CLE and RA. However HCQ is not available in Japan. [Methods] If a patient strongly wishes to use HCQ, the IRB addresses its risk and benefit in each case. If the IRB approves, the patient must import HCQ and follow the instruction by an expert of HCQ. Criteria: 1) cutaneous or musculoskeletal symptoms due to CTD 2) adverse effects or failure by the previous treatment. 3) mandatory eye exam every six months. [Results] IRB approved 13 cases (SLE 8, CLE 1, DM 2, RA 1, Eosinophilic fasciitis 1). No serious adverse events occurred except two minor skin eruption and minor GI symptoms. [Conclusion] Further investigation about efficacy and safety of HCQ in Japan is crucial with collaboration of industry-academic-government.

W81-2

A case of cutaneous lupus introduced hydroxychloroquine therapy

Tokutaro Tsuda, Erika Matsubara

Department of Rheumatology, JR Tokyo General Hospital, Tokyo, Japan

Case is 32 year-old female. She has a past history of depression since 2001. In Jan. 2008, she was suffered from malar rash after laser epilation. Although she was diagnosed SLE, she refused corticosteroid therapy. Her skin symptom remitted and relapsed recurrent-

ly. In Mar. 2009, she was admitted because of exacerbation of skin rash. Physical examinations revealed no specific findings but facial rash. Laboratory data showed leucopenia (3000/ μ L) and lymphopenia (710/ μ L). Moreover, anti-nuclear antibody (1280x.), anti-dsDNA, anti-Sm, anti-RNP and anti-SS-A antibodies were all positive. As topical corticosteroid and tacrolimus were ineffective, oral tacrolimus (3mg/d) was added in Mar 2010. Finally hydroxychloroquine (200mg/d), introduced in Sep.2010, improved her skin symptom in a month.

W81-3

Management of skin lesions in collagen disease with hydroxychloroquine

Akiko Tanikawa^{1,3}, Masayuki Amagai¹, Michito Hirakata²

¹Department of Dermatology, Keio university School of Medicine, Tokyo, Japan, ²Department of Rheumatology, Keio University School of Medicine, Tokyo, Japan, ³Japan hydroxychloroquine study group

Hydroxychloroquine is a standard and worldwide accepted therapeutic option for treatment of SLE, DLE and RA. It has been widely used for more than 50 years, have remained first-line therapeutic agent especially for LE, and the efficacy and safety of hydroxychloroquine has been proven. It not only works well with cutaneous LE which is resistant to topical agents, but also of benefit to joint symptoms and malaise that can accompany cutaneous LE. Here we present patients with SLE, DLE and Sjogren syndrome, whose skin manifestations are well controlled by hydroxychloroquine.

W81-4

Clinical course in 15 patients taking hydroxychloroquine

Mitsumasa Kishimoto^{1,2}, Hikaru Eto^{2,3}, Ken-ichi Yamaguchi¹, Masato Okada^{1,2}

¹Section of Allergy and Rheumatology, St Luke's International Hospital, Tokyo, Japan, ²Japanese Hydroxychloroquine Study Group, ³Department of Dermatology

Hydroxychloroquine (HCQ) is the standard to systemic lupus erythematosus (SLE) treatment in Europe and America, HCQ is also used to prevent exacerbation of lupus activity. In addition, antiplatelet effect in antiphospholipid antibody syndrome and therapeutic effect in cutaneous lupus are reported. HCQ is not widely marketed or prescribed in Japan, excluding for prolonged use in returnees from foreign countries, though recent appeals for authorization have originated from both patients' associations as well as professional organizations of rheumatologists and dermatologists. Here, we report the clinical course in 15 patients continuously taking HCQ (13 SLE, 1 discoid lupus erythematosus (DLE), and 1 RA) at our hospital.

W81-5

The hydroxychloroquine therapy for the intractable Japanese LE skin lesions

Takaharu Ikeda^{1,2}, Fukumi Furukawa^{1,2}

¹Wakayama Medical University, Department of Dermatology, Wakayama, Japan, ²Japan Hydroxychloroquine Study Group

Intractable cutaneous lupus erythematosus (CLE) and the skin lesions of systemic lupus erythematosus (SLE) are administered corticosteroids or immunosuppressants orally which often have serious side effects. Hydroxychloroquine (HCQ) is unapproved in Japan but it is administered to CLE and skin lesions of SLE in Europe and America. As the pilot study in Japan we have administered HCQ to

intractable CLE or the skin lesions of SLE cases which received corticosteroids equivalent to prednisolone under 20 mg/day or the topical therapies, and evaluated the changes of the skin lesions using CLASI. They did not have active or exacerbated internal organ damages and gave the informed consents. Three of 5 cases which had administrated HCQ for 3 months improved the skin lesions.

W82-1

Clinical effect of 2nd biologics in patients with RA who failed anti-TNF therapy

Tomonori Kobayakawa¹, Yuichiro Yabe², Tomone Shioura³, Kiwamu Saito⁴, Nobuyuki Asai⁵, Atsushi Kaneko⁴, Hisato Ishikawa⁶, Seiji Tsuboi³, Yuji Hirano¹, Yukiyo Oishi¹, Toshihisa Kojima⁷, Naoki Ishiguro⁷

¹Toyohashi Municipal Hospital, ²Tokyo Kosei Nenkin Hospital, ³Shizuoka Kousei Hospital, ⁴Nagoya Medical Center, ⁵Nakatsugawa Municipal General Hospital, ⁶Nagano Red Cross Hospital, ⁷Nagoya University

The aim of this study is to compare clinical efficacy of second TNF inhibitor with that of tocilizumab in patients with RA who failed first anti-TNF therapy. The database used was Tsurumi Biologics Communication (TBC). 98 cases who failed anti-TNF agent as first biologics were observed for 24 weeks after the second biologics were initiated. anti-TNF group consisted of 43 cases and TCZ group of 55 cases. SJ, CRP, ESR, and DAS28 were significantly improved in TCZ group compared with the anti-TNF group. It is suggested that TCZ is effective as a second biologics due to its different pharmacological action from those of anti-TNF agents. TCZ is thought to be better as a second biologics in patients who failed first anti-TNF therapy.

W82-2

Tocilizumab is effective in RA who had an inadequate response to etanercept

Ayako Kubota¹, Takashi Nakamura¹, Yoshiyasu Miyazaki¹, Hideko Torihata¹, Masayuki Sekiguchi¹, Toyomitsu Tsuchida², Toru Suguro¹, Kazuaki Tsuchiya¹

¹Department of Orthopaedic Surgery, Toho University School of Medicine, Tokyo, Japan, ²Tsuchida clinic

[Objective] We investigated the efficacy of tocilizumab in rheumatoid arthritis (RA) patients with an inadequate response to etanercept. **[Methods]** 24 RA patients who had an inadequate response to etanercept were analyzed. The surgeries were performed in 12 patients. The clinical efficacy was analyzed by the DAS28 ESR. The synovial tissue, which was obtained during operation, was observed using hematoxylin and eosin stain. **[Results]** The incidence of Good response was 13 joints, Moderate 12 joints. Tocilizumab was well tolerated without serious complications. The synovial histological findings showed the clinical improvement. **[Conclusion]** This study demonstrated that tocilizumab in RA patients who had an inadequate response to etanercept has an efficacy.

W82-3

In TNF failure RA, which is better switching to tocilizumab or alternative anti-TNF?

Naoki Sawa, Yoshifumi Ubara, Eiko Hasegawa, Tatsuya Suwabe, Keiichi Sumida, Rikako Hiramatsu, Masayuki Yamanouchi, Noriko Hayami, Kenmei Takaichi

Kidney Center, Toranomon Hospital, Tokyo, Japan

Background: RA patients with anti-TNF failure (TFRA) may switch to an alternative TNF agent (alt TNF) or tocilizumab (aIL6). It remains unclear which is more beneficial.

Objective: To analyze the effectiveness of aIL6 versus alt TNF on drug survival rate in TFRA.

Methods: A retrospective study of TFRA subsequently received either aIL6 or an 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 65 TFRA patients included; 26 received aIL6 and 39 received an alt TNF. At 24 months, aIL6 group had higher drug survival rate, with significant change. (84.6% vs 50%: p=0.01)

Conclusion: This observational study suggests that switching to aIL6 is more effective than to alt TNF in TFRA.

W82-4

Ten cases of RA patients switching from tocilizumab (TCZ) to TNF α agents

Takako Miura¹, Tomomi Yamashita², Keiko Funahashi², Takafumi Hagiwara¹, Takeshi Nakamura¹, Hiroshi Sunami³, Kosuke Okuda³, Tsukasa Matsubara³

¹Matsubara Mayflower Hospital, Kato, Hyogo, Japan, ²Matsubara Mayflower Hospital, Kato, Hyogo, Japan, ³Matsubara Mayflower Hospital, Kato, Hyogo, Japan

Purpose: TCZ is hardly used as a first-line therapy as it's recommended for TNF α resistant cases. We studied the switching of treatment from TCZ to TNF α agents, assessing patients by CDAI and DAS28-ESR.

Target: 10 RA patients treated with TCZ for 3 months or more. TCZ was switched to infliximab for 3, etanercept for 4, and adalimumab for 3. Reasons for switching; for 7, TCZ was not effective, for 2, end of clinical trial, for 1, an adverse event (pneumonia).

Result: Switching, 2 patients showed low disease activity by CDAI, 4, moderate and 4, high. By DAS, 1 patient achieved clinical remission, 1 showed low disease activity, 4 showed moderate and 4, high.

Conclusion: As the number of subjects was small, 2 out of 10 cases were effective. Evaluation by CDAI tends to be more severe than DAS.

W82-5

Comparison of effects and continuation of biologics therapy for RA patients

Hisanori Nakayama¹, Kanako Iwata¹, Shinichi Nogi¹, Hidekazu Futami¹, Hirokazu Takaoka¹, Yoshiyuki Arinuma¹, Atsushi Hashimoto¹, Toshihiro Matsui¹, Shigeto Tohma²

¹Department of Rheumatology, Sagami National Hospital, National Hospital Organization, ²Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami National Hospital, National Hospital Organization

We examined effects and continuation rates of biologic (Bio) agents therapy for RA patients in our hospital. 192 RA patients had been administrated Bio agents, infliximab (IFX) for 38 patients, etanercept (ETN) for 105, adalimumab (ADM) for 33 and tocilizumab (TCZ) for 16 as initial Bio. 122 patients continued the same Bio therapy, but 47 switched another Bio, and 23 discontinued Bio therapy. The number of patients currently treated with IFX, ETN or ADM decreased (IFX:21, ETN:76, ADM:27), however, TCZ user increased (45). 42.3% of the Bio user reached DAS28 remission level.

el, and 35.3% of them attained CDAI remission. In the patient group treated by TCZ, the reduction of DAS28, CDAI or mHAQ score was greatest relatively, and treatment continuation rate was highest of all Bio groups.

W83-1

Examination of the usefulness of tocilizumab (TCZ) for RA treatment at week 52

Koji Nishimura¹, Takahiko Kurasawa¹, Tsuneo Kondo¹, Ayumi Okuyama¹, Eiko Nishi¹, Hirofumi Takei¹, Hayato Nagasawa¹, Koichi Amano¹, Hideto Kameda², Tsutomu Takeuchi²

¹Department of Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University, Saitama, Japan, ²Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Faculty of Medicine, Keio University, Tokyo, Japan

[Purpose] We investigated the usefulness of TCZ 52 weeks after the start of administration. [Subjects] The subjects were 98 patients with rheumatoid arthritis (RA) (17 males, 81 females). The mean age was 57.2 years. The mean disease duration was 133 months. In 55 patients, MTX (mean dose: 7.5 mg/w) was combined with TCZ. [Results] The continuation rate was 57.1%. The DAS28 (ESR) value decreased from 5.52 to 2.95. An EULAR good response (GR) was achieved in 63 patients (64%), and remission in 47 (48%). Of 55 patients receiving combination therapy with MTX, the DAS28 (ESR) value decreased from 6.15 to 3.16 in 15 in whom MTX was discontinued, and from 5.55 to 3.10 in 40 in whom it was continued. [Conclusion] Its efficacy was confirmed regardless of the presence or absence of MTX.

W83-2

Long-term efficacy of tocilizumab in RA patients in real clinical practice

Yasuhiko Hirabayashi¹, Tomonori Ishii², Michinoku Tocilizumab Study Group^{1,2}

¹Department of Rheumatology, Hikarigaoka Spellman Hospital, Sendai, Japan, ²Department of Hematology and Rheumatology, Tohoku University Graduate School of Medicine, Sendai, Japan

Objective. To evaluate the safety and efficacy of long-term tocilizumab therapy for RA patients in real clinical practice. **Methods.** RA patients who started tocilizumab treatment at several centers between 1 Apr 2008 and 31 Dec 2010 will be surveyed for at least 3 years. Disease activity, laboratory data, and safety issues will be evaluated for all 338 (male 74) patients. **Results.** Mean patient age was 59.3 years, and mean disease duration 10.4 years. Mean DAS28-ESR was 5.1 initially, falling to 2.1 after 1 year. Frequency of adverse events was no more than that for TNF inhibitors. One-year persistence rate was 78.1 %. **Conclusion.** In one-year interim analysis, treatment with tocilizumab was shown to be highly efficacious and generally safe and well tolerated even in a real clinical setting.

W83-3

Tocilizumab has great continuation rate

Yoshihiro Hishitani, Yoshihito Shima, Atsushi Ogata, Masashi Narazaki, Keisuke Hagihara, Toru Hirano, Mari Kawai, Atsuyoshi Morishima

Department of Respiratory Medicine, Allergy and Rheumatic Disease, Graduate School of Medicine, Osaka University

Objective: We examined the continuation rate of biologics for the treatment of rheumatoid arthritis (RA). **Method:** We retrospectively reviewed charts of patients whom we started or changed biologics. **Results:** Of total 195 cases, we were able to follow 183 cases to September 2010 or to the end of administration of biologics. TCZ, Infliximab (IFX), Etanercept (ETN), Adalimumab (ADA) was administered to 74, 77, 48, 46 cases respectively. And they have been continued in 65 (87.8%), 24 (31.2%), 25 (52.1%), 34 (73.9%) cases respectively. Especially, we have used TCZ over 9 years in 8 cases. We stopped IFX, ETN, ADA mainly for the first or the second failure. We stopped TCZ mainly for infection, but the number is same as IFX. **Conclusion:** We were able to use tocilizumab for very long-term, safely.

W83-4

Maintenance of long-term remission of rheumatoid arthritis by tocilizumab

Mitsuhiro Iwahashi, Keisuke Kobayashi, Jiro Yamana, Rie Sasaki, Motoaki Kin, Seizo Yamana

Institute of Rheumatology, Higashihirosima memorial hospital, Higashihirosima, Japan

Subjects and methods: Remission rates were studied in 50 RA patients on TCZ, 70 on IFX and 71 on ETN who started administration of the biological agents by October 2008 and were administered them for 2 years in our hospital. **Results:** Remission was induced after 6 months in 15 (30%), 11 (15.7%) and 17 (23.9%) patients respectively. Remission was maintained after 1 year in TCZ 12 (80.0%), IFX 6 (54.5%) and ETN 12 (70.6%) patients and after 2 years in TCZ 13 (86.7%), IFX 7 (63.6%) and ETN 11 (64.7%) patients respectively. In TCZ 35, IFX 59 and ETN 54 patients who did not achieve remission after 6 months, remission was induced after 1 year in TCZ 14 (40%), IFX 9 (15.3 %), and ETN 7 (13.0%) patients respectively. **Conclusion:** TCZ showed high RA remission induction and maintenance rates.

W83-5

Adherence to biological agents of RA patients in a single institute

Akihide Nampei¹, Hideki Tsuboi², Kenrin Shi³

¹Department of Orthopaedic Surgery, Osaka Rosai Hospital, ²Department of Orthopaedic Surgery, National Hospital Organization Osaka Minami Medical Center, ³Department of Orthopaedics, Osaka University Graduate School of Medicine

Utilization and Adherence to biological agents of 202 RA patients in our institute was examined between November 2003 to July 2010. The kind of biologics selected at first was IFX 94, ETN 51, ADA 14, TCZ 43. Adherence of first bio was IFX 1 year 69.5%, 2 year 57.6%, 4 year 32.8%, ETN 1 year 86.4%, 2 year 69.2%, 4 year 59.3%, ADA 1 year 100%, TCZ 1 year 92.7%. The reason of discontinuance was remission 3, primary failure 16, secondary failure 14, complication 17 in IFX, remission 2, primary failure 3 secondary failure 4, complication 2 in ETN, secondary failure 1 in ADA, remission 3, complication 1 in TCZ. Adherence to biologics selected secondary was IFX 66.7%, ETN 61.6%, ADA 55.6%, TCZ 85.7%. Adherence of first bio was high in ETN, ADA, TCZ, and that of second bio was high in TCZ.

W83-6

The curative effect and a continuance rate of tocilizumab in patients with RA

Fumiharu Yamashita¹, Takanori Nagaoka¹, Noboru Funakoshi¹, Daisuke Mori¹, Mioko Ohzeki¹, Megumi Ito², Taku Yamashita³

¹Kyoto Shimogamo Hospital, ²Meiji University of Integrative Medicine, ³Yamashita

We examined the curative effect and continuance rate of tocilizumab (TCZ) in the patients with RA. [Methods] 30 patients with RA were treated with TCZ infusion from April, 2008 to May, 2010. The average age was 57.2 y.o., mean disease duration 12.8 years, and 23 patients (76.6%) had biological treatment history.

[Result] Mean frequency of TCZ administration was 14.3 times. The continuance rate was 90% after 1 year and 84% after 2 years at the end of October, 2010. 4 cases were withdrawals because of an inefficacy and three adverse events. Curative effects showed 18 complete responses, 8 effectives, 1 inefficacy. The numbers of tenderness joint improved from 6.2 to 1.1, and the numbers of swelling joint from 9.2 to 2.3. The effect attenuation was not seen and the high effect was maintained.

W84-1

Change of finger joint synovial vascularity in response to biologics

Jun Fukae¹, Akihiro Narita¹, Mihoko Henmi¹, Fumihiko Sakamoto¹, Akemi Kitano¹, Yuko Aoki¹, Masato Isobe¹, Masato Shimizu¹, Megumi Matsuhashi¹, Takeya Ito¹, Akio Mitsuzaki¹, Tamotsu Kamishima², Kazuhide Tanimura¹

¹Hokkaido Medical Center for Rheumatic diseases, Sapporo, Japan,

²Department of Radiology, Hokkaido University Hospital, Sapporo, Japan

Background and Objective: Tight control of disease activity enable to achieve complete remission in rheumatoid arthritis (RA). Sensitive and accurate index of therapeutic effect should be needed. We examined change of joint synovial vascularity responded to biologics. Methods: We studied 25 patients with active RA who had started biologics (ADA 10, TCZ 15). Radiography was performed at baseline and the 20th week. Power Doppler ultrasonography was performed at baseline and the 4th week. Results: Sum of 20 finger joints vascularity for each patient significantly decreased from baseline to 4th week (ADA, TCZ, $P=0.0479$, $P=0.0078$). Discussion: Change rate of synovial vascularity decreased in short-term. We next analyze relation of vascularity change and bone destruction in single finger joint.

W84-2

The impact of PRF setting on the synovial Doppler flow

Kei Ikeda¹, Yohei Seto², Shigeru Ohno³, Fumihiko Sakamoto⁴, Mihoko Henmi⁴, Jun Fukae⁴, Akihiro Narita⁴, Daiki Nakagomi¹, Kazuhide Tanimura⁴, Takao Koike⁵

¹Department of Allergy and Clinical Immunology, Chiba University Hospital, Chiba, Japan, ²Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, ³Yokohama City University Medical Center, Center for Rheumatic Diseases, Kanagawa, Japan,

⁴Hokkaido Medical Center for Rheumatic Diseases, Hokkaido, Japan, ⁵Department of Medicine, Hokkaido University Graduate School of Medicine, Hokkaido, Japan

Synovial blood flow in small (2nd MCP) and large (knee) joint in two RA patients was evaluated with semi-quantitative (0-3) and

quantitative (pixel number) scores. The inter-rater reproducibility was remarkably high (ICC: 0.908-0.969). Although there was no significant difference in the Doppler scores among three PRF settings (1300/ 800/ 500 Hz), Doppler signals tended to be rated higher with low PRF than with high PRF in large joint (semi-quantitative score: small joint $p=0.368$, large joint $p=0.097$, Friedman test; quantitative score: small joint $p=0.883$, large joint $p=0.150$, Oneway ANOVA). The result suggests that large joint may require lower PRF setting for sensitive assessment of synovial Doppler flow as compared with small joint.

W84-3

Quantitative analysis of synovitis using 3D ultrasonography with power doppler.

Tsuneo Watanabe¹, Masao Takemura², Masao Sato³, Katsuji Shimizu³

¹Department of Sports Medicine and Sports Science, Gifu University Graduate School of Medicine, Gifu, Japan, ²Section of Clinical Laboratory, Gifu University Hospital, Gifu, Japan, ³Department of Orthopaedic Surgery, Gifu University Graduate School of Medicine, Gifu, Japan

Objective: The purpose of this study was to assess synovial blood flows by three-dimensional volumetric ultrasonography (3DUS) in patients with rheumatoid arthritis (RA). **Methods:** Bilateral 2nd/3rd MP and PIP joints in 25 RA patients were examined by 3DUS. **Results:** Intraobserver reproducibility was high for both observers (observer A, intraclass correlation coefficient (CC) = 0.983; observer B, intraclass CC = 0.969); inter-observer reproducibility was also high (interclass CC = 0.949). 3DUS values were significantly higher in non-responders than those of responders. **Conclusions:** Quantification of 3DUS showed high intra- interobserver agreement. The measurement of 3D power Doppler ultrasound signals might be a valuable tool for the evaluation of the inflammation in RA finger joints.

W84-4

Relationship between synovial blood flow signals and angiogenesis factors

Kenichiro Hirai¹, Makiko Nishioka², Ken Yoshida¹, Daitaro Kurosaka¹, Akio Yamada¹

¹Division of Rheumatology, Department of Internal Medicine, Jikei University of Medicine, Tokyo, Japan, ²Department of Radiology, Jikei University School of Medicine, Tokyo, Japan

Methods: The subjects were 70 patients with RA who fulfilled the diagnostic criteria of the American College of Rheumatology. Ten joints were examined by PDUS. The total blood flow scores of the 10 joints was calculated as the total signal score (TSS). The vascular endothelial growth factor, angiopoietin-1, angiopoietin-2 levels were determined by ELISA. Results: Significant correlations were observed between the TSS and serum VEGF, and Ang-2. 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.

W84-5

Synovitis scoring in ultrasonography;synovial measurement as a reference.

Atsushi Ihata¹, Kouji Kobayashi¹, Kayo Terauchi¹, Toshiyuki Watanabe¹, Reikou Watanabe¹, Sei Samukawa¹, Kaoru Takase¹, Maasa Hama¹, Ryusuke Yoshimi¹, Hiroshi Kobayashi¹, Atsuhisa Ueda¹, Mitsuhiro Takeno¹, Yoshiaki Ishigatsubo¹, Shigeru Ohno²

¹Yokohama City University Graduate School of Medicine, Department of Internal Medicine and Clinical Immunology, Yokohama, Japan, ²Center for Rheumatic Diseases, Yokohama City University Medical Center, Yokohama, Japan

Objective:To Examine the validity of synovial measurement (SyM) as a reference of synovitis scoring (0-3) in small joints.

Method:Fifty cases were randomly selected among 1202 cases. Synovitis score (SySc) was evaluated twice respectively by 3 expert physicians. Cut-off value of SyM was determined using RoC curve analysis. The correlation between Clinical parameters and SySc were assessed in 1202 cases. **Results:**SySc;SyM (sensitivity/specificity) MP joint 0;0-0.7mm (0.7/0.7),1;0.8-1.5mm (0.8/0.7), 2;1.6-2.3mm (0.7/0.8),3;2.4mm-. PIP joint 0;0-0.6mm (0.7/0.7), 1;0.7-1.0mm (0.7/0.6),2;1.1-2.0mm (0.7/0.7),3;2.1mm-. There are no difference between the group using reference and group to evaluate directly in the correlation of SySc and clinical parameters. **Conclusion:**SyM was helpful reference to determine SySc.

W84-6

Evaluation of ultrasonography for RA patients receiving adalimumab

Kazutoshi Aoki, Kentaro Chino
Saitama Social Insurance Hospital

Adalimumab (ADA) is the antiTNF α antibody drug that administration is possible without using MTX, but an effect sometimes recognizes an insufficient case to administer ADA without using MTX. Therefore, we performed ultrasonography (US) to the group of MTX combination, and compared it with the group that did not use MTX. US was performed to 21 patients with RA. Synovial hypertrophy and power Doppler were recorded for each joint with semi-quantitative score (0-3). A group of MTX combination was lower with total SH score and total PD score than the MTX unused group. In conclusion, It was thought that the total SH score and the total PD score were low in ADA and MTX combined use group, and the inflammation of joints could be controlled more.

W85-1

The comparison of ¹⁸FDG-PET and MRI of rheumatoid shoulder

Yukio Yonemoto, Koichi Okamura, Tsutomu Kobayashi, Tetsuya Kaneko, Tsuyoshi Ichinose, Kenji Takagishi
Department of Orthopaedic Surgery, Gunma University Graduate School of Medicine

We assess rheumatoid arthritis (RA) synovitis of shoulder joints with ¹⁸FDG-PET (PET) in comparison with MRI. 42 shoulders in 41 patients (35 women and 6 men) with RA were assessed with PET and MRI. Mean age (range) was 54 (36-75) years and mean disease duration was 9.0 (1-40) years. We measured the SUV of the shoulder joint in PET. We examined axillary pouch (AP), subacromial bursa (SAB), subdeltoid bursa (SDB), rotator interval (RI) and acromioclavicular joint (ACJ) of the shoulder joint synovitis in MRI. AP, SAB, SDB synovitis in MRI were significantly correlated with

SUV. The total number of the synovitis site were significantly correlated with SUV. We thought that the SUV of the PET reflected synovitis by the MRI of the shoulder joint.

W85-2

Usefulness of FDG-PET and MRI in diagnosis of spondyloarthritis (SpA)

Mayuko Tsukida, Azusa Umemoto, Kazuhiko Uchiyama, Noriyuki Sakurai, Hidekazu Ikeuchi, Toru Sakairi, Akito Maeshima, Takashi Kuroiwa, Keiju Hiromura, Yoshihisa Nojima
Department of Medicine and Clinical Science, Gunma University Graduate School of Medicine

We evaluated efficacy of FDG-PET and MRI in diagnosing 5 patients with spondyloarthritis who were admitted to our hospital in 2010. Abnormal uptake of FDG was observed at various axial or peripheral joints in 4 patients. Two patients with high uptake of FDG at sacroiliac joints showed widespread bone edema around the respective area (high signal intensity on STIR) by MRI. On the other hand, remaining 3 patients without significant uptake of FDG at sacroiliac joints showed bone sclerosis (1), small bone edema (1), or no significant change (1) by MRI. FDG-PET is potent to detect axial arthritis in diagnosing SpA. However, combined examination of MRI is more helpful to disclose sacroiliitis because MRI can detect not only sclerosis but also small bone edema which are undetectable in FDG-PET.

W85-3

Imaging analysis of synovitis and bone metabolism by modalities including PET

Toshiyuki Watanabe, Yoshiaki Ishigatsubo, Mitsuhiro Takeno, Atsuhisa Ueda, Atsushi Ihata, Hiroshi Kobayashi, Maasa Hama, Kaoru Takase, Sei Samukawa
Yokohama City University Medical Center

We examined synovitis and bone destruction by multiple modalities including X-ray, MRI, US, FDG-PET, and NaF-PET in two RA patients. In patient 1 who had relapse after discontinuation of tocilizumab, NaF accumulation was found in abnormal joints in X-ray and MRI, whereas FDG accumulation was also accompanied in most, but not all the joints. In patient 2, NaF and FDG-PET detected bone lesions and synovitis, respectively, both of which were illustrated by MRI and US, though X-ray was intact. Six months later after starting etanercept, FDG accumulation and US findings were improved, though strong NaF signals remained in some joints. The present study showed that increased local bone metabolism, bone destruction or repair, continued after inflammatory signs were subsided.

W85-4

Usability of gadolinium-enhanced MRI of bilateral hands for the diagnosis of RA

Yasushi Miura^{1,2}, Koji Fukuda², Masayasu Takahashi², Koji Tateishi³, Masahiro Kurosaka²
¹Department of Rehabilitation Science, Kobe University Graduate School of Health Sciences, Kobe, Japan, ²Department of Orthopaedic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan, ³Konan Kakogawa Hospital

OBJECTIVE: Magnetic resonance imaging (MRI) is considered as a useful tool for the diagnosis of early rheumatoid arthritis (RA). The purpose of this study is to develop and evaluate the sys-

tem for high quality enhanced MRI of bilateral hands for diagnosis of RA.

METHODS: 1.5 Tesla Echelon Vega (HITACHI) was used as the imaging system and added the options including a small table to rest bilateral hands horizontally and a high sensitivity cardiac coil optimized for hand imaging, and a computer analysis software.

RESULTS: Gadolinium-enhanced MRI revealed localized synovitis in hands of patients with RA. The horizontally located images of bilateral hands are comprehensible easily.

CONCLUSION: Enhanced MRI of bilateral hands taken with the system is useful for diagnosis and evaluation of RA.

W85-5

The utility of ultrasonography and MRI in patients with rheumatoid arthritis.

Hiroshi Ogishima, Hiroto Tsuboi, Shinya Hagiwara, Tomoya Hirota, Naoto Umeda, Masanobu Horikoshi, Yuya Kondo, Makoto Sugihara, Takeshi Suzuki, Taichi Hayashi, Isao Matsumoto, Takayuki Sumida

Division of Clinical Immunology, Doctorial Program in Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Ibaraki, Japan

[Purpose] To assess the utility of US and plane MRI in the patients with RA. [Methods] Both hands of 34 RA patients, a total of 748 joints, were examined by US-PD and MRI. [Results] (1)The sensitivity and specificity of US-PD for the swollen joints were 38.9% and 89.8%, respectively. 10.2% of the joints without swelling had vascular signal by US-PD. (2)The sensitivity and specificity of MRI for the swollen joints were 58.0% and 86.2%, respectively. 13.8% of the joints without swelling showed synovitis by MRI. (3)17.8% of the joints without swelling had active synovitis by US-PD and/or MRI. [Conclusion] The sensitivity of MRI for the swollen joints was higher than US-PD. US-PD and MRI were useful tools to detect latent synovitis of RA patients.

W85-6

A comparison of articular US and enhanced MRI in rheumatoid arthritis diagnosis

Hidetaka Ishino, Masataka Kohno, Amane Nakabayashi, Takashi Kida, Hidetake Nagahara, Wataru Fujii, Ken Murakami, Kaoru Nakamura, Takahiro Seno, Aihiro Yamamoto, Yutaka Kawahito
Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Objective: To compare gray scale, power doppler ultrasonography (GSUS, PDUS) and enhanced magnetic resonance imaging (MRI) maximum intensity projection (MIP) method in the diagnosis of rheumatoid arthritis (RA).

Methods: Sixteen RA patients (2men, 14 women) were enrolled. Mean age was 58.4 years, and mean DAS28 (ESR) was 4.6. The MCP and PIP and bilateral wrists joints were scanned by GSUS PDUS and MRI.

Results: Out of 352 joints, arthritis were detected in 176 joints on MRI, 144 joints on PDUS. Sensitivity of PDUS arthritis to MRI-detected arthritis was 82%. The majority of PDUS vascularity is compatible MRI synovitis.

Conclusion: GSUS might be more sensitive than MRI for detecting early arthritis and useful for followup arthritis. MRI imaging might be more detectable in active synovitis than PDUS.

W86-1

The Safty and Efficacy of Abatacept in Patients with Rheumatoid Arthritis

Shuji Ohta, Seiji Mogi

Taga General Hospital Hitachi Ltd, Department of Rheumatology, Ibaraki, Japan

Objectives: To assess the efficacy and safety of Abatacept (ABT) during 96-weeks of the Phase3 trial in patients with rheumatoid arthritis (RA).

Methods: Safety and efficacy (DAS28-CRP, CDAI) in our institute were assessed through 96-weeks.

Results: A total of eight patients were treated (women:7, mean ages: 54.9years, mean duration of RA:12.0years); Two patients had previously failed other biologics and all were on MTX combination. All patients were continued, seven achieved DAS-CRP remission ($2.3 >$), mean:1.8, CDAI remission ($2.8 \geq$) was two:25%, mean5.0. Adverse events (AEs):seven patients, 88%, serious AEs:one, 12.5%, was occurred. But no discontinuations due to AEs.

Conclusions: These data suggests that ABT can provide sustained disease modification in patients with RA.

W86-2

Experiences of Abatacept therapy for RA in the open-label extension trial

Eiko Nishi¹, Koichi Amano¹, Hayato Nagasawa¹, Hirofumi Takei¹, Ayumi Okuyama¹, Takahiko Kurasawa¹, Tsuneo Kondo¹, Koji Nishimura¹, Tsutomu Takeuchi²

¹Saitama Medical Center, Saitama Medical University, Saitama, Japan, ²Division of Rheumatology and Clinical immunology, Department of internal Medicine, Faculty of Medicine, Keio University, Tokyo, Japan

Objectives: To assess the efficacy and safety of Abatacept (ABT) in Rheumatoid Arthritis (RA). **Methods:** Clinical efficacy and safety profile were assessed for patients enrolled in our institute at 96-weeks. DAS28-CRP was assessed and all safety data were collected. **Results:** A total of 9 patients were enrolled (female: 6; mean ages: 53.1 years; mean duration of RA: 10.8 years). Eight were on MTX combination and one on ABT monotherapy of 10mg/kg. All patient were continued at the 96-week point, and 6 achieved DAS-CRP remission defined by <2.3 . No serious AE was occurred. **Conclusions:** Abatacept showed good clinical efficacy as well as favorable safety profiles.

W86-3

Efficacy and safety in the treatment of abatacept to the patients with RA

Hisato Ishikawa¹, Toshihisa Kanamono^{1,2}, Toshihisa Kojima², Atsushi Kaneko³, Naoki Ishiguro²

¹Department of Orthopedics, Nagano Red Cross Hospital, ²Department of Orthopaedic, Nagoya University School of Medicine, ³Department of Orthopedics, Nagoya Medical Center

【 purpose 】We reports about efficacy and safety of the patient treated by Abatacept in the Tsurumai Biologics Communication participation facilities. 【 method 】Efficacy and safety were examined about 15 patients that began from long-term administering examination. 【 result 】12 of 14 patient of beginning Abatacept from Phase II and the continued administration in the long-term administering examination of 15 including three new putting in examples now excluding the dropout by the adverse event of one example. As for ef-

fectiveness, the EULAR improvement standard, nine examples were good response, and five examples were moderate response. 【 conclusion 】For 15 cases of the long-term administering examination, in this examination, efficacy and the safety of Abatacept were confirmed.

W86-4

Analysis of the clinical efficacy index for Abatacept (ABT)

Keiko Funahashi¹, Tomomi Mamashita¹, Takafumi Hagiwara², Kosuke Okuda², Takeshi Nakamura², Takako Miura², Tsukasa Matsubara^{1,2}

¹department of Clinical research, Matsubara Mayflower Hospital, Hyogo, Japan, ²department of Rheumatology, Matsubara mayflower Hospital, Hyogo, Japan

(Object) ABT is the fifth biologic product to be used in Japan, but its mechanism of action differs from other biologics. To determine its best use, we sought for methods to assess efficacy.(Method) We assessed data of 28 ABT-treated patients from a clinical trial using DAS28-CRP, DAS28-ESR, CDAI and SDAI for clinical evaluations and CRP, ESR, MMP-3, and SAA for blood tests to determine the best markers to assess efficacy. (Results) Six months after administration all relations among markers correlated except CRP and CDAI, and ESR and DAS28-CRP. MMP-3 correlated with the evaluation index for drug efficacy and SDAI correlated with blood test values. Also, SAA showed a stronger correlation than CRP. (Conclusion) SDAI is the best method of evaluation and SAA and MMP-3 are as important as CRP.

W86-5

Sub-analysis of Abatacept Clinical Trial Results in Japanese RA patients

Yukitomo Urata^{1,6}, Tohru Abe^{2,6}, Tsutomu Takeuchi^{3,6}, Ami Yamamoto⁴, Nobuyuki Miyasaka^{5,6}

¹Seihoku Chuoh Hospital, ²Saitama Medical Center, ³Division of Rheumatology, Keio University School of Medicine, ⁴Clinical Strategy, Bristol-Myers Squibb Japan, ⁵Department of Medicine and Rheumatology, Tokyo Medical and Dental University, ⁶Japan Abatacept Study Group

Background: Abatacept, a fusion protein of CTLA-4 and Fc portion of IgG1, is a new biologic agent for RA treatment. Long-term efficacy and safety were confirmed and reported (Matsubara et al, JCR 2010). Here we report the sub-analysis of the relationship between baseline characteristics and efficacy or safety profiles at 48 weeks.Methods:The relationship between DAS28 remission at 48W and the BL characteristics were evaluated. Relationships among infections, SAEs as well as anti-abatacept positivity with efficacy, were also analyzed.Results:DAS28 remission strongly associated with BL DAS, tender joint numbers, steroid dosing and previous biologics usage. No clear risk factors related to infections and SAEs were confirmed. Anti-ABT Ab positivity was not associated with decrease of efficacy.

W86-6

Experiences of treatment of Rheumatoid Arthritis with Abatacept

Masaya Mukai¹, Tatsuya Atsumi², Makoto Kondo¹, Takao Koike²

¹Sapporo City General Hospital, ²Department of Medicine II. Hokkaido University School of Medicine

Objective: To clarify the clinical usage of abatacept (ABT) in treatment of RA. Method : We evaluated 11 RA patients (8 female,3 male) who participated in ABT Phase II and III trials in our hospitals. The mean age was 52 years and the mean duration of RA was 6 years. Results: Throughout the P II to the 96-week point of long-extension P III trial, five out of 8 (62.5%) achieved low disease activity at the point of 96-week of PIII, and 50.0% (4/8) achieved DAS28 remission (DAS28-CRP<2.6).Three of the 11 patients discontinued during this period until 96 weeks, one due to lack of efficacy and one adverse events (interstitial pneumonia) and the other one due to withdrawal of consent.Conclusion: ABT showed favorable efficacy and safety in RA treatment.

W87-1

The study of choice and effect with anti-cytokine therapy in RA patients

Shino Yuasa¹, Kenji Tani¹, Shingo Kawaminami¹, Ryo Tabata¹, Akifumi Honjoh¹, Harutaka Yamaguchi¹, Mitsuhiro Kohno¹, Teruki Shimizu², Junya Miyata³, Mayuko Nakayama⁴, Jun Kishi⁵, Yuko Toyoda⁵, Saburo Sone⁵

¹Department of General Medicine, Tokushima University Graduate School, ²Tohyoh Hospital, ³Mino Hospital, ⁴Hanoura orthopedic and internal Hospital, ⁵Department of General Medicine and Department of Respiratory Medicine & Rheumatology, Tokushima University

We investigated the frequency of use, clinical effects and adverse events of anti-cytokine therapies (BIO) in RA patients. 79 patients treated with BIO at the first time from April in2009 to October in 2010 were evaluated. We checked backward-looking the kind of BIO and switching, use of MTX, clinical effect by DAS28-CRP, and adverse events. There were 22 cases in IFX, 36 cases in ETN, 10 cases in ADM, and 11 cases in TCZ as the first BIO. MTX was used in 35 cases. Change of BIO was needed in 12 cases because of poor response or adverse events; 5 cases in IFX, 4 cases in ETN, a case in ADA, and a case in TCZ. ETN, ADA, and TCZ were selected in 4 cases, 5 cases, and 2 cases, respectively, as the second BIO. IFX was most frequently changed to another one, and was not used in the second line.

W87-2

Comparison of infliximab and etanercept - LUNDEX from a 5-year observation

Koji Takasugi¹, Misuzu Yamashita¹, Masamitsu Natsumeda¹, Ryutaro Yamanaka¹, Kayo Ezawa¹, Kazuhiko Ezawa¹, Yoshihisa Nasu², Keiichiro Nishida³, Shinichiro Fujita⁴, Sanae Ishii⁵, Wataru Yamamoto⁶

¹Department of Internal Medicine, Kurashiki Kosai Hospital, Kurashiki, Japan, ²Department of Orthopaedic Surgery, Kurashiki Kosai Hospital, Kurashiki, Japan, ³Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, ⁴Department of Rehabilitation, Kurashiki Kosai Hospital, Kurashiki, Japan, ⁵Department of Nursing, Kurashiki Kosai Hospital, Kurashiki, Japan, ⁶Department of Health Information Manage, Kurashiki Kosai Hospital, Kurashiki, Japan

【Purpose】The crinical study of ETN and IFX. 【Method】Eighty two patients (ETN:n=40, IFX:n=42) was initiated for 60 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 5 years were 37.5% (ETN), 31% (IFX). DAS28 remission: 27.5% (ETN), 28% (IFX). LUNDEX-DAS28 remission: 10.3 (ETN), 8.9 (IFX). In ETN, 45.5% of patients had no radiographic progression, compared with 34.5% in IFX. First-line ETN had higher overall LUNDEX values compared with second-line ETN and IFX, mostly because of a higher rate of adherence. **【Conclusion】**As for first-line ETN, an especially useful possibility was suggested at effectiveness and the continuance rate.

W87-3

Comparison of biological agents as drugs of second choice in our department

Wataru Shimada¹, Yasunori Itoh¹, Masakatsu Saito¹, Hiraku Kikuchi¹, Harutoshi Tsujimoto²

¹Department of Orthopaedic Surgery, Sakai Hospital Faculty of Kinki University School of Medicine, Osaka, Japan, ²Department of Rehabilitation, Sakai Hospital Faculty of Kinki University School of Medicine, Osaka, Japan

Objective: To investigate which is more useful, another TNF inhibitor or IL-6 receptor antagonist with a different action target in a switch from a TNF inhibitor as the 1st drug to a 2nd drug. **Method:** We evaluated changes in DAS28 and MMP3 at 6 months and the completion rate for 1 year in 21 pts switched to a 2nd biological agent (BA). **Results:** Pretreatment drugs in the IL-6 receptor antagonist (group I) were ETN in 8, IFX in 1 and ADA in 1 pt. In the TNF inhibitor group (group T), they were ETN in 5, IFX in 5 and ADA in 1. In group I, DAS28 was 4.99 at switch and 3.06 after 6 months and MMP3 491.7/123.1. In group T, DAS28 was 5.12/4.57 and MMP3 278.0/407.7. Completion rates were 90.0% in group I and 36.3% in group T. **Conclusion:** IL-6 receptor antagonist was an excellent BA of 2nd choice.

W87-4

The comparison of survival rate and clinical results in three TNF inhibitors

Tsuyoshi Ichinose^{1,2}, Takeo Sakurai^{2,3}, Yasuyuki Tamura², Yoshihiro Yamashina², Takenobu Iso³, Koichi Okamura¹, Yukio Yonemoto¹, Hiroshi Inoue^{2,3}, Kenji Takagishi¹

¹Department of Orthopaedic Surgery Gunma University Graduate School of Medicine, ²Inoue Hospital, ³Gunma RA clinic

The aim of this study is to compare three TNFa inhibitors regarding the drug survival rate and the clinical results.

We included 76 patients administered the TNFa inhibitor, infliximab (INF) or etanercept (ETN), or adalimumab (ADA). We investigated the drug survival rates, and the dose of MTX, PSL, DAS28, CRP at 0 month, 6 months and 12 months after the administration by medical records.

There was no statistical difference in drug survival rates among three drugs, but DAS28 in INF at 6 months and at 12 months were significantly higher than that in ETN.

A past study reported that ETN had the longest drug survival rates, ADA had the highest, and INF had the lowest rates of treatment response. Our study showed no statistical difference in drug survival rates, but showed similar clinical results.

W87-5

Prediction of clinical effect by DAS28 at the 6 months after biologics therapy.

Ken Hasegawa¹, Syunichi Imai²

¹Department of Orthopaedic Surgery, Chiaki Hospital, Ichinomiya, Japan, ²Rheumatoid Arthritis Center, Minami Medical Health Cooperation, Nagoya, Japan

Background. It was examined whether subsequent clinical response is predicted by disease activity score at the six months after biologics therapy. **Methods.** DAS28<3.2 (effective) group was compared to DAS28≥3.2 (ineffective) group in 77 RA patients who continued biologics therapy over 6 months (including 33 IFX, 31 ETN, 9 ADA, and 22 TCZ patients). **Results.** At the 12 months after biologics therapy, DAS28 of TCZ ineffective group tended to improve, however that of IFX, ETN and ADA ineffective group did not improve, and clinical remission cases were seen in IFX, TCZ ineffective group, however were not seen in ETN, ADA ineffective group. **Conclusions.** DAS28 at the six months after biologics therapy should be a useful index in clinical decision whether to switch or to continue biologics therapy.

W87-6

Improvement of QOL in RA patients treated with IL-6 inhibitor and TNFa inhibitor

Mie Fusama¹, Hideko Nakahara², Yoshimasa Hamano², Takashi Hosokawa², Masayuki Nishide², Keisuke Kawamoto², U Rin², Shinji Higa², Tsuyoshi Igarashi², Taro Kuritani², Keiji Maeda²

¹Division of Nursing, NTT West Osaka Hospital, ²Division of Allergy, Rheumatology and Connective Tissue Diseases, Department of Internal Medicine, NTT West Osaka Hospital

We examined QOL of RA patients treated with IL-6 inhibitor (tocilizumab (TCZ)) or TNFa inhibitor (infliximab (INF), etanercept (ETN)). SF-36 and AIMS-2 were examined at 1, 3, 6 months in 36 RA patients (TCZ: 20, IFX: 13, ETN: 3) who were satisfied with good or moderate response in EULAR response criteria at 6 months (average DAS28-CRP (IL-6 inhibitor: TNF inhibitor); at baseline (5.5: 5.5), at 6 months (2.4: 2.3)). Baseline characteristics did not differ between two groups. Three scores (Physical, Work, Psychological) of AIMS-2 and three subclasses (PF, RP, VT) of SF-36 improved significantly at 1 month by IFX, while at 3 months by TCZ. At 6 months, all scores except social interaction in AIMS-2 improved. These data indicate that TNF group improved QOL slightly rapidly compared with TCZ.

W88-1

Thrombospondin-2 augments type I collagen in scleroderma

Ikko Kajihara¹, Masatoshi Jinnin¹, Takamitsu Makino¹, Minoru Hasegawa², Manabu Fujimoto², Hironobu Ihn¹

¹Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan, ²Department of Dermatology, Kanazawa University Graduate School of Medical Science

Scleroderma (SSc) is an acquired disorder which typically results in fibrosis of the skin and internal organs. The thrombospondins (TSPs) family consists of 5 subtypes. TSP-1 and TSP-5 was shown to be increased in SSc fibroblasts. In this study, we investigated the expression pattern and role of TSP-2 in SSc in the pathogenesis of this disease. In SSc, TSP-2 synthesis inside the fibroblasts is down-regulated at the transcriptional level, whereas the extracellular

accumulation of TSP-2 protein in the tissue and serum is increased due to the decreased degradation activity of TSP-2 protein. The extracellularly increased TSP-2 deposition contributes to the tissue fibrosis by its inductive effect on collagen expression.

W88-2

Platelet-derived microparticles in patients with connective tissue diseases

Chinami Oyabu¹, Akio Morinobu², Daisuke Sugiyama³, Jun Saegusa³, Sahoko Morinobu², Goh Tsuji², Shimpei Kasagi², Seiji Kawano^{1,2}, Shunichi Kumagai^{2,3}

¹Department of Clinical Laboratory, Kobe University Hospital, ²Department of Clinical Pathology and Immunology, Kobe University Graduate School of Medicine, ³Department of Evidence-Based Laboratory Medicine, Kobe University Graduate School of Medicine

Plasma PDMP levels were measured by ELISA in patients with SLE, SSc, PM/DM, and MCTD. PDMP levels were higher in patients with MCTD and SSc than in controls. Patients with Raynaud's phenomenon showed higher PDMP levels than those without. PDMP levels in individual patient did not fluctuate significantly over several months. PDMP level could be a novel marker for Raynaud's phenomenon.

W88-3

Long term follow-up of therapeutic angiogenesis against intractable skin ulcer

Kouji Kobayashi, Yoshiaki Ishigatsubo, Mitsuhiro Takeno, Atsuhisa Ueda, Shigeru Ohno, Atsushi Ihata, Hiroshi Kobayashi, Ryusuke Yoshimi, Maasa Hama, Kaoru Takase, Sei Samukawa, Reikou Watanabe

Yokohama City University Graduate School of Medicine, Department of Internal Medicine and Clinical Immunology, Kanagawa, Japan

Objective: To examine the long term safety and efficacy of angiogenesis by the autologous transplantation of bone-marrow derived cells in patients who have ulcers resistant to conventional therapy. **Patients and Methods:** Eleven cases which received autologous transplantation were observed for more than two years. Relapse of ulcer, new ulcer and serious adverse effect are evaluated at every 6 months. The duration of follow-up was 410 men•months. **Results:** In all cases, ulcers are once cured. Four cases were relapsed and the median time to relapse of ulcer was 16 months. Two cases were recovered by the second autologous transplantation. There were no serious adverse effects in all cases. **Discussion:** therapeutic angiogenesis was found to be a novel and useful approach to intractable ulcers.

W88-4

The Effectiveness of aPBSCT for Interstitial Lung Diseases in Systemic Sclerosis

Toshio Odani, Shinsuke Yasuda, Yuka Shimizu, Michihito Kono, Yusaku Kanetsuka, Takashi Kurita, Yuichiro Fujieda, Masaru Kato, Kotaro Otomo, Shinji Fukaya, Tetsuya Horita, Tatsuya Atsumi, Takao Koike

Department of Internal Medicine II Hokkaido University Graduate School of Medicine, Sapporo, Japan

Objectives: To evaluate the effectiveness of auto-PBSCT on ILD in patients with SSc. **Methods:** ILD was evaluated using high resolution computed tomography images (HRCT), respiratory function, serum KL-6 and serum LDH for 2 years and compared be-

tween 10 early patients treated with aPBSCT and 28 without. HRCT findings was classified into improve, conservation or worsening, based on interpretation by radiologists. **Results:** In the aPBSCT group, 6 had ILD in the observation period. ILD was improved in 3 patients and was worsened in 2 patients. In the conventional treatment group, 18 had ILD. Whereas none of them showed improvement in ILD, worsening of ILD was observed in 6 patients. Other items showed no difference. **Conclusions:** aPBSCT may stabilize the worsening of ILD in patients with SSc.

W88-5

CD34+ selected and unmanipulated autologous HSCT for systemic sclerosis

Hiroshi Tsukamoto¹, Takahiko Horiuchi¹, Hiroaki Niiro¹, Yojiro Arinobu², Yasushi Inoue¹, Kentaro To¹, Naoyasu Ueda¹, Atsushi Tanaka¹, Shun-ichiro Ota¹, Mine Harada³, Koichi Akashi¹

¹Department of Clinical Immunology, Rheumatology, and Infectious Diseases, Kyushu University Hospital, Fukuoka, Japan, ²Center for Cellular and Molecular Medicine, Kyushu University Hospital, Fukuoka, Japan, ³National Hospital Organization, Omuta Hospital, Omuta, Japan

[Objective] To study and compare the efficacy and safety of CD34+ selected and unmanipulated autologous hematopoietic stem cell transplantation (auto-HSCT) for systemic sclerosis (SSc). **[Methods]** Nineteen patients with SSc were received auto-HSCT with (n=11) or without (n=8) CD34+ selection. **[Results]** Skin sclerosis and interstitial pneumonia was improved and the serum levels of anti-Scl-70 and KL-6 were significantly decreased for 5 years after auto-HSCT. CD34+ selected auto-HSCT was significantly more effective on skin sclerosis, on the other hand, was more strongly associated with viral infection. The delayed and Th1-skewed reconstitution of CD4+ T cells was observed in both groups. **[Conclusion]** CD34+ selected auto-HSCT is more immunosuppressive than unmanipulated auto-HSCT.

W89-1

High Expression of Gene Transcripts Systemic Sclerosis with ILD

Toshio Odani, Shinsuke Yasuda, Yuka Shimizu, Michihito Kono, Yusaku Kanetsuka, Takashi Kurita, Yuichiro Fujieda, Masaru Kato, Kotaro Otomo, Shinji Fukaya, Tetsuya Horita, Tatsuya Atsumi, Takao Koike

Department of Internal Medicine II Hokkaido University Graduate School of Medicine, Sapporo, Japan

Objectives: To identify gene expression in SSc patients with ILD.

Methods: Mixed RNA samples prepared from peripheral blood mononuclear cells (PBMCs) were subjected to gene expression arrays (2sets). Gene which were commonly up-regulated in ILD patients were further investigated. PBMCs were collected from 43 SSc patients (25 with ILD), and 71 patients with other autoimmune disease (39 with ILD). The expression levels of the gene in each individual were evaluated by real-time qPCR.

Results: HLA-DRB5 was the only up-regulated gene in both sets. HLA-DRB5 expressions were significantly higher in PBMCs from SSc with ILD compared with those without (p=0.007).

Conclusion: Up-regulated expression of HLA-DRB5 was correlated with the development of ILD in patients with SSc.

W89-2

The efficacy of inhaled NAC in SSc patients with chronic interstitial pneumonia

Yoshiko Sumita, Mariko Sato, Mayuko Moriyama, Masahiro Kondo, Yohko Murakawa

Department of Rheumatology, Shimane University Faculty of Medicine, Izumo, Japan

We report that 2 patients diagnosed as systemic sclerosis (SSc) with chronic interstitial pneumonia. They were effectively treated with inhaled N-acetylcysteine (NAC) as additional therapy to immunosuppressant. The inhaled NAC treatment was continued for 6 months. The clinical courses, lung function (%FVC, %DLco), changes of chest CT, and changes in serum markers for interstitial pneumonia (KL-6) were examined. After the inhalation NAC was added, the symptom of dyspnea, lung function and KL-6 were improved without change of immunosuppressant in both cases. Our cases suggested that NAC inhalation is safety and useful for the treatment of chronic interstitial pneumonia with SSc.

W89-3

Quantitative analysis of GI symptoms of patients with SSc by ¹³C breath tests

Tatsuhiro Yamamoto, Hirahito Endo, Koutarou Shikano, Makoto Kaburaki, Sei Muraoka, Nahoko Tanaka, Kaichi Kaneko, Yoshie Kusunoki, Shinichi Kawai

Division of Rheumatology, Department of internal Medicine (Omori) School of medicine, Faculty of Medicine, Toho University, Tokyo, Japan

To determined the quantitative analysis of the severity of GI symptoms and therapeutic strategy in patients with SSc, we measured ¹³C-fatty acid and ¹³C-acetate breath test. ¹³C-fatty acid breath test were performed in 30 patients with SSc and normal subjects for control. Using breath test data fatty acid absorption were calculated by the time peak excretion (T max) and cumulative ¹³C excretion for 8 hours. ¹³C-acetate breath test collected for ¹³CO₂ and hydrogen gas. A Tmax in SSc was markedly longer than control. ¹³C cumulative excretion curve was correlated with a disease severity score for clinical GI symptoms in SSc. High level of hydrogen in emptying excretion breath showed bacterial overgrowth in intestine. ¹³C-absorption breath test is a useful tool for evaluation of GI symptoms.

W89-4

The small intestinal clearance in patients with systemic sclerosis

Naoaki Hashimoto^{1,2}, Masahiro Sekiguchi¹, Naoto Azuma¹, Masayasu Kitano¹, Kiyoshi Matsui¹, Tsuyoshi Iwasaki³, Hajime Sano¹, Takenori Hashimoto²

¹Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan, ²Hashimoto Clinic for Rheumatic Diseases, Osaka, Japan, ³Department of Pharmacy, School of Pharmacy, Hyogo University of Health Sciences, Kobe, Japan

Objective: The aim of this study was to evaluate the small intestinal clearance (SIC) in SSc patients using the barium meal follow through (BMFT) test. **Methods:** The BMFT were performed in 86 SSc patients. The SIC was classified according to barium meal reach at 30 min after intake, grade I (>2/3 of the whole small intestine), grade II (1/3~2/3), grade III (<1/3), grade IV (until the duodenum). **Results:** The SICs of SSc patients were 30.2% in grade I; 30.2% in grade II; 29.1% in grade III; 10.5% in grade IV. The mean of diame-

ters (mm) of esophagus were 22.6 in grade I, 28.0 in grade II, 38.8 in grade III, 40.7 in grade IV. There was close correlation between SIC grading and esophageal diameter (p<0.0001). **Conclusion:** These results indicate that the BMFT is useful for the evaluation of SIC in SSc patients.

W89-5

Number of dermis mast cells at distal finger correlates with severity of SSc

Sonosuke Yukawa, Kunihiro Yamaoka, Norifumi Sawamukai, Kazuyoshi Saito, Yoshiya Tanaka

The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan

Although the involvement of mast cells (MCs) in human SSc pathology has been suggested, co-relation with organ involvement has not been clarified. Skin biopsy from finger and forearm was performed in 54 cases in the purpose of diagnosis of SSc. Number of dermis MCs at finger but not forearm highly co-related with increased mRSS. In addition, patients with positive anti-Scl-70 antibody showed increased MC numbers. Accordingly, MCs was increased in patients with PAH, showing strong relation with estimated mean PAP measured by ultrasound. Our results further support the notion of MC involvement in the pathology of SSc and also suggest the usefulness of skin biopsy from distal finger. As a conclusion, MCs can be a new treatment target for SSc, a disease with a few treatment strategies.

W89-6

Notch pathway is activated in Systemic Sclerosis (SSc).

Kae Takagi, Yasushi Kawaguchi, Chikako Fukazawa, Yuko Ota, Akiko Tochimoto, Sayumi Baba, Hisae Ichida, Yuko Okamoto, Takahisa Gono, Yasuhiro Katsumata, Masako Hara, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's medical University, Tokyo, Japan

Objective

Notch pathway has been implicated in the process of human development and cellular differentiation. Association of Notch1 in fibrosis was reported. Contribution of Notch pathway in fibrosis of Systemic sclerosis (SSc) was investigated.

Methods

The expression of Notch and ligand was determined by real-time quantitative RT-PCR and immunohistochemistry (IHC) in skin fibroblasts of SSc and healthy controls (HC). Modulation of Notch pathway by TGFβ and PDGF was also investigated.

Results

Expression of Notch1, 2, 3, and DLL1, 4, JAG1 was detected in fibroblast. Expression of Notch1 and 3 was lower in SSc than HC. TGFβ but not PDGF stimulation down regulated Notch1 mRNA Expression. **Conclusion**

Notch signaling pathway may play a critical role for fibrosis in SSc patient.

W90-1

Vascular manifestations of Behçet's disease in Japan: a survey of 98 patients

Akiko Suda¹, Haruko Ideguchi², Mitsuhiro Takeno³, Shohei Nagaoka¹, Yoshiaki Ishigatsubo³

¹Department of Rheumatology, Yokohama Minamikyosai Hospital, Yokohama, Japan, ²Center for Rheumatic Disease, Yokohama City

University Medical Center, Yokohama, Japan, ³Department of Internal Medicine and Clinical Immunology, Yokohama, Japan, ⁴Department of Epidemiology and Environmental Health, Jyuntendou University, Tokyo, Japan, ⁵Department Of Public Health, Faculty Of Medicine, Saitama Medical University, Saitama, Japan, ⁶Department of Public Health, Jichi Medical University, Tochigi, Japan

We collected data of 98 vasculo-BD patients from 37 hospitals from all over the Japan by questionnaires. Of 98 patients, 69 (70%) were male, onset of BD and vascular lesions were 40.5 and 45.2 y.o., respectively. Of arterial lesions (65%), arterial aneurysm was the most common (42%), whereas deep vein thrombosis the leading venous lesion (41%) in the all venous lesions (52%). Seventeen patients had the both. Surgical operation was conducted in 50 patients (51%), including 6 patients having reoperation. Prednisone and immunosuppressants were given to 69 (70%) and 23 patients (23%), respectively. Infliximab was given to 5 patients (5%), but 4 of them were treated for concurrent gastrointestinal involvement. Although warfarin was used in 46%, lethal hemoptysis was not seen.

W90-2

Characteristics of vascular involvement in Japanese Behçet's disease

Haruko Ideguchi¹, Akiko Suda^{2,3}, Mitsuhiro Takeno², Atsuhisa Ueda², Shigeru Ohno¹, Yoshiaki Ishigatsubo²

¹Center for Rheumatic Diseases, Yokohama City University Medical Center, Yokohama, Japan, ²Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan, ³Department of Rheumatology, Yokohama Minami Kyousai Hospital, Yokohama, Japan

We retrospectively examined clinical features of 26 patients (male 16) with large vessel involvement in 412 BD patients receiving care in our two hospitals from 1991 to 2007. Arterial and venous lesions were found in 8 (31%) and 21 patients (81%), respectively, including 3 patients (12%) having both. Pulmonary artery occlusion (19%), and deep vein thrombosis of the limbs (77%) were the most common of arterial and venous lesions, respectively. Lower frequency of ocular involvement ($p < 0.05$) and higher incidence of gastrointestinal involvement ($p < 0.001$) were found in vasculo-BD patients when compared with the other subtypes of patients. Nine patients received warfarin without bleeding events including hemoptysis. There was one postoperative death due to aortic aneurysm.

W90-3

Efficacy of anti-TNF therapy in patients with refractory entero- Behçet's disease

Ippei Miyagawa, Kazuyoshi Saito, Shigeru Iwata, Kunihiro Yamaoka, Shintaro Hirata, Shizuyo Tsujimura, Masao Nawata, Yoshiya Tanaka

The First Department of Internal Medicine, University of Occupational & Environmental Health, School of Medicine, Kitakyushu, Japan

Entero- Behçet's disease (BD) is one of the serious pathological conditions that determine prognosis in BD patients. Although high dose of corticosteroid (CS) and immunosuppressants are widely used for treatment, refractory entero-BD is difficult to manage and effective treatment remains elusive. We assessed the efficacy of anti-TNF therapy, in 17 patients with entero-BD who failed to respond to conventional therapy. The patients including 4 men and 13 women were enrolled. The mean age was 40.7 years and mean duration of

Entero-BD was 34.5 months. 13 patients showed improvement of gastrointestinal symptoms and disease-associated complications. Furthermore, the dose of CS was significantly reduced. The results suggest that anti-TNF therapy is an effective treatment for Entero-BD patients.

W90-4

The effectiveness of Infliximab therapy for Behçet's disease in Japan

Reikou Watanabe¹, Mitsuhiro Takeno¹, Yoshiaki Ishigatsubo¹

¹Department of Internal Medicine and Clinical Immunology, Yokohama City Graduate School of Medicine, ²Department of Advanced Therapeutics for GI Diseases, Graduate School, ³Department of Epidemiology and Environmental Health, Juntendo University School of Medicine, ⁴Department of Public Health, Jichi Medical University, ⁵Department of Public Health, Faculty of Medicine, Saitama Medical University

We retrospectively collected clinical data of 89 patients who had received infliximab (IFX) therapy for intestinal Behçet's disease from 38 institutes in all over the Japan by using a questionnaire form. Ileocecal ulcers were the most common. Most of patients had refractory intestinal lesions to conventional therapies including corticosteroids, whereas 33% of the patients had received operation. Any protocols of IFX therapy showed clinical and endoscopic improvement in 81% and 52% of the patients, respectively. Favorable responses were associated with presence of ocular lesions, whereas patients with esophageal lesions were resistant to the therapy. IFX was discontinued in 5 patients because of remission and in 19 patients due to insufficiency efficacy or adverse effects.

W90-5

Quantitative utility of brainstem atrophy in neuro-Behçet's disease

Maki Takayama¹, Kurumi Asako¹, Hirotoshi Kikuchi¹, Hajime Kono¹, Shunsei Hirohata²

¹Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan, ²Department of Rheumatology and Infectious Disease, Kitasato University School of medicine, Kanagawa, Japan

We demonstrated that chronic progressive neuro-Behçet's disease (CPNB) exhibited atrophy of the brainstem compared with acute neuro-Behçet's disease (ANB) in brain MRI. To analyze the ROC curve regarding the area of the brainstem on mid-sagittal MRI at the first visit. 22 patients (8 ANB and 14 CPNB were finally diagnosed) who had been diagnosed as having Behçet's disease (BD) with neuropsychiatric manifestations. The area of the mesencephalic tegmentum was set at a cutoff value of 111.7 mm²; sensitivity 57.1%, specificity 87.5%, AUC 0.87, p -value 0.005. The area of the pons was set at a cutoff value of 465.4 mm²; sensitivity 78.6%, specificity 87.5%, AUC 0.83, p -value 0.01. Measuring the area of the brainstem with MRI was useful for the differential diagnosis between CPNB and ANB.

W90-6

The association between clinical characteristics and Th17 in Behçet's disease

Hidekata Yasuoka, Tsutomu Takeuchi, Masataka Kuwana

Behcet's disease (BD) is an inflammatory disease, however, the pathogenesis is still unknown. Our recent report suggests that the recruitment of Th17 is involved in the pathogenesis. To further clarify the role of Th17 in BD, 20 BD and 14 controls were examined in this study. Th17 precursors were evaluated by RORC mRNA expression in PBMCs using RT-PCR. Proportion of Th17 in CD4⁺ T cells was detected by flow cytometry. Association between clinical characteristics and proportion of Th17 was also examined. Expression of RORC mRNA and proportion of Th17 were increased in BD compared with controls ($p < 0.05$ and $p < 0.05$, respectively). Proportion of Th17 was higher in BD with ocular lesion than those without ($p < 0.04$). These results suggest that Th17 is associated with the pathogenesis of BD.

W91-1

Involvement of ICAM-1 and PDGF-B in autoinflammatory granuloma formation

Nobuo Kanazawa¹, Ikuo Okafuji², Naotomo Kambe³, Fukumi Furukawa¹

¹Department of Dermatology, Wakayama Medical University, ²Department of Pediatrics, Kobe City Medical Center General Hospital, ³Department of Dermatology, Chiba University Graduate School of Medicine

Early-onset sarcoidosis and Blau syndrome form a distinct granuloma-forming autoinflammatory syndrome associated with *NOD2* mutations causing constitutive NF- κ B activation. To clarify the precise mechanism of such autoinflammatory granuloma formation, human monocytic THP-1 cells expressing disease-associated *NOD2* mutations were generated. Without stimulation, no difference of cytokine expressions was observed among THP-1 derivatives. After PMA addition, mutant THP-1 cells long attached to the plate, in correlation with sustained surface ICAM-1 expression. Transient PDGF-B mRNA expression was specifically induced in mutant THP-1 cell. Expression of ICAM-1 and PDGF-B was actually observed in *Nod2*-expressing giant cells in the granulomatous skin lesion of a patient with a *NOD2* mutation.

W91-2

Analyses of gene mutations in clinically periodic fever syndrome

Sayuri Kataoka, Yasushi Kawaguchi, Manabu Kawamoto, Akiko Tochimoto, Hisae Ichida, Kae Takagi, Yasuhiro Katsumata, Takahisa Gono, Masanori Hanaoka, Hisashi Yamanaka
Institute of Rheumatology, Tokyo Women's Medical University

Periodic fever syndrome refers to a group of autoinflammatory disease sharing symptoms and characterized by recurrent unproved inflammation. These diseases primarily include familial Mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS), hyper IgD syndrome, and cryopyrin-associated periodic syndrome (CAPS). In the present study, we investigated a comprehensive analysis of mutations in *MEFV*, *TNFRSF1A*, *MVK* and *CIAS1* genes. Analyses of 63 patients with clinically periodic fever indicated that the mutations were found in 19 patients (30%). One patient of them had two mutations both of *MEFV* and *TNFRSF1A*. These findings indicated hereditary periodic fever syndrome may not be rare in the Japanese population.

W91-3

Expression of CD64 on neutrophils in patients with familial Mediterranean fever

Kiyoshi Migita¹, Kazunaga Agematsu², Kazuko Yamasaki², Ayako Suzuki³, Yasumori Izumi¹, Taiichiro Miyashita¹, Tomohiro Koga⁴, Satoshi Yamasaki⁴, Atsushi Kawakami⁴, Masahide Yazaki³

¹Department of Rheumatology Nagasaki Medical Center, ²Department of Immunology and infectious disease, Shinshu University,

³Department of Neurology and Rheumatology, Shinshu University,

⁴Department of Rheumatology Nagasaki University Hospital

FMF is a genetic autoinflammatory disease. We examined the utility of CD64 expression on neutrophils (PMNs) as clinical parameters in FMF. We studied 9 FMF cases (mean age; 24.3 ± 16.8 yrs, M/F:2/7), patients with RA ($n=38$), SLE ($n=15$) and 12 healthy subjects. CD64 expression was determined using flow cytometry. The quantitative expression of CD64 in patients with FMF (1772.8 ± 783.8 molecules per PMN) was significantly higher than in healthy subjects (547.8 ± 229.5 , $p=0.003$) or in patients with RA and SLE. The increased CD64 expression in untreated FMF patients was downregulated by colchicine. NLRP3 activation using MDP resulted in the increased CD64 expression on PMNs. Our results suggest that quantitative measurement of CD64 expression on PMNs can be a valuable tool for the diagnosis of FMF.

W91-4

Relationship between the *MEFV* gene mutations and clinical phenotypes in FMF

Dai Kishida, Ayako Suzuki, Masahide Yazaki, Masayuki Matsuda, Shu-ichi Ikeda

Department of Rheumatology, Shinshu University School of Medicine, Matsumoto, Japan

Various mutations in the *MEFV* gene have been identified, but there is no report of relationship between genotype and phenotype in the Japanese FMF patients. We examined the relationship in 77 definite and suspected FMF patients having the mutations. Many patients with mutations of compound heterozygote for M694I/L110P and M694I/E148Q, homozygote for M694I, heterozygote for M694I alone, homozygote for E148Q, or L110P-E148Q variant showed almost typical phenotype of FMF. Whilst, the patients with P369S-R408Q variant showed the atypical phenotype such as frequent attacks or fever lasting for several weeks. The patients with E148Q alone had mild symptoms. These results implicated that the genotype of the *MEFV* gene might relate with the phenotype of Japanese FMF or the suspected cases.

W91-5

A Japanese case of familial Mediterranean fever (FMF)

Nobuo Negoro¹, Satoru Asai¹, Jin Tsukamoto¹, Ryuta Nishikomori²

¹Clinical Immunology and Rheumatology, Osaka City University Medical School, Osaka, Japan, ²Department of Pediatrics, Kyoto University School of Medicine, Kyoto, Japan

We experienced a 36-year-old Japanese woman with familial Mediterranean fever (FMF). The beginning of her recurrent high fever with chest pain started when she was 5 year old and the duration of fever was within 48 hours. The frequency of fever was gradually increased to once or 2 times a month. Her young sister had also the same episode of fever with unknown origin. The result of gene analysis to determine the cause of familial recurrent fever showed that she had heterozygote mutations of M961I and E148Q in the familial

Mediterranean fever gene (MEFV), which mutations were often found in the Japanese patients with FMF. From these results, we diagnosed that she had FMF with 6 scores of the Tel Hashomer severity for FMF. FMF could be one of causes of fever of unknown origin in Japan.

W91-6

National survey of TRAPS in Japan

Naoyasu Ueda¹, Hiroshi Tsukamoto¹, Yoshiaki Ishigatsubo², Koichi Kusuha³, Syuji Takei⁴, Seiji Minota⁵, Masakazu Washio⁶, Hiroaki Ida⁷, Hiroki Takahashi⁸, Takao Fujii⁹, Tomoko Tahira¹⁰, Shun-ichiro Ota¹, Atsushi Tanaka¹, Kentaro To¹, Makio Furukawa¹, Yasushi Inoue¹, Yojiro Arinobu^{1,10}, Hiroaki Niuro¹, Koichi Akashi¹⁰, Takahiko Horiuchi¹

¹Department of Clinical Immunology, Rheumatology, and Infectious diseases, Kyushu University Hospital, Fukuoka, Japan, ²Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan, ³Department of Pediatrics, University of Occupational & Environmental Health, Japan, Kitakyushu, Japan, ⁴School of Health Sciences, Faculty of Medicine, Kagoshima University, Kagoshima, Japan, ⁵Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Jichi Medical University, Tochigi, Japan, ⁶Faculty of Nursing, St.Mary's College, Kurume, Japan, ⁷Division of Respiratory, Neurology, and Rheumatology, Department of Medicine, Kurume University School of Medicine, Kurume, Japan, ⁸First Department of Internal Medicine, Sapporo Medical University School of Medicine, Japan, ⁹Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine, Kyoto, Japan, ¹⁰Division of Genome Analysis, Research Center for Genetic Information, Medical Institute of Bioregulation, Kyushu University, Fukuoka, Japan

TRAPS is an autosomal dominant inherited disorder associated with TNFR1 gene mutations. Most of the reported families are of European or of American and a few of Asian including Japanese. The Ministry of Health, Labor and Welfare study group for TRAPS conducted a national survey. We sent primary survey questionnaire to the doctors in the hospitals with more than 200 beds and asked whether they had the patients 1) who met the preliminary diagnostic criteria proposed by Hull et al or 2) who were diagnosed as systemic juvenile idiopathic arthritis but were refractory and had no chronic arthritis, in 2009. We had responses from 1801 out of 2900 facilities and 251 cases satisfied above criteria. We are conducting secondary survey regarding clinical data and gene analysis.

W92-1

Nakajo-Nishimura syndrome: a new infant case and reported similar foreign cases

Nobuo Kanazawa¹, Fukumi Furukawa¹, Hiroaki Ida²

¹Department of Dermatology, Wakayama Medical University, ²Division of Respiratory, Neurology and Rheumatology, Department of Medicine, Kurume University School of Medicine

Nakajo-Nishimura syndrome is an inheritable inflammatory and wasting disease which onsets with pernio-like eruptions in infancy and gradually develops emaciation and characteristic long-clubbed fingers with periodic fever and erythematous nodules. Recently, a causative genetic mutation has been identified and the disease has been shown the first inheritable proteasome-dysfunction disease. Patients are concentrated in limited areas, especially in Wakayama district. No novel case was identified by national surveillance, but a new infant case has been discovered in Wakayama. The case is a 5-

year-old boy with the mutation, who developed pernio-like eruptions and periodic fever at 2 months of age. Also reported is the comparison with similar cases, recently reported from foreign countries.

W92-2

A novel point mutation causing proteasome dysfunction in NNS

Kazuhiko Arima¹, Hiroaki Ida², Tomoki Origuchi³, Nobuo Kanazawa⁴, Katsumi Eguchi⁵

¹Nagasaki University Graduate School of Biomedical Sciences, Department of Medical Gene Technology, Nagasaki, Japan, ²First Department of Internal Medicine, Kurume University, Kurume, Japan, ³Nagasaki University School of Health Sciences, Nagasaki, Japan, ⁴Department of Dermatology, Wakayama Medical University, Wakayama, Japan, ⁵Sasebo City hospital, Sasebo, Japan

Background: Nakajo-Nishimura syndrome (NNS) is a systemic inflammatory disorder that segregates in an autosomal recessive fashion.

Objective: To identify the causative mutation of NNS.

Methods: Genomic DNA samples collected from 5 patients and 3 unaffected sibs of the patients were analyzed. The extracts from immortalized cell lines were assayed for 3 different peptidase activities of the proteasome.

Results: A novel mutation was identified in a gene encoding a proteasome subunit in all NNS patients. The proteasome activities were reduced with a gene dosage effect.

Conclusion: This is the first direct evidence of proteasome dysfunction causing a human disease. This provides a new insight into the pathogenesis of other persistent inflammatory diseases.

W92-3

Study on Diagnostic Clinical Features of Autoinflammatory Disorders Patients.

Tomohiro Kubota¹, Yuichi Yamasaki¹, Yukiko Nonaka¹, Harumi Akaike^{1,2}, Yasuhito Nerome¹, Tomoko Takezaki^{1,3}, Hiroyuki Imanaka^{1,4}, Syuji Takei^{1,5}

¹Pediatric Medical Center, Kagoshima University Hospital, Kagoshima, Japan, ²Yamabiko Medical Welfare Center, ³Kagoshima Seikyo Hospital, Kagoshima, Japan, ⁴Ikeda Hospital, Kagoshima, Japan, ⁵School of Health Sciences, Faculty of Medicine, Kagoshima University, Kagoshima, Japan

Diagnostic clinical features should be evaluated before examining the gene abnormalities for auto-inflammatory disorders, therefore, clinical findings that lead to proper diagnosis was retrospectively examined in 13 patients of EOS (n=7), FMF (n=3), TRAPS (n=2), and CINCA (n=1) at a single medical center. Of the 13 patients diagnosed by gene survey, 9 were initially diagnosed as systemic JIA (sJIA) and 3 were as RF negative polyarticular JIA (pJIA). All of 7 patients with EOS were initially diagnosed as JIA (sJIA in 4 and RF-pJIA in 3), and had cystic swelling on bilateral back of the hands and the top side of the feet, and 5 suffered from chronic uveitis. In conclusion, patients diagnosed as sJIA should be carefully examined the possibility of other type of autoinflammatory disorders.

W92-4

More than a quarter of CINCA syndrome patients carry NLRP3 somatic mosaicism

Naoko Tanaka¹, Kazushi Izawa¹, Ryuta Nishikomori¹, Naotomo Kambe⁶, Tomoki Kawai¹, Hidemasa Sakai¹, Takahiro Yasumi¹, Toshio Heike¹

¹Department of Pediatrics Kyoto University Graduate School of Medicine, Kyoto, Japan, ²Clinical Application Department, Center for iPS cell research and application (CiRA), Kyoto University, Kyoto, Japan, ³Center for Medical Education, Kyoto University Graduate School of Medicine, Kyoto, Japan, ⁴Department of Human Genome Research, Kazusa DNA Research Institute, Chiba, Japan, ⁵Laboratory for Immunogenomics RIKEN Research Center for Allergy and Immunology RIKEN Yokohama Institute, Yokohama, Japan, ⁶Department of Dermatology, Chiba University Graduate School of Medicine, Chiba, Japan

CINCA syndrome is a systemic autoinflammatory disorder in which abnormal activation of NLRP3 inflammasome results in overproduction of IL-1 β . However, almost half of the patients lack *NLRP3* mutations. Considering our experiences of three Japanese cases with NLRP3 somatic mosaicism, we carried out international surveillance to clarify the prevalence and clinical manifestation of NLRP3 somatic mosaicism. Of 26 mutation-negative patients examined, 18 patients revealed *NLRP3* mosaicism. No mosaicism was detected in 19 family members. Functional analysis of mutations suggests these are disease-causative. More than a quarter of patients of CINCA syndrome are estimated to carry NLRP3 somatic mosaicism and strong association of somatic mosaicism with NLRP3-somatic mosaicism is certified.

W92-5

Image evaluation by FDG PET and prediction of refractory state in AOSD

Tomohiro Kameda, Kentaro Susaki, Mihar Izumikawa, Yohei Takeuchi, Shusaku Nakashima, Hiromi Kizu, Hiroaki Dobashi
Division of Endocrinology and Metabolism, Hematology, Rheumatology and Respiratory Medicine, Department of Internal Medicine, Faculty of Medicine, Kagawa University

[Objective]We study the usefulness of FDG PET in the diagnosis of AOSD, and examine the predictive factor for refractory AOSD. **[Methods]**Eleven AOSD patients were enrolled. Ten patients had undergone FDG PET, and the inflammatory lesion was evaluated SUV. We examined the correlation of SUV and serological markers (CRP, WBC, sIL-2R and ferritin). All patients were treated with only corticosteroid (responder group) or combined with immunosuppressant (non-responder group). We examined the difference between two groups. **[Result]**Ferritin and sIL-2R showed close correlation with SUV. In addition, SUV and the level of ferritin were high in non-responder group. **[Conclusion]**FDG PET is useful for diagnosis of AOSD. In addition, SUV and ferritin may become predictive factor for refractory AOSD.

W92-6

A case of CINCA syndrome treated with surgical procedures for severe arthropathy

Chieko Nakamura
Shiga Medical Center for Children

Chronic infantile neurologic, cutaneous, articular (CINCA) syndrome is a chronic autoinflammatory disorder characterized by the

triad of skin rash, arthropathy, and central nervous system manifestations. We describe a patient with severe knee arthropathy performed surgical treatments. Case: At age of 22 months, he had abnormal gait, and diagnosed as arthritis of the knees. His knee abnormalities developed and led to gait disturbance caused by knee contractures. At 11 years, he underwent posterior release of knee contractures. At 15 years, he diagnosed CINCA syndrome, and treated with IL-1 receptor antagonist. At 18 years, he underwent staple epiphyseodesis of the right distal femur to prevent progression of genu valgus. Both procedures improved his knee abnormalities without complications.

W93-1

Efficacy of the biologics in adult onset Still's disease: multicenter results

Rie Suematsu¹, Akihito Ohta², Emi Matsuura², Hiroki Takahashi³, Takao Fujii⁴, Takahiko Horiuchi⁵, Seiji Minota⁶, Yoshiaki Ishigatsubo⁷, Toshiyuki Ohta⁸, Sachiko Soejima¹, Hisako Inoue¹, Syuichi Koarada¹, Yoshifumi Tada¹, Kohei Nagasawa¹

¹Department of Rheumatology, Saga University School of Medicine, Saga, Japan, ²Department of Adult & Gerontological Nursing, Saga University School of Medicine, Saga, Japan, ³1st Department of Internal Medicine, Sapporo Medical University, Sapporo, Japan, ⁴Department of Rheumatology & Clinical Immunology, Kyoto University Graduate School of Medicine, Kyoto, Japan, ⁵Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Science, Fukuoka Japan, ⁶Division of Rheumatology / Clinical Immunology, Department of Internal Medicine, Jichi Medical University, Tochigi, Japan, ⁷Department of Internal Medicine & Clinical Immunology, Yokohama City University Graduate School of Medicine, Kanagawa, Japan, ⁸Department of Laboratory & Transfusion Medicine, University of Occupational and Environmental Health, Fukuoka, Japan

There have been several reports on the therapeutic use of the biological agents in patients with adult onset Still's disease (AOSD) with varying results of the efficacy. Here we present the effectiveness of the biological agents, especially of tocilizumab, in 16 AOSD patients collected through the multicenter survey in Japan. Infliximab was used in 9 cases, etanercept in 4, and tocilizumab in 11. Half of the patients who had been treated initially with infliximab or etanercept were switched to use another biologics due to ineffectiveness or adverse effects. Tocilizumab was found to be effective in all these switched cases as well as in those who used it as an initial drug. Tocilizumab can be useful in refractory AOSD patients.

W93-2

Biologic agents in refractory adult onset of Still's disease: a study of 8 cases

Rumi Minami, Tomoya Miyamura, Yoshiro Horai, Soichiro Takahama, Karin Shimada, Motoko Ishida, Masahiro Yamamoto, Eiichi Suematsu

Internal Medicine, Clinical Research Center, National Hospital Organization, Kyushu Medical Center

We assessed the biological agents in the treatment of 8 patients with refractory adult onset Still's syndrome (AOSD). The clinical expression was predominantly systemic in six patients and polyarticular in 2. Infliximab was used to treat 2 patients, etanercept and tocilizumab used for 1. One had switched from infliximab to adalimumab because of a side effect. In all patients, symptoms and serological variables improved within three courses of treatments. At a mean follow up of 12 months, complete remission had occurred in four ca-

ses, and partial response was observed in 4 cases (some arthritis was remained). Two cases had side effects; one was infection, and the other was hypotension. These data suggest biologic agents may be helpful for some patients with refractory AOSD.

W93-3

The examination about the treatment for adult onset still disease

Takashi Watanabe, Souichiro Nakano, Seiichiro Ando, Kentaro Minowa, Hirofumi Amano, Shinji Morimoto, Yoshinari Takasaki
Internal and Rheumatology medicine, Juntendo University School of Medicine, Tokyo, Japan

Purpose: We examined the state of recurrence after the first time treatment for AOSD. **Method:** For AOSD20 cases, we divided it into recurrent group 13 cases, no recurrent group 7 cases and examined in a symptom and laboratory findings / treatment contents / progress. **Result:** The cases that recurred had many pattern of steroid independent and arthralgia at the time of the onset. Many cases which used an immunosuppressive agent together from the early days were seen in no revival group. A lot of revival within 3 years was seen than primary care. **Conclusion:** Depending on a symptom, it was thought that it could lower a risk of the revival from the early stage enough to perform combination therapy.

W93-4

A case of relapsing polychondritis positive for anti-type II collagen antibody

Takahisa Suzuki¹, Hideki Nakamura², Yoshikazu Nakashima¹, Eriko Isomoto¹, Akitomo Okada², Junko Kita², Tomohiro Koga², Shin-ya Kawashiri², Mami Tamai², Satoshi Yamasaki², Tomoki Origuchi³, Atsushi Kawakami²

¹Department of Immunology and Rheumatology, Nagasaki University Hospital, Nagasaki, Japan, ²Unit of Translational Medicine, Department of Immunology and Rheumatology, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan, ³Nagasaki University School of Health Sciences, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan

A 69-year-old man who suffered persistent fever resistant to antibiotics, was admitted to our hospital in July 2010. Careful examination was performed, but there was no obvious infectious disease. In addition to hearing loss, auricular swelling and uveitis appeared in August. The pathology of the auricular cartilage showed inflammatory cells infiltration. We diagnosed relapsing polychondritis (RP), and started prednisolone (PSL) 20mg/day treatment. Clinical symptoms and laboratory data were improved after initiation therapy. In October, RP activity was relapsed subsequently to reduction of PSL 17.5mg/day. Steroid pulse therapy was started, but not effective. Then, we attempted to adalimumab for refractory RP. Here we report a case of RP refractory to steroid therapy.

W93-5

Increased expression of TREM-1 in patients with relapsing polychondritis

Yoshihisa Yamano¹, Tomoo Sato¹, Utano Tomaru², Takahiro Okazaki³, Hiroko Nagafuchi³, Shoichi Ozaki³, Jun Shimizu⁴, Kazuo Yudo¹, Hiroshi Oka¹, Noboru Suzuki^{1,4}

¹Institute of Medical Science, St. Marianna University School of Medicine, Kawasaki, Japan, ²Department of Pathology, Hokkaido University Graduate School of Medicine, Sapporo, Japan, ³Division of Rheumatology and Allergy, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan, ⁴Department

of Immunology and Medicine, St. Marianna University School of Medicine, Kawasaki, Japan

Relapsing polychondritis (RP) is a rare inflammatory disorder of unknown aetiology. Most RP patients show elevated CRP levels; however, some RP patients with insidiously advancing fibrosis do not. Therefore, the identification of a more sensitive biomarker is essential for monitoring disease activity. Here, we measured multiple cytokines and chemokines quantitatively in the serum samples of 16 RP patients and 16 HDs by using enzyme-linked immunosorbent assay or cytometric bead array. The serum levels of sTREM-1, IFN- γ , MIP-1 β , MMP-3, VEGF, and IP-10 in RP patients were significantly higher than those in HDs. Among these molecules, sTREM-1 had the highest sensitivity. Thus, our findings showed that compared to other molecules such as CRP, sTREM-1 might be a better biomarker of RP.

W93-6

A steroid-resistant case of relapsing polychondritis treated with DDS and MZB.

Shinji Akioka¹

¹Saiseikai Kyoto Hospital, ²Kyoto Prefectural University of Medicine

Relapsing polychondritis (RP) is a rare inflammatory disease, mainly occurred in young female. The prognosis is largely improved with the early intervention with immunosuppressive drugs. However, it is still observed to be resistant to steroid therapy, especially in case with respiratory symptoms, subsequently resulting in airway narrowing and loss of life. We report here a female case of RP, initially diagnosed at 14 years old with dyspnea by severe chondritis in larynx, trachea and costae. Trach tube was required with steroid therapy more than 7 years, finally resolved by additional treatment of Dapsone (DDS) and Mizolibine (MZB). They were effective and safe even in era of biological agents. This strategy should be recommended for resistant RP case especially in pre-pregnant female.

W94-1

Analysis of the predictive factor of corticosteroid effects in PMR patients

Atsushi Omoto¹, Wataru Fukuda¹, Toru Tanaka¹, Yutaka Kawahito²

¹Division of Diabetes, Endocrinology and Rheumatology, Japanese Red Cross Kyoto Daiichi Hospital, Kyoto, Japan, ²Division of Rheumatology and Allergy, Department of Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Objective: To investigate the predictive factor of corticosteroid (CS) effects in patients with polymyalgia rheumatica (PMR). **Methods:** Hospital records over 1 year were reviewed for PMR patients (including giant cell arteritis) who were first diagnosed between 2004 and 2009. We compared clinical characteristics of the low level of C-reactive protein (CRP) (<4.0mg/dl), middle level of CRP (4.1-8.0), and high level of CRP (>8.1) retrospectively. **Results:** 44 patients with PMR (mean age 71.9) were included. The group of low CRP levels was significantly able to reduce the dosage of CS and to discontinue the CS therapy compared with the other group. **Conclusion:** Our results suggest that low CRP levels before initial CS therapy are associated with the predictive factor of CS effects.

W94-2

The prognostic factors of polymyalgia rheumatica in Japanese patients

Kenji Fujii^{1,2,3}, Toshiyuki Ota^{1,2}

¹Department of Laboratory and Transfusion Medicine, University of Occupational and Environmental Health, Fukuoka Japan, ²Division of Rheumatology, Iizuka Hospital, Fukuoka, Japan, ³Kaita Hospital, Fukuoka, Japan

Objectives: We evaluated the prognostic factors of polymyalgia rheumatica (PMR) about favourable clinical course (group A) and recurrence or shifting to rheumatoid arthritis (group B).

Method: 30 new-onset PMR cases (A:21, B:9) were evaluated based on serum laboratory data, imaging study of hands (US, MRI) and the each items of new ACR/EULAR classification criteria for RA.

Results: There were no significant difference in serum data and items of ACR/EULAR classification criteria for RA. In peripheral joints, erosion (A vs B: 57% vs 83%), synovitis (50% vs 67%), bone marrow edema (14% vs 50%) in MRI and synovial hypertrophy (70% vs 100%) in US were seen with a high frequency in B group.

Conclusions: Each items of MRI and US at the diagnosis might be useful for the prognostic prediction of PMR.

W94-3

Clinical outcomes of 79 patients with polymyalgia rheumatica

Mika Okabe¹, Naoaki Hashimoto¹, Mai Morimoto¹, Aki Nishioka¹, Masahiro Sekiguchi¹, Naoto Azuma¹, Masayasu Kitano¹, Kiyoshi Matsui¹, Tsuyoshi Iwasaki², Hajime Sano¹

¹Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan, ²Department of Pharmacotherapy, Hyogo University of Health Science

Objective: The aim of this study was to investigate the clinical feature of the patients with PMR in our hospital. **Methods:** Seventy-nine patients with PMR diagnosed according to Bird's criteria were studied. We examined the items of Bird's criteria, laboratory data and dosage of prednisolone (PSL). **Results:** The mean of dosage of PSL was 14.3 ± 5.7 mg/day. In 8 patients (10.1%), PSL therapy could be completely withdrawn. The dosage of PSL was not related with laboratory data and number of Bird's criteria. The dosage of PSL was higher in PMR patients with "depression or loss of weight" and "male" than in PMR patients without these items ($p < 0.01$). **Conclusion:** The dosage of PSL in the treatment of PMR tended to be decided by physique and physical status compared to the result of laboratory data.

W94-4

MMP-3 in Polymyalgia Rheumatica

Takuya Nemoto¹, Akira Katagiri¹, Toshiyuki Kaneko¹, Masato Yamada¹, Noboru Iida¹, Yoshinari Takasaki²

¹Department of Internal Medicine and Rheumatology, Juntendo University Shizuoka Hospital, ²Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine

[Purpose and Method] Polymyalgia rheumatica (PMR) is principle diagnosis by exclusion, it is difficult that PMR is discriminated with early stage of Rheumatoid arthritis (RA). And it was reported that MMP-3 value that is one of the activity markers of RA becomes positive in PMR. To discuss whether PMR and RA were able to be discriminated by the MMP-3 or CRP, MMP-3 and CRP of 22 PMR cases when diagnosed it was evaluated. **[Results]** MMP-3 of 9 cases (86.4%) were positive, and average of it was 260 in male, 320

ng/ml in female. Average of CRP was 9.0 mg/dl, MMP-3 and CRP were higher than early stage RA in the significance. **[Discussion]** PMR and RA cannot be discriminated by MMP-3 positive. It is necessary to consider PMR when MMP-3 and CRP are high at the first medical examination.

W94-5

Enthesopathy detected by 18F-FDG-PET/CT in patients with polymyalgia rheumatica

Hirofumi Yamashita¹, Kazuo Kubota², Yuko Takahashi¹, Hiroshi Kaneko¹, Akio Mimori¹

¹Division of Rheumatic Diseases, National Center for Global Health and Medicine, ²Department of Radiology, National Center for Global Health and Medicine

Backgrounds:

The exact pathologic nature of PMR is unknown. In this study, we demonstrate additional findings for PMR using FDG-PET/CT.

Patients and methods:

The number of patients and the mean age was 14 and 72.6 ± 8.6 years, respectively. All 14 patients underwent a PET/CT scan before starting steroid therapy. FDG uptake was evaluated by calculating SUVmax, the scoring system and a 'total vascular score'.

Results:

FDG uptake was detected in the large joints (86%) and spinous processes (71%) in accordance with previous reports. Large vessel involvement was detected in 2 patients. In addition, enthesopathies such as ischial tuberosities were FDG-positive in 86% of the patients. Some of the FDG-positive lesions were detected on MRI.

Conclusion:

FDG-PET/CT shows that enthesopathy may be common in PMR.

W94-6

A Study of Clinical and Imaging Findings in patients with PMR and RS3PE Synd.

Koei Oh¹, Osamu Namiki¹, Yoichi Toyoshima¹, Katsunori Inagaki¹, Raita Amemiya²

¹Department of Orthopaedic Surgery, Showa University School of Medicine, ²Amemiya Hospital

To study the clinical and imaging findings in patients with PMR and RS3PE admitted to our hospital. A retrospective study of 29 patients with PMR and 12 patients with RS3PE diagnosed. The patients had the joint contraction of the shoulder (61%) and knee (50%). Swelling of the hands and foot was observed not only patients with RS3PE, but also 34% patients with PMR. In the imaging findings, every patient was found to have tenosynovitis and joint inflammation. And it was also confirmed bone erosion for every patient with PMR. The symptoms commonly with PMR and RS3PE are tenosynovitis, joint inflammation, and bursitis. RS3PE is considered to be a subset of PMR. It has been said bone erosion does not occur in patients with PMR, but we consider that it may occur based on the CT and the pathology.

W95-1

Orthopaedic surgery in patients with rheumatoid arthritis treated with biologics

Mamoru Fujita¹, Ken Urabe¹, Jun Aikawa¹, Katsufumi Uchiyama¹, Kenji Onuma¹, Akira Ishikawa², Sumiaki Tanaka², Jun Okada³, Hirahito Endo⁴, Shunsei Hirohata²

¹Department of Orthopaedic Surgery, Kitasato University School of Medicine, Kanagawa, Japan, ²Department of Rheumatology and In-

fectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan, ³Kitasato University Health Care Center, Kanagawa Japan, ⁴Division of Rheumatology, Department of Internal Medicine (Omori), School of Medicine, Faculty of Medicine, Toho University, Tokyo, Japan, ⁵Department of Orthopaedic Surgery, Kyushu Rosai Hospital, Fukuoka, Japan

We investigated that post operative complication in patients with rheumatoid arthritis treated with biologic agent undergoing orthopaedic surgery. Objects of this study are 16 surgeries in Infliximab (IFX) group, 23 surgeries in Etanercept (ETN) group, 2 surgeries in Adalimumab (ADA) group and 3 surgeries in Tocilizumab (TCZ) group. Pre-operative discontinued period of biological agent was 35.9 days in IFX group, 20.9 days in ETN group, 26.5 days in ADA group and 18 days in TCZ group. Biologic agent was resumed 27.3 days in IFX group, 30.5 days in ETN group, 13.5 days in ADA group and 39 days in TCZ group. In ETN group, one patient who had undergone total knee arthroplasty had deep infection in operated knee joint. Delay of wound healing was occurred in one patient in TCZ group.

W95-2

Rheumatoid joint surgery with using the biologics - 82 cases in our hospital -

Yukio Esaki¹, Hisaaki Miyahara¹, Goh Hirata¹, Masanobu Ohishi², Kiyoshi Miyazaki¹, Nobutaka Kaibara¹, Fuyuki Tominaga¹, Masakazu Kondo³

¹Department of Orthopaedic Surgery, Kyushu Medicaol Center, National Hospital Organization, Fukuoka, Japan, ²Department of Orthopaedic Surgery, Kyushu University, ³Kondo Clinic for Rheumatism and Orthopaedics

82 rheumatoid patients receiving the biologics were treated with joint surgery in our hospital. Joint replacement surgery were performed in 55 cases, arthrodesis in 13, arthroplasty in 5, synovectomy in 4, and others in 5. They included 41 cases receiving ETN, 13 receiving IFX, 23 receiving TCZ, 5 receiving ADA. We never found severe bone loss or deformity in primary joint replacement. Synovitis was disappeared in patients with good control. Fibrosis and bone with good quality were appeared in such cases. SSI occurred in one case receiving ETN underwent TAA, and also in one case receiving TCZ underwent TKA. The incidence was 2.4%. Preventing progression of joint lesion with the biologics gave favorable effect on the joint surgery. However, caution must be taken in the occurrence of SSI.

W95-3

Perioperative complication in patients with RA treated biologics

Ayako Kubota¹, Takashi Nakamura¹, Yoshiyasu Miyazaki¹, Hideko Torihata¹, Masayuki Sekiguchi¹, Toyomitsu Tsuchida², Toru Suguro¹, Kazuaki Tsuchiya¹

¹Department of Orthopaedic Surgery, Toho University School of Medicine, Tokyo, Japan, ²Tsuchida clinic

We investigated the risk of perioperative complication in patients with RA undergoing orthopedic surgery treated 241 joints were treated with biologics and 177 joints were treated with non biologics. Postoperative complications included infections (0.6%), and wound healing complications (8.7%). We have no significant association between wound healing and early infectious complications.

W95-4

The evaluation of RA patients who received surgery under biologics.

Naoki Kondo¹, Katsumitsu Arai², Junichi Fujisawa¹, Takahiro Netsu¹, Yoko Wada³, Shuichi Murakami³, Takeshi Kuroda⁴

¹Division of Orthopaedic Surgery, Niigata University, Niigata, Japan, ²Division of Orthopaedic Surgery, Niigata Prefectural Chuo Hospital, Joetsu, Niigata, Japan, ³Division of Clinical Nephrology and Rheumatology, Niigata University, Niigata, Japan, ⁴Health Administration Center, Niigata University, Niigata, Japan

In our facility, orthopaedic surgeries were performed for 63 cases in rheumatoid arthritis (RA) patients under biologics from 2004 to 2010. The percentages of biologics-treated cases were 2.2, 3.2, 8.4, 21.1, 13.1, 21.9, and 31.5 % in 2004 through 2010, showing gradual increase. Treated biologics were as follows; 6 for Infliximab, 46 for etanercept, 10 for tocilizumab, and 1 for adalimumab. The average duration from RA onset to surgery was 13.3 years; 12 cases (19%) was less than 5 years, 16 cases (25%) was 5 to 10 years, and 35 cases (56%) was more than 10 years, respectively. Two superficial surgical site infections (SSI) and 2 deep SSIs were detected (3 for etanercept and 1 for tocilizumab). Careful perioperative treatments should be taken for surgeries under biologics in RA patients.

W95-5

Analysis of peri-operative general status of RA patients with biologic agents

Katsushi Ishii¹, Yuichi Mochida¹, Kengo Harigane¹, Naoto Mitsugi², Naoya Taki², Yasushi Akamatsu², Tomoyuki Saito³

¹Center for Rheumatic Diseases, Yokohama City University Medical Center, Yokohama, Japan, ²Department of Orthopaedic Surgery, Yokohama City Medical Center, Yokohama, Japan, ³Department of Orthopaedic Surgery, Yokohama City University, Yokohama, Japan

Purposes: To analyze peri-operative general status and post-operative wound complications in RA patients with or without biologic agents. **Materials and Methods:** 34 cases with biologic agents (group A) and 49 cases without biologic agents (group B) were analyzed. Levels of total protein (TP), MMP-3, dose of steroid and MTX, and post-operative wound complications were analyzed. **Results:** There was no difference between 2 groups in levels of MMP-3 and TP. Mean dose of MTX in group A and PSL in group B were significantly higher than the other group. When group A was divided into major or minor surgery, delayed wound healing were observed in 5 cases of major surgeries, 4 of which were in group B. **Conclusion:** The use of biologic agents did not affect peri-operative status and wound complications.

W95-6

Clinical results of surgical cure for the cases with RA receiving biologics

Yusuke Ueda¹, Norihiro Ichikawa¹, Takanori Saito¹, Taketoshi Kushida²

¹Department of Orthopedic Surgery, Kansai Medical University, Takii Hospital, Moriguchi, Osaka, Japan, ²Department of Orthopedic Surgery, Kansai Medical University, Hirakata Hospital, Hirakata, Osaka, Japan

[Objectives] Biologic agents are considered most effective treatment for the patients with rheumatoid arthritis. However in the cases with developed joint destructions, unpredictable traumas and other diseases, the surgical treatment will be needed. In perioperative peri-

ods, there have been serious problems that biologic agents may cause surgical site infection (SSI) or healing complications. In this study, we evaluate the perioperative courses in the patients receiving biologic agents. [Patients and Methods] Fifteen patients with rheumatoid arthritis receiving biological agents have been underwent several surgical treatments (21 operations). [Results] Never flaring up and SSI were detected, but one case was appeared delay of wound healing. Other major complications didn't have been noted.

W96-1

Efficacy and safety of high-dose mizoribine and MTX combination in RA patients

Fuminori Hirano^{1,2}, Satoru Kodama¹, Atsushi Kobayashi¹, Naoki Maruyama¹, Keiji Komura¹, Kensaku Okamoto¹, Yuichi Makino¹, Masakazu Haneda¹

¹Department of Medicine, Asahikawa Medical University, Asahikawa, Japan, ²Department of Medicine, Asahikawa Medical Center, Asahikawa, Japan

The aim of this study is to evaluate the efficacy and safety of high-dose mizoribine (MZR) therapy in combination with MTX in MTX -resistant RA patients. Mizoribine was orally administrated to thirteen RA patients at a dose of 150 mg/day once a day for 12 weeks. When efficacy was insufficient at 12 weeks, MZR was administrated at a dose of 300 mg/day every other day for additional 12 weeks. DAS28-ESR was significantly decreased from 5.2 ± 0.8 to 4.2 ± 0.4 at 12 weeks, 3.2 ± 0.4 at 24 weeks. Eight patients (61.5%) achieved significant improvement of DAS28-ESR and five patients (38.5%) achieved clinical remission. Four patients found adverse events which were not severe. The combination therapy of single administration of high-dose MZR every other day and weekly MTX was effective for RA patients.

W96-2

The usefulness of MTX to treat rheumatoid arthritis receiving MZR

Teruyuki Nakatani, Shinsuke Ishii

Department of Orthopaedic Surgery, Kishiwada City Hospital

【Objective】The usefulness of methotrexate (MTX) was assessed in patients with rheumatoid arthritis receiving mizoribine (MZR) combined with MTX (group A) and those receiving MZR alone (group B). **【Subjects and Methods】**Groups A and B were compared with respect to DAS28-CRP at baseline and 6 months of treatment and plasma MZR level 3 hours post-dose at 6 months.

【Results and Discussion】Mean DAS28 decreased in groups A and B. Mean plasma MZR concentration was $>1.0 \mu\text{g/ml}$ in these groups, yet somewhat inferior in therapeutic response in group A compared to group B. This might be attributable to the fact that group A patients were younger and less responsive to MTX.

【Conclusion】The data failed to demonstrate the usefulness of MTX combined with MZR, but suggested the usefulness of MZR alone.

W96-3

A Study on Additional Concomitant Mizoribine Therapy for Rheumatoid Arthritis

Kohei Yabuno, Suguru Osawa, Toshiaki Koizumi
Sumitomo Hospital, Osaka, Japan

【Objective】 A single-dose concomitant use of mizoribine was assessed in patients with rheumatoid arthritis. **【Subjects】** Thirteen RA patients (2 males and 11 females with a mean age of 67 years)

were included in the assessment. Twelve patients were on methotrexate and 5 on biological products. **【Methods】** Mizoribine was administered at 150-200 mg once to 3 times weekly. The disease activity score (DAS) was assessed according to the European League Against Rheumatism (EULAR) Criteria before and at 3 months after the start of mizoribine and thereafter. **【Results】** Moderate response was observed in 4 patients and no response in 9. Four patients receiving the once-weekly regimen were non-responders. **【Conclusion】** Mizoribine should be administered twice or more weekly to attain the clinical benefit.

W96-4

Effect of Mizoribine (MZR) pulse therapy on Rheumatoid Arthritis (RA)

Tsuyoshi Kobashigawa^{1,2}, Eiichi Tanaka², Hisashi Yamanaka², Noriaki Nakagawa¹

¹Department of Internal Medicine, Division of Rheumatology, Tokyo Women's Medical University Yachiyo Medical Center., ²Institute of Rheumatology, Tokyo Women's Medical University

Purpose: To describe the effect of MZR pulse therapy on RA. **Methods:** Twenty three patients with RA in our hospital have been treated with MZR (3 times a week: morning, evening, and next morning, each time 100mg taking). We analyzed the effect of 3 month MZR pulse therapy in 10 RA patients (3 male and 7 female, mean age: 58.5 year-old, mean duration of disease: 39 months, mean DAS28-CRP: 3.3, 7 MZR alone therapy and 3 MZR and MTX therapy) out of the 23 patients, using DAS28-CRP at 3 months later. **Results:** Four patients out of 10 patients were moderate responders in the EULAR response criteria. DAS28-CRP in 10 patients was significantly improved with MZR therapy ($P < 0.05$). Moreover, MZR alone therapy was also effective on RA. **Conclusions:** Mizoribine pulse therapy was effective on RA.

W96-5

The effect of methotrexate plus mizoribine pulse therapy on the activity of RA

Arisa Shimizu¹, Yuichi Nishioka², Kenji Ito¹, Akio Mimori¹

¹Department of Rheumatology, National Center for Global Health and Medicine, Tokyo, Japan, ²Nishioka Clinic RA, Yamanashi, Japan

The aim of this study is to evaluate the efficacy and safety of mizoribine (MZR) pulse therapy in combination with methotrexate (MTX) in RA patients who were refractory to MTX. 23 patients with active RA were enrolled. They were administered MZR in combination with MTX and were followed for 24 weeks. 4 patients dropped out due to withdrawal of MZR (mild side effects: 1 mild liver dysfunction, 1 aphtha) or addition of other DMARD or steroid. No serious adverse event was observed. DAS28 at weeks 12 and 24 were significantly lower than baseline (3.6 ± 0.37 , 3.2 ± 0.37 ($p < 0.05$), 3.1 ± 0.29 ($p < 0.01$) respectively) and efficacy rates were 37% and 32% at week 12 and 24. This result suggests the potential of MZR as a safe and effective alternative to increasing MTX dose or introducing biologics.

W96-6

The effect of mizoribine pulse therapy for biologics-resistant RA
Asako Oguma, Soshi Takahashi, Hiroshi Miyagawa, Junji Otsuka, Takuya Sawabe

[Objective] To assess the efficacy of mizoribine (MZR) pulse therapy for biologics-resistant RA. [Patients] RA patients resistant to biologics (infliximab for 3, etanercept for 1, adalimumab for 2, and tocilizumab for 1). [Methods] Analysis of EULAR response criteria, DAS28, MHAQ, RF, and MMP-3 before and after MZR pulse therapy (300mg/week). [Results] At 12 weeks (7 cases): good response 3, moderate response 3, no response 1. At 24 weeks (5 cases): good response 5. MHAQ, RF, and MMP-3 were improved. PSL or DMARDs were reduced in 4 cases. MZR peak blood level was above 1 µg/ml in 4 cases. [Discussion] It has been reported the efficacy of MZR depends on its peak blood level. Our findings suggest MZR pulse therapy can be an effective treatment for biologics-resistant RA.

W97-1

Long-term therapeutic effects of tacrolimus added to MTX in patients with RA

Takeyuki Kanzaki, Kimito Kawahata, Risa Akahira, Kazuya Michishita, Kazuhiko Yamamoto

Department of Allergy and Rheumatology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

Objective. To assess the long-term safety and efficacy of tacrolimus (Tac) added to methotrexate (MTX) in patients with rheumatoid arthritis (RA). Methods. DAS28-ESR (3) and side effects of 24 RA patients who received Tac added to MTX at single center were evaluated retrospectively for 3 years. Results. Tac was continued in 19 patients (79%). Two cases were discontinued for adverse events and 3 cases for inadequate response. After 3 years, DAS28-ESR (3) was decreased from 4.72 to 3.41 ($p < 0.05$) and doses of prednisolone was decreased from 4.4 to 3.2mg/day ($p < 0.05$). Conclusion. In RA patients resistant to MTX, Tac added to MTX is safe and well-tolerated and provides clinical benefit for a long time. Further studies are required for determining the safety and efficacy of this treatment.

W97-2

Early induction of low dose tacrolimus and MTX results in better control of RA

Yoichiro Akiyama¹, Kanami Tongu², Yuichi Nishioka²

¹Yamanashi prefectural central hospital, ²Nishioka Clinic for Rheumatic Diseases and Allergic Diseases, ³INSYSTEM K.K.

To evaluate the efficacy and safety of low dose of tacrolimus (LD-Tac) and methotrexate (MTX), patients with disease duration of less than 2years, were recruited to the combination therapy of LD-Tac and MTX in year 2008. 29 patients, received MTX more than 3months, and still DAS28ESR persisted >3.2 , introduced 1mg/day of tac, and 2 -year observation was made. No patient reported death, and two cases moved to other hospitals, 8 patients required bio-DMARDs to control disease activity. Thus, after 2-year, retention rate for LD-Tac and MTX is 65.5%. With this 19 patients who survived with LD-Tac plus MTX, average CRP before treatment was 2.23 and after 2-year, 0.21. Average DAS28ESR before was 3.38 and after 2.07. 13 patients showed no deterioration of bone structure after 2-year follow up.

W97-3

Radiologic results of tacrolimus combination therapy in treatment-resistant RA

Yuya Takakubo¹, Michiaki Takagi¹, Yasunobu Tamaki¹, Tomoyuki Hirayama¹, Akiko Sasaki¹, Haruki Nakano¹, Hiroharu Ohki¹, Suran Yang¹, Kiyoshi Iwazaki¹, Kan Sasaki¹, Hiroshi Orui², Toshihiko Ogino¹

¹Department of Orthopaedic Surgery, Yamagata University School of Medicine, Yamagata, Japan, ²Department of Orthopaedic Surgery, Yamagata National Hospital, Yamagata, Japan

<Introduction> We have treated by add-on tacrolimus (TAC) in a combination with biologics (BIO) and/or non-BIO DMARDs (Non-BIO) in treatment-resistant RA patients. <Methods> Seven RA patients in TAC added-on to BIO (TAC/BIO) and in twenty-five to non-BIO DMARDs (TAC/Non-BIO) were estimated Δ modified total Sharp score (Δ mTSS) and disease activity score (DAS) 28-CRP(4). <Results> The median of Δ mTSS decreased from 43 during the year preceding the baseline to 3 during the first year after adding TAC in the TAC/BIO group and from 22 to 12 in the TAC/Non-BIO group ($p < 0.01$). The mean DAS28-CRP(4) decreased from 5.3 to 4.4 and from 5.0 to 3.9 ($p < 0.01$). <Conclusion> The combination therapy of add-on TAC represents a potential of preventing joint destructions in treatment-resistant RA.

W97-4

Adding tacrolimus in RA patients with insufficient MTX dose for some reasons.

Shigeru Matsuda, Natsuko Nakagawa, Koji Tateishi, Kiminobu Yokoyama, Yasuhiro Terashima, Kohzoh Kohyama, Chihiro Tanaka, Miki Murata, Takashi Yamane, Ryosuke Yoshihara, Yasushi Tanaka, Kazuko Shiozawa, Shigeaki Imura
Rheumatic disease center, Konan Kakogawa Hospital, Hyogo, Japan

We evaluated the efficacy of Tacrolimus (TAC) as add-on therapy in RA patients with MTX administration less than 8mg/w due to some reason.

In this study, 22 RA patients using MTX (average 5.0mg/w) treated with TAC (average 1.2mg/d). Clinical efficacy was assessed according to DAS, CRP and ESR from their records retrospectively.

Most of reason was liver dysfunction why MTX was not able to be increased enough. 9 patients in total were excluded. 6 of them dropped out within 6 months and bio-DMARDs were administered. At 6 months, 16 patients continued TAC add-on therapy, and their clinical results were improved significantly (DAS 3.75→2.90, CRP 2.5→0.49).

The tacrolimus add-on therapy becomes a choice in treatment to RA patients that were unable to increase MTX enough for some reasons.

W97-5

Combination therapy with tacrolimus and methotrexate in rheumatoid arthritis

Kenta Hoshi, Sumiaki Tanaka, Junichi Tanaka, Tatsuhiko Wada, Tatsuo Nagai, Akira Ishikawa, Jun Okada, Shunsei Hirohata
Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan

To clarify the efficacy of combination therapy with tacrolimus and methotrexate (TAC+MTX) in patients with rheumatoid arthritis (RA), we evaluated RA patients treated with TAC (n=142) from 2006 to 2010 by retrospective cohort study design. At baseline of TAC treatment, average of age, DAS28 and dosage of PSL was

66yo, 4.04 and 6.6mg, respectively. 62 patients were treated with TAC+MTX, 80 patients were treated with TAC alone. 53 patients were treated with TAC after 1 year. We evaluated DAS28 which was adjusted for sex, age, dosage of PSL and treatment group by multivariate analysis of variance. DAS28 at baseline was 4.02, and more improved to 2.37 after induction of TAC in TAC+MTX group than 3.29 in TAC alone group. These results showed that TAC+MTX is a potent efficacious strategy for RA.

W97-6

Low dose tacrolimus add to MTX results in no deterioration of safety in 5 years

Yuichi Nishioka¹, Kanami Tongu¹

¹Nishioka Clinic for Rheumatic Diseases and Allergic Diseases, ²IN-SYSTEM, ³Yamanashi Pref Hospital

Addition of tacrolimus (tac) to RA therapy with MTX resulted in better control of disease activity, but no report is made on safety. Patients on MTX prior to 2005, was 307, on that year, 53 patients received 1mg/day of tac (LD-Tac) add to MTX. We compared LD-Tac (+) MTX to the rest of patient with MTX but no tac (LD-Tac (-) MTX), 254. Furthermore, 79 patients with 1.5year observation, each for before and after add of tac, infection events were evaluated. LD-Tac (+) MTX, one patient died, 98.1% survived (In LD-Tac (-) MTX group, 95.7%). 41.5% of LD-Tac (+) MTX group is still on this combination, but 28 patients received additional bio-DMARDs. Before and after addition of tac to MTX, infection events rate is 0.73/person-years, and 0.60. There exist no deterioration of safety after addition of Tac to MTX.

W98-1

Analysis of the background of patients with RA undergoing surgery by using NinJa

Kimio Masuda^{1,5}, Toshihito Mori^{1,5}, Takuo Juji^{1,5}, Mitsuyasu Iwasawa^{1,5}, Ryushi Marutani^{2,5}, Toshihiro Matsui^{3,5}, Shigeto Tohma^{4,5}

¹Department of Orthopaedic Surgery, National Hospital Organization Sagamihara Hospital, Kanagawa, Japan, ²Department of Rehabilitation, National Hospital Organization Sagamihara Hospital, Kanagawa, Japan, ³Department of Rheumatology, National Hospital Organization Sagamihara Hospital, Kanagawa, Japan, ⁴Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagamihara Hospital, Kanagawa, Japan, ⁵iR-net

We investigated the clinical data of patients undergoing surgery from April 2009 through March 2010 by using NinJa (National Database of Rheumatic Diseases by iR-net in Japan) to examine the background of these patients. For this period, 504 patients (7.1%) underwent surgery, including 212 total joint arthroplasties (TJA). Mean age at surgery was 64.8 years old and mean disease duration was 16.9 years. Mean DAS (disease activity score) 28 was 4.04. MTX was used in 246 cases (48.8%) and biologics in 111 cases (22.0%). Moreover, in patients with TJA (1375 patients), MTX was used in 756 cases (55.0%) and biologics in 349 cases (25.4%), suggesting that prevention of infection, especially late-stage infection, could be an important issue in the postoperative follow-up.

W98-2

Total Hip Arthroplasty with Impaction Bone Graft for Protrusio Acetabuli

Akira Maeyama, Hiroshi Jojima, Tomoko Nagano, Satoshi Kamada, Daisuke Kuroda, Katsuhisa Miyake, Hitoshi Nakashima, Masatoshi Naito

Department of Orthopaedic Surgery, School of medicine, Fukuoka University

Seven total hip arthroplasties done in six patients with protrusio acetabuli secondary to rheumatoid arthritis were reviewed. The deficient acetabulum was reconstructed with allogenic bone graft from the femoral head. We evaluated the results of total hip arthroplasty with JOA score for clinical evaluation and Sotelo-Garza classification, the existence of loosening of acetabular component for radiographic evaluation. JOA score was improved from 39.7 points (pre-op) to 90.1 points (post-op). There was no patients with loosening of acetabular component or revision surgery. This technique is a good option in cases with protrusio acetabuli due to rheumatoid arthritis.

W98-3

Total knee arthroplasty without patellar resurfacing in rheumatoid patients

Gen Kuroyanagi, Yukio Yoshida, Toshiyuki Kawanishi, Atsunori Murase

East Medical Center Higashi Municipal Hospital, City of Nagoya, Japan

Eleven knees in 8 rheumatoid patients underwent total knee arthroplasty without patellar resurfacing. Resurfacing was not performed if a slight deformity of the patella was detected. We measured lateral tilt, lateral subluxation, and the length, width, and height of the patella immediately after the operation and at the final follow-up visit. We observed no significant change in lateral tilt. Although lateral subluxation showed a slight increase, patellofemoral dysfunctions, such as dislocation or subluxation of the patella, were absent. The length, width, and height of the patella were approximately equal. Our findings suggest that it may be possible to perform total knee arthroplasty without patellar resurfacing in rheumatoid patients with well-controlled disease.

W98-4

Knee joint gap characters of rheumatoid arthritis and osteoarthritis

Ryutaku Kaneyama¹, Hideaki Shiratsuchi¹, Makoto Otsuka²

¹Funabashi Orthopedic Hospital, Chiba, Japan, ²Kimitsu Chuo Hospital, Department of Orthopedics, Chiba, Japan

Flexion and extension gaps (FG and EG) were measured with PCL remained intra-operatively in 28 RA knees and 163 OA knees. The gaps were made by measured resection technique but FG was made about 4mm smaller than usual by femoral posterior condylar pre-cut (PCP). PS component was selected in case of smaller flexion gap. EG was 16.6±3.4mm and FG was 16.6±2.3mm in RA and EG was 17.6±3.3mm and FG was 16.6±3.6mm in OA. There were wide variations in both gaps of RA and OA. In spite of pre-cut, FG was not so small compared with EG. CR component was selected in 25 RA knees and 127 OA knees from the results. There was no difference between RA and OA. It is difficult to use only one implant, CR

or PS, in every case. PCP is useful to decide which implant should be used in each case.

W98-5

The patients with knee arthropathy have highly risk of lumbar canal stenosis

Hideaki Murata

Hachiya Orthopaedic Hospital

I investigated merger rate of the severe knee arthropathy and lumbar canal stenosis. I intended for a TKA enforcement patient of 199 cases. I did spinal MRI inspection before a TKA operation and examined frequency of the lumbar canal stenosis and degree. It was 181 cases (91%) to have accepted severe stenosis by MRI inspection among these patients. From the viewpoint of diagnosis, treatment and rehabilitation of the severe knee arthropathy, it is important to grasp the state of the lumbar canal before a TKA operation.

W98-6

Ankle arthrodesis using retrograde intramedullary nail with rheumatoid arthritis

Norihiro Ichikawa

Department of Orthopaedics Surgery KANSAI MEDICAL UNIVERSITY Takii hospital, Moriguchi, Osaka, Japan

(Objectives) We reported our outcome for ankle arthrodesis using retrograde intramedullary nail. (Patients and Methods) Between 1997 and 2010, 12 patients (14 ankles) with rheumatoid arthritis were underwent ankle arthrodesis using nails. Eight patients (9 ankles) were underwent arthrodesis using a nail with fins, 4 patients (5 ankles) using a locked nail. (Results) Bone union was detected in all ankles and pain was disappeared in all. However, 2 patients who used a nail with fins were required repeat arthrodesis due to displacement. (discussion) Retrograde intramedullary arthrodesis can be considered an efficient method for severe hindfoot deformity. Patients with severely defect of bone stock in tibiotalar calcaneal joint or severely bone atrophy of talus or calcaneus must be used a locked nail.

W99-1

The assessment of arteriosclerosis in patients with rheumatoid arthritis (RA)

Yumiko Inoue, Yuko Kaneko, Hidetaka Yasuoka, Noriyuki Seta, Hideto Kameda, Masataka Kuwana, Tsutomu Takeuchi

Department of Internal Medicine, Keio University School of Medicine

To investigate the influence of duration of untreated RA from onset of symptom on arteriosclerosis, 69 women patients with untreated RA and without diabetes, hypertension and hyperlipidemia were enrolled in the study using SAKURA data base. Arteriosclerosis of the carotid artery was scored using the following criteria: 1 pulse wave velocity (PWV) ≥ 1400 and no plaque, 2 any plaques only, 3 PWV ≥ 1400 and any plaques. In patients < 60 years old, the score of cases with RA duration ≥ 10 months is significantly higher than that of cases with RA duration < 10 months. (1.25 ± 0.67 vs 0.36 ± 0.67 ; $p = 0.016$), while there is no difference between those two groups in those ≥ 60 years old. These results indicate that the influence of RA duration on arteriosclerosis is larger in younger patients.

W99-2

Algorithm using SNP analysis to interstitial pneumonia in RA patients

Takeshi Nakamura¹, Satoru Koyano², Keiko Funahashi¹, Takafumi Hagiwara¹, Takako Miura¹, Kosuke Okuda¹, Akira Sagawa³, Takeo Sakurai⁴, Hiroaki Matsuno⁵, Tomomaro Izumihara⁶, Eisuke Shono⁷, Tsukasa Matsubara¹

¹Matsubara Mayflower Hospital, Kato, Japan, ²Research Institute of Joint Diseases, Kobe, Japan, ³Sagawa Akira Rheumatology Clinic, Sapporo, Japan, ⁴Inoue Hospital, Takasaki, Japan, ⁵Matsuno Clinic for Rheumatic Diseases, Toyama, Japan, ⁶Izumihara Rheumatic and Medical Clinic, Kagoshima, Japan, ⁷Shono Rheumatology Clinic, Fukuoka, Japan

Purpose: Interstitial pneumonia (IP), a serious complication for collagen diseases such as RA is strongly associated with prognosis. We established an algorithm based on genome-wide SNP analysis for predicting IP in RA patients. **Methods:** The first population had 41 IP and 174 non-IP patients, the second, 15 IP and 26 non-IP patients. Genome-wide SNP genotyping was done by HumanHap300K chip. We selected 10 SNPs associated with IP, common in analyses of both the 1st and 2nd population ($p < 0.02$). Then estimated a total score of 10 SNPs and examined the relationships between IP and non-IP patients, and the total score. **Results:** Accuracy, specificity, and sensitivity of the IP algorithm was 86-91%. **Conclusion:** This highly accurate SNP algorithm may be useful in predicting IP in RA patients.

W99-3

Cerebral vasculitis in a patient with rheumatoid arthritis

Kensaku Okamoto, Naoki Maruyama, Satoru Kodama, Atsushi Kobayashi, Keiji Komura, Yuichi Makino, Fuminori Hirano, Masakazu Haneda

Section of Metabolism and Biosystemic Science, Department of Internal Medicine, Asahikawa Medical University

A 30 year-old woman was diagnosed as rheumatoid arthritis and had been treated with DMARDs and prednisolone (PSL) since 2002. Etanercept (ETN) was administered from February 2007. She was referred to our hospital because of fever in January 2009. ETN was stopped because of multiple lymphadenopathy. Fever and lymphadenopathy were ameliorated and she was discharged. She developed fever and consciousness disturbance on 8th June, and admitted to our hospital. MRI demonstrated multiple high intensity area in the white matter. She did not respond to methyl-PSL pulse therapy and administration of anti-viral agent, anti-biotics, γ -globulin. Brain biopsy revealed cerebral vasculitis, and after repeated methyl-PSL pulse therapy and high dosage of PSL administration, she recovered her consciousness.

W99-4

Gastroesophageal reflux disease (GERD) evaluated with FSSG in patients with RA

Yasushi Miura^{1,2}, Koji Fukuda², Masayasu Takahashi², Shinya Hayashi², Masahiro Kurosaka²

¹Department of Rehabilitation Science, Kobe University Graduate School of Health Sciences, Kobe, Japan, ²Department of Orthopaedic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan

OBJECTIVE: 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 prevalence of GERD and correlation with clinical characteristics of RA were analyzed.

RESULTS: 209 patients were investigated. The prevalence of GERD in RA (21.3%) was significantly higher than that in Japanese population (11.5%) ($p < 0.001$). A positive correlation between FSSG and mHAQ was observed ($r = 0.332$). Between GERD positive and negative groups, mHAQ, VAS, TJC, DAS-CRP, and DAS-ESR were significantly higher in the positive.

CONCLUSION: GERD should be considered as a complication of patients with RA in low ADL score and high disease activity.

W99-5

Serum uric acid relates to disease activity in rheumatoid arthritis patients

Ayako Nakajima, Eisuke Inoue, Atsuo Taniguchi, Eiichi Tanaka, Kumi Shidara, Daisuke Hoshi, Eri Sato, Mariko Kitahama, Yohei Seto, Toru Yamada, Naoki Sugimoto, Shigeki Momohara, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University

[Objective] To determine the association of serum uric acid (sUA) with disease activity in patients with RA

[Methods] sUA level was measured in 5,224 RA patients in the IORRA survey in October 2009. The association of sUA levels with many variables was assessed.

[Results] sUA level increased with male sex, age, disease activity, disease duration, body mass index, physical function, triglyceride, LDL- and HDL-cholesterol ($p < 0.05$). sUA level was increased 0.07, 0.15, 0.45 mg/dl, respectively, in the group of patients with low, moderate, or high disease activity compared to that with remission ($p < 0.001$ for trend).

[Conclusion] This study suggests that sUA is independently associated with RA disease activity. This may interpret the relation between RA disease activity and cardiovascular events.

W99-6

Renal function in patients with rheumatoid arthritis

Keiichi Sumida, Yoshifumi Ubara, Tatsuya Suwabe, Noriko Hayami, Yoshinari Hattori, Rikako Hiramatsu, Eiko Hasegawa, Masayuki Yamanouchi, Junichi Hoshino, Naoki Sawa, Kenmei Takaichi

Department of Nephrology and Rheumatology, Toranomon Hospital, Tokyo, Japan

There are some patients of rheumatoid arthritis (RA) with renal insufficiency without any abnormal findings in urinalysis. In this study, we evaluated renal function of RA patients by 24-hour CCr, estimated GFR (eGFR), and eGFR calculated by serum cystatin C (CyC-GFR). The percentage of patients with moderate to severe renal insufficiency (GFR below 60ml/min/1.73m²) was 48.1% in CCr, 28.9% in eGFR, and 54.2% in CyC-GFR. We have demonstrated relatively high incidence of nephrosclerosis in renal biopsy specimens in RA patients. Recently, the increased risk of cardiovascular disease (CVD) has been reported in RA patients under chronic inflammation. Our results suggest that renal insufficiency in RA patients may be due to nephrosclerotic change induced by almost the same pathogenesis as CVD.

W100-1

Effect of Pneumococcal Vaccination in patients treated with TNF inhibitors

Satoshi Kubo, Kazuyoshi Saito, Kunihiro Yamaoka, Shintaro Hirata, Shizuyo Tsujimura, Masao Nawata, Takayuki Katsuyama, Yoshiya Tanaka

the first department of internal medicine, University of Occupational and Environmental Health, Japan.

Higher incidence of bacterial pneumonia in rheumatoid arthritis patients treated with TNF inhibitors (TNF-I) is known. However, the effect of pneumococcal vaccine (PPV) remains unclear. The post marketing survey of TNF-I in Japan have shown that pulmonary disease, diabetes mellitus, oral glucocorticoid (GC) and age over 65 were the risk factors for pneumonia. Therefore, patients with more than 3 risk factors were vaccinated since 2008 (group A). On the other hand, our data before 2008 indicated that pulmonary disease and oral GC were the risk factors and patients with this factor were vaccinated since 2009 (group B). The incidence of pneumonia was 1.7 (/100 person-year) compared with 2.9 in group A. In conclusion, PPV is recommended in patients with coexisting pulmonary disease or oral GC.

W100-2

Survey of patients with rheumatoid arthritis admitted with infectious pneumonia

Atsushi Hashimoto¹, Shinichi Nogi¹, Kanako Iwata¹, Hidekazu Futami¹, Hirokazu Takaoka¹, Yoshiyuki Arinuma¹, Tatsuhiko Ikenaka¹, Kota Shimada³, Hisanori Nakayama¹, Hiroshi Furukawa¹, Akiko Komiya¹, Toshihiro Matsui¹, Shigeto Tohma¹

¹Department of Rheumatology, Sagami National Hospital, National Hospital Organization, ²Sagami National Hospital, National Hospital Organization, ³Department of Internal Medicine, Tokyo metropolitan Tama medical center

Objective. To find risk factors of infectious pneumonia in patients with rheumatoid arthritis (RA). **Method.** Clinical features of RA patients admitted to our hospital with infectious pneumonia between 2006 and 2010 were analyzed and compared with age- and sex-matched RA patients without admission. **Results.** In 91 RA patients with infection 50 had pneumonia: 47 bacterial, 1 atypical, 1 fungal, and 1 tuberculous. Staphylococcus species were most frequently isolated by sputum culture. Patients with admission compared with those without admission, had significantly higher DAS28 scores and lower serum albumin, and consisted of more Class4 patients and more patients with serum creatinine higher than 1 mg/dl. **Conclusion.** RA patients with risk factors acquiring pneumonia should be treated carefully.

W100-3

Prophylaxis using TMP - SMX for PCP in RA patients with biologics

Takayuki Katsuyama, Kazuyoshi Saito, Kunihiro Yamaoka, Shintaro Hirata, Shizuyo Tsujimura, Masao Nawata, Ippei Miyagawa, Satoshi Kubo, Maiko Yoshikawa, Eri Hirakawa, Yoshiya Tanaka

First department of Internal Medicine, University of Occupational and Environmental Health

We analyzed 702 RA patients treated with biologics (IFX, ETN, ADA, TCZ) to identify risk factors for PCP. 9 patients developed PCP, and NNT led the conclusion that patients with at least two of

three risk factors (age ≥ 65 , coexisting pulmonary disease and usage of glucocorticoids) benefit from primary prophylaxis against PCP. We investigated the efficacy and safety of this procedure for 231 RA patients started biologics after Oct. 2009. The prophylaxis was administered in 103 patients (44.6%). 14 patients received inhaled pentamidine because of renal dysfunction, and TMP - SMX prophylaxis was administered in 89. Liver dysfunction (4 patients), cytopenia (2), skin rash (1), were identified in TMP - SMX group. No patient developed PCP in this study, to prove the efficacy of this procedure.

W100-4

Efficacy of ST prophylaxis in RA with bronchiectasis, received biologics.

Tatsuo Hirose, Yuji Tasaka

Department of Internal Medicine, Saitama City Hospital, Saitama, Japan

The risk of the infection is high in the patients with RA complicated with bronchiectasis. When these patients were receiving biologics, we tried with or without ST as primary prophylaxis. The bronchiectasis was confirmed to 8 cases from 60 RA patient having biologics. We assigned These 8 patients to receive ST prophylactic medication (4 cases) or standard care without prophylactic medication (4 cases). Primary end points were incidences of pneumonia. Patients receiving standard care without prophylaxis, had pneumonia in 4 of 4 cases. The rates of pneumonia in the prophylactic group were significantly low (1 of 4 cases) compared with standard group without prophylaxis. Our data suggests that patients treated with ST prophylactic medication had a lower rate of a pneumonia complication.

W100-5

Analysis of specificity of pneumocystis pneumonia with collagen vascular disease

Haruo Abe, Kensei Tsuzaka

Ichikawa General Hospital Tokyo Dental College, Chiba, Japan

Objective

To clarify the specificity of pneumocystis pneumonia with collagen vascular disease(CTD-PCP).

Metod

Bronchoalveolar lavage or sputum specimens from CTD-PCP 7 patients and HIV-PCP 5 patients were used for DNA extraction. Pj DNA quantitative analysis by real time PCR method was performed and the relation between condition of PCP and amount of Pj DNA were evaluated with serum β -D-glucan levels.

Result

Pj DNA concentrations (pg/ml) were extremely higher ($P < 0.01$) in HIV-PCP group (19~2142, median 71) than in CTD-PCP group (0.001~7.6, median; 3.5). While serum β -D-glucan level (pg/ml) were no significant difference between each groups (CTD-PCP; 12.5~1067, median; 136, HIV-PCP; 0~1720, median; 271).

Conclusion

Serum β D-glucan/amount of Pj DNA in respiratory specimen in CTD-PCP group increased.

W100-6

Difference between ILD associated with collagen disease and IIP

Morihiro Tajiri, Hiroaki Ida, Shinjiro Kaieda, Seiyo Honda, Takaaki Fukuda

Division of Respiriology, Neurology and Rheumatology, Department of Medicine, Kurume University School of Medicine

Interstitial lung disease associated with collagen disease (ILD-CD) is one of serious complications and prognostic factors in the collagen diseases. In this study, we examined bronchoalveolar lavage (BAL) examination in the patients with ILD-CD (12 cases; RA: 5, PSS:3, MCTD:2, SjS:1, PM/DM:1) in comparison to the patients with idiopathic interstitial pneumonia (IIP) (14 cases). The percentage of macrophages derived from BAL fluid is higher in the ILD-CD patients compared with the IIP patients. However, we could not detect the unique findings from BAL analysis in ILD-CD, demonstrating that BAL examination can not lead to the prediction of response to therapy for ILD-CD.

W101-1

Organizing pneumonia in rheumatoid arthritis patients under biologic therapy

Hiddenaga Kawasumi, Eiichi Tanaka, Shinya Futamura, Mikiko Shinozaki, Akiko Tochimoto, Yasuhiro Katsumata, Yasushi Kawaguchi, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Objective: To evaluate case series of organizing pneumonia (OP) in RA patients under biologic therapy.

Methods: We analyzed clinical features of 12 OP events (10 patients) which occurred under biologics from 2008 to 2010.

Results: The average age was 54.5 y.o.. Nine events were in women. Biologics used when they developed OP were Infliximab (7), Etanercept (3), and Tocilizmab and Ocrelizmab (each 1 event). Average duration of biologics use was 20.8 months. DAS28 status at OP occurrence were low in 4, moderate in 7 and high disease activity in 1 event. Although clinical findings were improved with corticosteroid in all events, radiological findings were resistant in 2 events.

Conclusions: OP should be considered when pulmonary consolidations appeared in RA patients under biologic therapy.

W101-2

Characterization of extensive interstitial pneumonia in rheumatoid arthritis

Yoshiteru Haga¹, Satoshi Hachisuka¹, Hidetoshi Miyakawa¹, Naoki Katsuyama¹, Takahito Kimata¹, Masaomi Yamasaki¹, Shoichi Ozaki²

¹Division of Rheumatology, Yokohama City Seibu Hospital, St.Marianna University School of Medicine, ²Division of Rheumatology and allergy, St.Marianna University School of Medicine

Objective. To investigate clinical characteristics of extensive interstitial lung disease (extILD) in rheumatoid arthritis (RA) patients. **Methods.** HRCT parameters and other clinical features were retrospectively analyzed in 3 patients with extILD. **Results.** All 3 patients had abnormal HRCT findings which were consistent with ILD. In HRCT findings, ILD were widely spread to whole lung at initial presentation. All patients show a rapidly progression of ILD. The type of radiological pattern such as cellular, fibrotic NSIP pattern, and UIP pattern were seen. Prognosis of the extILD were variable, cyclophosphamide is effective to one patient, but not in other two patients despite using other immunosuppressive agents. **Conclusion.** ExtILD is life-threatening complication in RA patients.

W101-3

Clinical analysis of lung disease associated with rheumatoid arthritis

Jun Kishi¹, Yuko Toyoda¹, Katsuhiro Kinoshita¹, Toshifumi Teduka¹, Masami Kishi¹, Yasuhiko Nishioka¹, Kenji Tani², Saburo Sone¹

¹Department of Respiratory Medicine and Rheumatology, Tokushima University Hospital, Tokushima, Japan, ²Department of General Medicine, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima, Japan

We investigated patients with lung disease complicated with rheumatoid arthritis by chest high resolution CT (HRCT). The patients with interstitial lung disease were classified in the chest HRCT patterns. We evaluated chest HRCT finding of 33 RA patients. Average age was 62.2 years old. Average duration of RA was 7.6 years. The lung disease were as follows, 23 interstitial pneumonia, 7 air way disease and 3 rheumatoid nodule. The 23 interstitial pneumonia patients were classified as follows, 10 usual interstitial pneumonia (UIP), 10 nonspecific interstitial pneumonia (NSIP) and 3 organizing pneumonia (OP). Serum KL-6 level in patients with interstitial pneumonia were elevated and more high titer in UIP patients.

W101-4

Clinical study of organizing pneumonia associated with rheumatoid arthritis

Shigeru Yoshizawa, Yasutaka Kimoto
Fukuoka National Hospital, Fukuoka, Japan

Clinical features of organizing pneumonia (OP) associated with rheumatoid arthritis (RA) were examined. During 10 years, eleven cases of OP associated with RA (OP-RA), 5 male and 6 female, the average age was 71.2 years old, were diagnosed by histopathological examination and/or radiological and clinical findings. In 7 biopsied cases, 4 cases were diagnosed by histopathologically. In 2 cases, OP complicated with UIP pattern interstitial pneumonia. Out of 11 cases, 3 cases showed simultaneous onset of RA and OP, and in one case OP preceded RA. Corticosteroid (CS) was medicated for OP-RA in 10 cases. All of the 10 cases responded to CS therapy, but in five cases OP-RA was relapsed. One case died by acute exacerbation of UIP. OP-RA was well responded for treatment of CS, but often relapsed.

W101-5

Characterization of interstitial pneumonia developed after etanercept treatment

Masaomi Yamasaki¹, Satoshi Hachisuka¹, Hidetoshi Miyakawa¹, Naoki Katsuyama¹, Takahito Kimata¹, Shoichi Ozaki²

¹Division of Rheumatology, Yokohama City Seibu Hospital, St. Marianna University School of Medicine, ²Division of Rheumatology and allergy, St. Marianna University School of Medicine

OBJECTIVE:To assess characteristics of interstitial pneumonia (IP) associated with etanercept (ETN) in RA patients. **METHODS:**Medical records of all the patients were systematically reviewed. **RESULTS:**Four (1 male, 3 female) patients developed abnormal findings on HRCT which were consistent with IP. All of the four patients had preexisting lung disease. Ave. age is 67.3 year old (62-75). All patients showed bilateral diffuse heterogeneous ground glass opacity. Compared to the patients have no lung adverse effects, there is a statistical significant higher in age (Ave. 67.4 year-

old vs. 57.6, $p=0.03$), and availability of exist lung diseases ($p=0.0004$). **CONCLUSION:**This report suggests that RA patients with preexisting lung disease and older patients must be aware of IP associated with ETN.

W101-6

Eleven cases of Cryptogenic organizing pneumonia with connective tissue disease

Yuko Kimura, Koji Nagai, Yuri Hiramatsu, Kenichiro Hata, Shyuzo Yoshida, Tohru Takeuchi, Shigeki Makino, Toshiaki Hanafusa
First Department of Internal Medicine, Osaka Medical College

Objective: To evaluate the clinical features, treatment and prognosis of cryptogenic organizing pneumonia (COP) with connective tissue disease (CTD). **Methods and Materials:** We investigated 11 COP patients with CTD who were admitted in our hospital from September 2000 to October 2010. **Results:** Mean age 58.9 years old. (3 men and 8 women). Seven patients were RA, 2 were Dermatomyositis, the others were Systemic sclerosis (SSc) and Mixed Connective Tissue Disease. All patients with RA and SSc had high titer anti-CCP antibody (≥ 13.5 U/ml). Four patients were treated with mPSL pulse, and 4 were treated with oral PSL. Two patients were relapsed. **Conclusion:** COP can be complicated with all CTD. Anti-CCP with all RA and SSc patients were high titers.

W102-1

Predicted factors for treatment response and adherence in RA treated with IFX

Yuko Sugioka¹, Shigeyuki Wakitani¹, Masahiro Tada¹, Tadashi Okano¹, Kenji Mamoto¹, Tatsuya Koike²

¹Department of Orthopaedic Surgery, Osaka City University Medical School, Osaka, Japan, ²Department of Rheumatology, Osaka City University Medical School, Osaka, Japan

Infliximab (IFX) is efficacious in RA treatment. Our objective was to evaluate IFX retention rates and their predisposing factors. 175 patients with RA who had received IFX therapy were enrolled in the study. The median time of receiving IFX was 119 weeks and the retention rate at month 12 and 24 was 83.9% and 66.8%. Treatment discontinuation was reported 68 patients and drug inefficacy represented 61.8%. Patients who discontinued for inefficacy were higher DAS-ESR than continued patients at 14 weeks after IFX initiation. Multivariate analysis indicated that Steinbrocker class 3,4 were independent predictor for discontinued for inefficacy (Relative risk 2.63, 95%CI 1.119-6.730). Discontinued for inefficacy were associated with response in early phase of IFX and physical activity.

W102-2

Intensive therapy of infliximab in patients with rheumatoid arthritis

Yuji Akiyama, Kyoichi Nakajima, Yoshihiro Yoshida, Mayuko Sakamoto, Yuki Shimada, Akinori Yamamoto, Muneo Ota, Yasufumi Shindo, Kazuhiro Yokota, Yasuto Araki, Hiroshi Kajiyama, Haruhiko Akiba, Kojiro Sato, Yu Asanuma, Toshihide Mimura

Department of Rheumatology and Applied Immunology, Saitama Medical University, Saitama, Japan

Objective To analyze intensive therapy of infliximab (IFX) in RA patients who had not responded to conventional IFX therapy. **Patients** Three males and 16 females, with a mean age of 58.6 years were studied. MTX dose: 7.4 ± 1.8 mg/w, DAS28-ESR4: $5.85 \pm$

1.05. **Results** 1) Short interval therapy; 3, High dose IFX therapy; 4, Combination; 12. 2) EULAR Good response (GR); 4, Moderate response (MR); 5, No response (NR); 10. 3) Five NR were changed to adalimumab (ADA); 3, etanercept (ETN); 2, and tocilizumab (TOC); 1. As ADA was ineffective, 2 were changed to TOC (MR), and 1 to abatacept. ETN induced MR. 4) Adverse events: Cerebral infarction; 1, Herpes zoster; 2, pneumonia; 1. **Conclusion** It was suggested that intensive IFX therapy could be useful strategy for conventional IFX therapy-resistant RA

W102-3

Continuation of TNF inhibitors and switching for discontinued cases in RA

Hiromitsu Takemori, Hiroshi Kanazawa

Dept. of Rheumatology, Aomori Prefectural Hospital, Aomori, Japan

RA patients treated with a TNF inhibitor (n=187. Sex; female 152, male 35. Age; 58.8±12.6 years. Disease duration; 10.4±8.1 years) were assessed about continuation and efficacy of switching of biologics in the discontinued cases. **Results.** 1) Survival rates; IFX (n=66): 1 year 76.7%, 2 year 58.9%. ETN (n=31): 1 year 87.1%, 2 year 64.5%. ADA (n=11): 1 year 54.5%. 2) Switching of biologics has done in 40 patients (21.4%). Reason for switching; no effect or inadequate response in 33 (82.5%), adverse effects in 5, complication in 1, cost in 1. Times of switching; once in 31, twice in 8, three times in 1. Disease activity after switching; low disease activity in 31 (77.5%), remission in 23 (57.5%). **Conclusion.** Switching of biologics is beneficial in RA patients failed to a TNF inhibitor.

W102-4

Infliximab continuation rates in patients with rheumatoid arthritis

Hideki Takagi¹, Toshihisa Kojima³, Hiroki Tsuchiya¹, Yasuhide Kanayama¹, Hisashi Iwata², Fumiaki Sugiura⁵, Daizo Kato³, Koji Funahashi³, Masahiro Hanabayashi³, Nobunori Takahashi⁴, Atsushi Kaneko⁴, Yuji Hirano⁶, Hisato Ishikawa⁷, Yuichiro Yabe⁸, Naoki Ishiguro³

¹Department of Orthopedic Surgery, Nagoya Kyoritsu Hospital, Nagoya, Japan, ²Rheumatology & Joint Replacement Center, Nagoya Kyoritsu Hospital, Nagoya, Japan, ³Department of Orthopedic Surgery & Rheumatology, Nagoya University School of Medicine, Nagoya, Japan, ⁴Department of Orthopedic Surgery, Nagoya Medical Treatment Center, Nagoya, Japan, ⁵Department of Orthopedic Surgery, Anjo Kosei Hospital, Anjo, Japan, ⁶Department of Rheumatology, Toyohashi City Hospital, Toyohashi, Japan, ⁷Department of Orthopedic Surgery, Nagano Red Cross Hospital, Nagano, Japan, ⁸Department of Rheumatology, Tokyo Kousei-Nenkin Hospital, Tokyo, Japan

Objective: To evaluate the differences by start time of survival rates of treatment of rheumatoid arthritis using infliximab (IFX) during first 7 years in Japan. **Materials & Methods:** 496 cases using IFX for the first biologics were registered in the multi-center study group for the treatment RA using biologics (Tsurumi Biologics Communication; TBC). And we compared background of patients at start and continuation rates between the prophase group (IFX had been administered from 2003 to 2005) and the latter period group (administered after 2006). **Results:** Patients with poor symptoms at start were more at the prophase group than the latter period group, but there was no significant difference of IFX continuation rates between two groups.

W102-5

Improvement of retention rate of infliximab – analysis of IOR-RA –

Eri Sato, Daisuke Hoshi, Kumi Shidara, Naoki Sugimoto, Eisuke Inoue, Yohei Seto, Toru Yamada, Eiichi Tanaka, Ayako Nakajima, Atsuo Taniguchi, Shigeki Momohara, Hisashi Yamanaka
Institute of rheumatology, Tokyo women's medical university

Purpose: To investigate the retention rate of RA patients with infliximab (IFX) therapy. **Methods:** RA patients in IORRA cohort treated with IFX were studied. The IFX retention rate was examined by the Kaplan-Meier method. Variables associated with IFX retention were analyzed by Cox model. **Result:** The retention rate of IFX commenced in 2003 (N=88) was 34% at year 4 and 28% at year 6 and that commenced in 2005 (N=176) at year 4 was improved to 60%. The retention rate of ≥4mg/kg of IFX use was better than that of 3mg/kg use (Log-rank test p<0.05). Variables independently associated with IFX retention were ≥4mg/kg of IFX use compared to 3mg/kg of IFX use [hazard ratio =4.2, 95% CI 2.2-8.2]. **Conclusion:** Increasing dose of IFX is one of the most important factors for improving IFX retention rate.

W102-6

The outcome of long term (over five years) infliximab therapy

Koji Funahashi¹, Toshihisa Kojima¹, Masatoshi Hayashi¹, Daizo Kato¹, Hiroyuki Matsubara¹, Masahiro Hanabayashi¹, Atsushi Kaneko², Nobunori Takahashi², Hisato Ishikawa³, Tomone Shioura⁴, Yuji Hirano⁵, Naoki Fukaya⁶, Hideki Takagi⁷, Yasuhide Kanayama⁷, Hiroyuki Miyake⁸, Yuichiro Yabe⁹, Kenya Terabe¹⁰, Naoki Ishiguro¹
¹Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan, ²Department of Orthopedic Surgery and Rheumatology, Nagoya Medical Center, National Hospital Organization, Nagoya, Japan, ³Department of Orthopedic Surgery, Nagano Red Cross Hospital, Nagano, Japan, ⁴Department of Orthopedic Surgery, Shizuoka Kosei Hospital, Shizuoka, Japan, ⁵Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan, ⁶Department of Orthopedic Surgery, KARIYA TOYOTA General Hospital, Kariya, Japan, ⁷Department of Orthopedic Surgery, Nagoya Kyoritsu Hospital, Nagoya, Japan, ⁸Department of Orthopedic Surgery, Ichinomiya Municipal Hospital Ichinomiya, Japan, ⁹Department of Rheumatology, Tokyo KoseiNenkin Hospital, Tokyo, Japan, ¹⁰Department of Orthopedic Surgery, Fukuroi Municipal Hospital, Fukuroi, Japan

【Objective】To evaluate the outcome of long term therapy with infliximab (IFX) administration for rheumatoid arthritis. **【Material&Methods】**60 cases treated by IFX infusion for 5 years or more were extracted from multi-center registry for the treatment of RA using biologics (Tsurumi Biologics Communications;TBC)database. **【Results】**98 cases started IFX therapy until December 2005, 60 of 98 cases are treated with IFX for 5 years(survival rate: 58.8%). 10 cases were treated by shortening the infusion intervals of IFX. 16 cases were performed IFX dose escalation. 4 of 60 cases discontinued IFX therapy because of loss of efficacy or adverse events. **【Conclusion】**Shortening infusion interval and/or dose escalation of IFX should be needed for the survival of the treatment for long term.

W103-1

Efficacy of TNF inhibitor for autoantibodies positive early arthritis

Junko Kita¹, Mami Tamai², Shin-ya Kawashiri¹, Naoki Iwamoto¹, Akitomo Okada¹, Tomohiro Koga¹, Yoshikazu Nakashima¹, Takahisa Suzuki¹, Satoshi Yamasaki¹, Hideki Nakamura¹, Tomoki

Origuchi³, Toshiyuki Aramaki⁴, Munetoshi Nakashima⁴, Keita Fujikawa⁵, Toshiaki Tsukada⁵, Kiyoshi Aoyagi⁶, Masataka Uetani⁷, Katsumi Eguchi⁸, Atsushi Kawakami¹

¹First Department of Internal Medicine, Nagasaki University, Nagasaki, JAPAN, ²Center for Health and Community Medicine, Nagasaki University, Nagasaki, JAPAN, ³Department of Rehabilitation Sciences, Nagasaki University, Nagasaki, JAPAN, ⁴Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki, JAPAN, ⁵Isahaya General Hospital, Isahaya, JAPAN, ⁶Department of Public Health, Nagasaki University, Nagasaki, JAPAN, ⁷Department of Radiology and Radiation Research, Nagasaki University, Nagasaki, JAPAN, ⁸Sasebo City General Hospital, Sasebo, JAPAN

We have tried to examine the efficacy of tight control DMARDs therapy toward early arthritis patients tested positive for autoantibodies. Twenty-two patients, whose mean disease duration at entry is 14 weeks, were enrolled. Initial DMARDs were MTX (N=19), SASP (N=2) and Tac (N=1), respectively. TNF inhibitors were added in 9 patients (IFX for 8 and ETN for 1) in case DAS28-ESR is still above moderate disease activity. Among the 9 patients, TNF inhibitors were introduced within 24 weeks for 4 patients whereas after 24 weeks for 5 patients. At 12 weeks after the initiation of TNF inhibitors, the rate of DAS28-ESR remission was 50% in the former whereas 80% in the latter. Our data indicate the efficacy of TNF inhibitor toward the early arthritis patients tested positive for autoantibodies.

W103-2

Efficacy and safety of shortening infusion times of IFX in patients with RA

Shunsuke Fukuyo, Kazuyoshi Saito, Masao Nawata, Kunihiro Yamaoka, Shintaro Hirata, Shizuyo Tsujimura
First Department of Medicine, University of Occupational and Environmental Health, Japan

We conducted shortening of IFX infusion times and assessed its efficacy and safety. Of the 141 patients who had completed the first to 6th infusion of IFX without any adverse effects at the usual rate of 2 hours, 94 patients went on to receive further infusions at a rate of 1 hour after obtaining IC. The overall incidence of infusion reaction including mild fever up and skin eruption to IFX was 0.5% (2 of 398 infusions), but administering was able to be continued by returning it to 2 hours infusion. There was no adverse effect and difference in DAS 28 between 2 hours infusion and shortening after 7th and 13th infusion. These results demonstrate shortening infusion time is useful for the save of space for infusion without an increase of adverse effects and decrease of efficacy of IFX.

W103-3

Clinical outcomes in RA patients treated with our infliximab protocol

Nobunori Takahashi, Daihei Kida, Atsushi Kaneko, Tomotaro Sato, Kiwamu Saito
Nagoya Medical Center

We have been trying to get better outcomes in rheumatoid arthritis patients by using original protocol for infliximab treatment since July 2009. We added 100mg at every administration if a patient did not achieve EULAR moderate response or low disease activity in DAS28 (ESR4). We prospectively studied 22 patients. Mean age was 56.4 years, and DAS28 was 4.96. The continuation rate was 94% at 22 weeks and 83% at 54 weeks. Mean DAS28 was

3.28 at 22 weeks and 3.15 at 54 weeks. In seven patients with dose escalation at 6 weeks the continuation rate was only 57% and DAS28 was 4.37 at 54 weeks, while 85% and 2.67 in 15 patients without dose escalation. Continuation rate was better than that before we applied new protocol. We seem to need improved protocol for the patients who need dose escalation.

W103-4

Comparison of Dose Escalation and Interval Reduction of Infliximab

Naohide Takigawa, Hiromitsu Moriuchi, Muneki Abe
Nishinomiya Kyoritsu Neurosurgical Hospital

Of the total of 6 RA patients who did not fully respond to normal doses and intervals, 3 patients in the dose escalation (DE) group were treated with a DE, and the other three patients in the interval reduction (IR) group were treated by 2 weeks IR. Using the EULAR response criteria there were no responses in 100% at 2 month in both groups, and a good response in 33%, moderate responses in 67%, at 6months in the IR group, and moderate responses in 67%, no response in 33% at 6 months in the DE group. It was difficult to evaluate improvements at 2 months for DE and IR. At 6 months, IR was better than DE as demonstrated by improvements in DAS28. Therefore we recommend IR of infliximab initially for RA patients who do not fully respond to the regular dose and regular treatment term.

W103-5

The efficacy of shortening intervals for IFX and dose escalation of IFX with RA

Koji Funahashi¹, Toshihisa Kojima¹, Masatoshi Hayashi¹, Daizo Kato¹, Hiroyuki Matsubara¹, Masahiro Hanabayashi¹, Atsushi Kaneko², Nobunori Takahashi², Yuji Hirano³, Tomone Shioura⁴, Hideki Takagi⁵, Yasuhide Kanayama⁵, Takayoshi Fujibayashi⁶, Yuichiro Yabe⁷, Naoki Fukaya⁸, Hiroyuki Miyake⁹, Kenya Terabe¹⁰, Naoki Ishiguro¹

¹Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan, ²Department of Orthopedic Surgery and Rheumatology, Nagoya Medical Center, National Hospital Organization, Nagoya, Japan, ³Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan, ⁴Department of Orthopedic Surgery, Shizuoka Kosei Hospital, Shizuoka, Japan, ⁵Department of Orthopedic Surgery, Nagoya Kyoritsu Hospital, Nagoya, Japan, ⁶Department of Orthopedic Surgery, Konan Kosei Hospital, Konan, Japan, ⁷Department of Rheumatology, Tokyo Kosei Nenkin Hospital, Tokyo, Japan, ⁸Department of Orthopedic Surgery, KAR-IYA TOYOTA General Hospital, Kariya, Japan, ⁹Department of Orthopedic Surgery, Ichinomiya Municipal Hospital Ichinomiya, Japan, ¹⁰Department of Orthopedic Surgery, Fukuroi Municipal Hospital, Fukuroi, Japan

【Objective】To evaluate the efficacy of shortening intervals of IFX with dose escalation of IFX. 【Methods】100 cases treated by shortening intervals of IFX to 7 weeks or less and 111 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, 25 cases discontinued IFX therapy because of loss of efficacy, 10 cases stopped IFX infusion because of adverse events (AEs). In dose escalation cases, 22 cases discontinued IFX therapy because of loss of efficacy, 10 cases stopped IFX infusion because of AEs. 【Conclusion】The short-

ening IFX therapy and dose escalation of IFX should be considered in case of loss of efficacy during IFX treatment with 3mg/kg dose.

W103-6

Effect of an IFX dose increase in RA patients in a multicenter trial, Part 1.

Takaaki Fukuda

Fukuoka RA Biologics Therapy Working Group, Fukuoka, Japan

Objective To evaluate the effect of an infliximab (IFX) dose increase in arthritis patients with insufficient response to IFX. **Patient background** Thirty-eight patients (71% female) completed the assessment for 6 months. They were an average age of 56 years with average disease duration of 13 years and average body weight of 58 kg. Patients had also received methotrexate 7.7 mg/week on average, and steroids were combined in 81% of the patients. **Results** Increasing the average IFX dose from 3.5 to 6.1 mg/kg resulted in a significant improvement in average DAS28 score from 4.6 to 3.6. A good or moderate EULAR response was seen in 71.1% patients and a decrease in DAS score by ≥ 1.2 were in 42.1% patients. **Conclusion** Dose increase of IFX is useful in arthritis patients with insufficient response to IFX.

W104-1

Discontinuation of Etanercept after Attaining Remission in Patients with RA

Shusuke Ota, Makoto Fukuda, Yohei Kawaguchi, Mitsuo Yatsuzuka
Shizuoka Medical Center, National Hospital Organization, Shizuoka, Japan

Objective: We investigated whether etanercept (ETN) might be discontinued after achievement of clinical remission (CR) in patients with rheumatoid arthritis (RA). **Methods:** Nine patients (mean age; 62.1 ± 7.1 years old, mean disease duration; 3.1 ± 1.4 years) who had received treatment with 50mg/w of ETN for 10.8 ± 7.2 months, were discontinued use of ETN after achievement of CR according to DAS28. **Results:** The mean DAS28 before treatment of ETN was 3.4 ± 1.1 . Four (44%) patients have maintained CR for 11.8 ± 5.6 months. Five (56%) patients were flared RA within 10 ± 7.8 months, and achieved low disease activity after readministration of 25mg/w of ETN. **Conclusion:** Four (44%) patients were able to discontinued use of ETN after attaining CR. Readministration of 25mg/w of ETN was effective in patients flared RA.

W104-2

Medical cooperation for RA patients treated etanercept

Atsushi Kaneko¹, Daihei Kida¹, Nobuteru Takahashi¹, Tomotaro Sato¹, Tomiaki Asai²

¹Department of Orthopaedic surgery and Rheumatology, Nagoya Medical Center, NHO, Nagoya, Japan, ²Department of Orthopaedic surgery and Rheumatology, Asai Clinic, Nagoya, Japan

Our hospital promotes medical cooperation with regional clinic for biologics, especially Asai Rheumatic and Orthopaedic clinic. We introduce the clinical results (drug survival, the reasons of discontinuation) of 67 RA patients in our medical cooperation. In results, Drug survival rate at 5 year was 80.2%. The reason of 15 discontinued patients were 8 for ineffectiveness, 3 for infectious disease, 2 for hospital transfer. One patients died for severe pneumonia. In our conclusion, etanercept is the best biologic for patients with RA

by medical cooperation with regional clinic and hospital because of high drug survival and safety.

W104-3

Hospital-clinic partnership in rheumatic diseases

Tamao Nakashita¹, Daisuke Kato², Yoshiaki Kuga³, Tamio Takahei³, Hiroshi Hozumi⁵, Akira Inoue¹, Natsuki Fujio¹, Shinji Motojima¹

¹Rheumatology and Allergy, Kameda Medical Center, Chiba, Japan, ²Kato Daisuke Clinic, Chiba, Japan, ³Tateyama Orthopedics Clinic, Chiba, Japan, ⁴Yamaguchi Hospital, Chiba, Japan, ⁵Asunaro-keiai Clinic, Chiba, Japan

Recently, the activity of RA can be dramatically suppressed by the use of biologics (BIOs). However, doctors working in private clinics are concerned about the introduction, and early detection and management of adverse events (AEs) after administration of BIOs. The number of patients is increasing who were introduced with BIOs by hospital-clinic partnership. Sixty-six patients with RA and arthralgia were referred to our department. Fifty-four were diagnosed as RA and BIOs were introduced to 29 patients. After that, injection of BIO was done in the reference clinics and the patients were also followed-up in our department. DAS28ESR decreased in all of the patients and 2 AEs were detected immediately. Hospital-clinic partnership can contribute greatly to patients' better QOL.

W104-4

Biological drugs are useful for arthritis and ADL in the family medicine center

Yasuhiro Osugi¹, Kenji Fujii²

¹Iizuka Kaita Family Medicine Program, ²Kaita Hospital

The evaluation of the disease activity of RA with the dementia and the intellectual disability is difficult. We experienced a case which resulted in a safe and excellent therapeutic process by carefully using biological drugs for RA patients who have dementia and intellectual disability in the family medicine center. We monitored 7 elderly patients. Etanercept 25mg once-weekly dosing was introduced after the use of DMARD. Because the evaluation of VAS was difficult, we evaluated the therapeutic gain from the change of the joint finding, and ESR or CRP. Four patients of them obtained good result. One of them recovered enough not to need Bio or DMARD any more. In patients who have dementia and intellectual disability, Bio drugs are useful for arthritis and ADL in the family medicine center.

W104-5

Comparison of efficacy between etanercept 25mg/week and 50mg/week in RA

Mikiko Shinozaki, Atsuo Taniguchi, Eisuke Inoue, Haruko Inoue, Wako Urano, Yumi Koseki, Naomi Ichikawa, Shigeki Momohara, Hisashi Yamanaka

Institute of rheumatology, Tokyo women's medical university

The aim of the study was to assess the clinical results at 6 months of etanercept (ETN) 25mg/week (wk) and 50mg/week in RA patients in clinical practice. 59 patients treated with ETN were randomly selected. Of those, 19 cases were administered ETN 25mg/wk during 6 months (group I). 7 patients were initially treated with ETN 25mg/wk and ETN was increased to 50mg/wk (group II). 33 patients were treated with ETN 50mg/wk during 6 months (group III). Initial DAS28-CRP of group II was significantly higher than that of Group I. DAS28-CRP at 6th month or improvement ratio of DAS28-CRP were not different between Group I and III. Prednisol-

lone and MTX doses of Group I were similar to those of Group III. Patient selection based on disease activity was suggested to be important for choice of ETN dosage.

W104-6

The efficacy of 25mg etanercept once weekly in patients with RA on TBC registry.

Masatoshi Hayashi¹, Toshihisa Kojima¹, Koji Funahashi¹, Daizo Kato¹, Hiroyuki Matsubara¹, Naoki Ishiguro¹, Takeshi Oguchi², Atsushi Kaneko³, Hideki Takagi⁴, Yasuhide Kanayama⁴, Yuji Hirano⁵, Hiroyuki Miyake⁶, Hisato Ishikawa⁷, Yuichiro Yabe⁸, Takefumi Kato⁹, Takayoshi Fujibayashi¹⁰

¹Departments of Orthopedics, Nagoya University Graduate School of Medicine, Nagoya, Japan, ²Anjo Kosei Hospital, ³Nagoya Medical Center, ⁴Nagoya Kyoritsu Hospital, ⁵Toyohashi Municipal Hospital, ⁶Ichinomiya Municipal Hospital, ⁷Nagano Red Cross Hospital, ⁸Tokyo Koseinenkin Hospital, ⁹Kato orthopedic clinic, ¹⁰Konan Kosei Hospital

OBJECTIVE: To assess the clinical results at 12 months of etanercept 25mg once and twice weekly in patients with rheumatoid arthritis. **METHODS:** Cases were studied to assess means of DAS28, MMP-3 and mean dosage of MTX, PSL in patients with RA treated etanercept 25mg given either once or twice weekly. **RESULT:** 762 patients had been treated with ETN for at least 12 months (188 once weekly, and 574 twice in total registered 1574). One year survival rates were 84.1% in once group and 81.2% in twice group. Values of DAS28-CRP improved dramatically in once group (from 4.9±1.0 to 2.2±1.0) as well as in twice group (from 5.0±1.2 to 3.1±1.3). **CONCLUSION:** The strong improvement in once group suggests it's clinical relief in some patients with RA as well as twice group.

W105-1

Multicenter 5-year continued etanercept use for rheumatoid arthritis (RA)

Eiichi Suematsu¹, Takashi Ishinishi², Eisuke Shono³, Tomomi Tsuru⁴, Ryuji Nagamine⁵, Hisaaki Miyahara⁶, Ken Wada⁷, Masakazu Kondo⁸

¹Fukuoka RA Biologics Treatment Society, Department of Internal Medicine and Rheumatology, Clinical Research Center, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan, ²Department of Orthopedic Surgery and Rheumatology, Fukuseikai Hospital, Fukuoka, Japan, ³Shono Rheumatism Clinic, Fukuoka, Japan, ⁴Medical Corporation Souseikai PS Clinic, Fukuoka, Japan, ⁵Department of Orthopedics Surgery Sugioka Memorial Hospital, Fukuoka, Japan, ⁶Department of Orthopedic Surgery and Rheumatology, Clinical Research Center, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan, ⁷Wada Orthopedic Clinic, Fukuoka, Japan, ⁸Kondo Clinic of Rheumatology and Orthopedic Surgery, Fukuoka, Japan

We examined long-term efficacy and continuation rate of etanercept (ETN) in RA patients (pts) who were started during Mar. 2005 to Mar. 2006 in 8 centers in/around Fukuoka City. We included 154 RA pts (139 females, 15 males) continuing ETN. Their mean age, 58.6±10.8 years, RA length, 10.5±6.5 years, and duration of ETN use, 173.3±104.0 weeks. Mean DAS28 was 5.82 at baseline. Those at weeks 12, 24 and each year until 5 years later were 4.00, 3.68, 3.70, 3.63, 3.77, 3.67, and 3.70, respectively. ETN was well maintained with continuation rate of 50.0% at 5 years, although half had long-term RA and Stage IV. Adverse events included upper respiratory infection, bronchitis and herpes zoster. ETN may sustain its

efficacy with high continuation rate and can be used without specific serious issues.

W105-2

Determination of factors that make the long-term etanercept use possible

Toyomitsu Tsuchida¹, Ayako Kubota²

¹Tsuchida Clinic, Chiba, Japan, ²Department of Orthopedic Surgery, Toho University, Tokyo, Japan

Background Continued use of biologics in RA patients (pts) can control disease activity (DA) and prevent bone destruction for long time, thus maintain QOL, but some pts discontinue treatment for various reasons. We examined what enables long-term use of etanercept (ETN). **Methods** We analyzed our hospital's ETN-treated pts' data to compare the characteristics. **Results** Among 110 RA pts 34 years from the start of ETN, 60.0% continued 4 years later. Compared to ETN continued pts (n=66), discontinued pts (22) due to AEs were significantly older and more likely to be class 3/4; compared to discontinued pts (6) due to lack of efficacy, there were no significant differences. **Conclusions** Younger age and lower impairment at the start of ETN may be associated w/ safe continuation of ETN.

W105-3

Comparison of the survival rate for combination with Etanercept and methotrexate

Hiroki Tsuchiya¹, Toshihisa Kojima², Hideki Takagi¹, Yasuhide Kanayama¹, Hisashi Iwata¹, Takeshi Oguchi³, Masatoshi Hayashi², Hiroyuki Matsubara², Yutaka Yoshioka⁴, Takuya Matsumoto⁵, Naoki Ishiguro²

¹Dept. of Orthopedic Surgery And Rheumatology, Nagoya Kyoritsu Hospital, Nagoya Jpn, ²Dept. of Orthopedic Surgery and Rheumatology, Nagoya University School of Medicine, Nagoya Jpn, ³Dept. of Orthopedic Surgery, Anjo Kosei Hospital, Aichi Jpn, ⁴Dept. of Orthopedic Surgery, Nagano Red Cross Hospital, Nagano Japan, ⁵Dept. of Orthopedic Surgery, Kariya Toyota Hospital, Aichi Japan

[Objective] To compare of the survival ratio for combination with Etanercept (ETA) and methotrexate (MTX) on patients with Rheumatoid arthritis. [Method] RA patients who were using biological agents from TBC were 1481 cases, 622 cases in that were using ETA as 1st biological agent. We compared the ratio of consecutive patients by Kaplan-Meier using that 622 cases. [Result] The 438 cases were treated with ETA and MTX, while the 224 cases were treated with ETA alone. Survival rate of ETA and MTX group was significant higher than that of ETA alone. [Conclusion] The combination treatment of ETA and MTX is superior to ETA alone.

W105-4

The patient characteristics and the continuation rate of etanercept in RA

Takeshi Oguchi¹, Fumiaki Sugiura¹, Toshihisa Kojima², Masatoshi Hayashi², Hiroyuki Matsubara², Naoki Ishiguro², Hideki Takagi³, Hiroki Tsuchiya³, Atsushi Kaneko⁴, Yuji Hirano⁵, Hiroyuki Miyake⁶, Hisato Ishikawa⁷, Yuichiro Yabe⁸

¹Department of Orthopedic Surgery, Anjo Kosei Hospital, Aichi, Japan, ²Department of Orthopedic Surgery, Nagoya University School of Medicine, Nagoya, Japan, ³Department of Orthopedic Surgery, Nagoya Kyoritsu Hospital, Nagoya, Japan, ⁴Department of Orthopedic Surgery, Nagoya Medical Center, National Hospital Organization, Nagoya, Japan, ⁵Department of Rheumatology, Toyohashi Mu-

municipal Hospital, Aichi, Japan, ⁶Department of Orthopedic Surgery, Ichinomiya Municipal Hospital, Aichi, Japan, ⁷Department of Orthopedic Surgery, Nagano Red Cross Hospital, Nagano, Japan, ⁸Department of Rheumatology, Tokyo Kosei Nenkin Hospital, Tokyo, Japan

Etanercept (ETN) was agreed officially in our country, and more than six years passed. We considered whether a change occurred in the patient characteristics and the continuation rate in the early years and recent years. The 739 patients which ETN was used for as a 1st biological drug out of 1481 patients registered in TBC were made the target. The 301 patients of patient characteristics and a continuation rate of the recent group (after 2008) were compared with the 438 patients of the initial group (2005-2007). The stage classification and the class classification changed in the one which a difficulty was rare, and it was short in the contraction period as well. Though a DAS28-CRP to start medication was low, a significant difference wasn't recognized in the continuation rate.

W105-5

The effect of disease activity at baseline on continuation rates of etanercept

Hiroyuki Matsubara¹, Toshihisa Kojima¹, Masatoshi Hayashi¹, Koji Funahashi¹, Daizo Kato¹, Atsushi Kaneko², Hideki Takagi³, Hiroyuki Miyake⁴, Takeshi Oguchi⁵, Yuji Hirano⁶, Hisato Ishikawa⁷, Yuichiro Yabe⁸, Naoki Ishiguro¹

¹Department of Orthopaedic Surgery, Nagoya University School of Medicine, ²Nagoya Medical Center, ³Department of Orthopaedic Surgery, Nagoya Kyouritsu Hospital, ⁴Department of Orthopaedic Surgery, Ichinomiya Municipal Hospital, ⁵Department of Orthopaedic Surgery, Anjou Kousei Hospital, ⁶Department of Rheumatology, Toyohashi Municipal Hospital, ⁷Department of Orthopaedic Surgery, Nagano Red Cross Hospital, ⁸Department of Rheumatology, Tokyo Kousei-nenkin Hospital

The aim of present study is to investigate whether the disease activity at baseline affects continuation rate of etanercept (ETN). 762 patients that used ETN as first biologics among 1574 patients from the biologics research group (Tsurumi Biologics Communications; TBC) were included. The mean age was 56 years old, and the mean disease duration was 11.5 years. The patients were divided into 3 groups by tertile of DAS28-CRP at baseline and the continuation rates of each groups were found by Kaplan-Meier method. The mean DAS28-CRP at baseline were 3.79, 4.89, 6.05. 5 years continuation rates were 77.8%, 58.2%, 58.9%, which tended to be better in low disease activity group. This study suggested that ETN might bring the low disease activity patients at baseline good continuation rate.

W105-6

Potential of TNF inhibitor (etanercept) to achieve drug-free remission

Kensei Tsuzaka¹, Yuka Itami¹, Haruo Abe¹, Masayoshi Nagata²

¹Tokyo Dental College Ichikawa General Hospital, ²Iruma Heart Hospital

At present, evidence of whether patients (pts) on etanercept (ETN) treatment are able or not to achieve drug-free remission is not sufficient. We conducted a retrospective study to analyze drug-free remission potential in ETN-treated pts. We studied 55 ETN treated pts in our affiliate institutions. Remission (DAS28ESR <2.6) was reported in 13 pts. Of these, 10 withdrew ETN with each pts' consent,

but 2 resumed ETN due to relapse. Remission was maintained in 8 pts including 3 men; mean age was 57.5 (21 - 77 y/o); mean RA duration was 46.4 months (3 - 240 months); 3 had been under treatment with concomitant DMARDs and 5 with ETN alone. Data suggest that drug-free remission may be achieved even in pts with longer RA duration as well as with ETN monotherapy without concomitant MTX usage.

W106-1

Vasculitis induced by T cells autoreactive with vascular endothelial cells

Akihiro Ishizu¹, Utano Tomaru², Takashi Yoshiki³

¹Faculty of Health Sciences, Hokkaido University, ²Department of Pathology, Hokkaido University Graduate School of Medicine, ³GeneticLab Co., Ltd.

We established T cell clones autoreactive with vascular endothelial cells from env-pX rats that developed vasculitis. The T cell clones showed a TCR $\alpha\beta^+$ CD3⁺CD4⁺CD8⁻CD25⁺NKR-P1A⁻ phenotype. The V β chain used by the clones was V β 8.6, and the amino acid sequence in the CDR3 was RPWGGRF. RT-PCR revealed that the cytokine/chemokine profile of the clones was positive for TNF- α , IL-4, IFN- γ , MCP-1, MIP-1 α , MIP-1 β , and rantes, but negative for IL-2, IL-10, IL-17, and eotaxin. Vasculitis was induced in the lung and other tissues of wild-type rats by intravenous injection of the cells, thus suggesting that the T cell clones autoreactive with vascular endothelial cells were regarded as pathogenic T cells for vasculitis.

W106-2

Effects of Imatinib Mesylate (IM) on the murine model of allergic vasculitis.

Nobuhito Sasaki¹, Naomi Suzuki¹, Okinori Murata¹, Hisashi Tanaka¹, Kouko Kowata¹, Yukari Ninomiya¹, Hitoshi Kobayashi¹, Kohei Yamauchi¹, Akihisa Kamataki², Takashi Sawai²

¹Division of Pulmonary medicine, Allergy and Rheumatology, Department of Internal Medicine, Iwate Medical University School of Medicine, Morioka, Japan, ²Department of Pathology, School of Medicine, Iwate Medical University, Morioka, Japan

Objectives: We investigated the effects of IM on vascular remodeling using the murine model of allergic vasculitis. **Methods:** The mice were sensitized with ovalbumin (OVA) and alum. The mice were administered with IM in parallel with daily exposure to aerosolized OVA for 7 days. On 7th day, bronchoalveolar lavage (BAL) was performed and the lungs were excised for pathological analysis. **Results:** The ratio of with eosinophils in total cell number reduced significantly in the IMs. The pathological scores reduced significantly in the IMs compared to the controls. Intra luminal infiltration and proliferation of myofibroblasts in pulmonary arteries were reduced dramatically in the IMs compared to the controls. **Conclusion:** IM suppressed pulmonary vascular remodeling in the murine model.

W106-3

Th17 cells in rheumatoid vasculitis

Nobuaki Ikeda¹, Yukie Yamaguchi¹, Kazuo Takahashi¹, Megumi Kondo¹, Tetsuo Sasaki², Zenro Ikezawa¹

¹Department of Dermatology, Yokohama City University Graduate School of Medicine, Kanagawa, Japan, ²Department of Dermatology

gy, International University of Health and Welfare Atami Hospital, Shizuoka, Japan

Rheumatoid vasculitis (RV) is known as one of the extra-articular manifestations of rheumatoid arthritis (RA). Since Th17 has been implicated in the pathogenesis of RA, we investigated the association of Th17 in RV by evaluating cytokine and chemokine levels, number of Th17 cells in circulation and affected tissues in RV patients. In eight RV patients, all had elevated serum levels of sICAM-1, fractalkine, and E-selectin. The serum levels of IL-17 were increased in three patients. There was no significant difference in the proportion of circulating Th17 cells between RV patients and controls. Further, infiltrated Th17 cells in affected skin were detected in half of RV patients by immunohistochemistry. These results suggest that Th17 cell is partially involved in the pathogenesis of RV.

W106-4

Hsp60 proteolysis by proteinase 3 induces neutrophil degranulation

Shinji Sato, Noriko Sasaki, Kiri Honda, Eiko Saito, Takayuki Wakabayashi, Chiho Yamada, Yasuo Suzuki
Department of Internal Medicine, Division of Rheumatology, Tokai University School of Medicine, Isehara, Japan

To address whether PR3-mediated proteolysis of Hsp60 released in the Wegener's granulomatosis (WG) microenvironment contributes to the inflammatory response, isolated polymorphonuclear cells (PMNs) were co-incubated with intact or PR3-cleaved human Hsp60. PMN degranulation was quantified by the b-glucuronidase release assay. PR3-cleaved HSP60 caused significant b-glucuronidase release compared to intact Hsp60 ($p=0.01$). Moreover, subsequent incubation of fresh, non-primed PMNs with Hsp60 incubated with supernatants from TNF α -primed PMNs caused significant degranulation compared to those from non-TNF α -primed PMNs ($p=0.005$). Hsp60 is highly expressed in the giant cells of WG lung granulomata. PMN degranulation induced by PR3-cleaved Hsp60 might play an important role in pathogenesis of WG.

W106-5

Efficacy of TNF blockers for refractory cutaneous vasculitis with skin ulcers.

Takao Sugiyama¹, Makoto Sueishi¹, Toyohiko Sugimoto¹, Masaaki Furukawa¹, Yukiko Hiramatsu¹, Emiko Tanabe²

¹Department of Rheumatology, Shimoshizu National Hospital, Yotsukaido, Japan, ²Chiba Central Skin Clinic, Chiba, Japan

OBJECTIVES: To test the efficacy of treatment with TNF blockers for refractory skin ulcers in patients with cutaneous vasculitis. **METHODS:** Retrospective study of one male and two female patient with skin ulcers due to vasculitis, negative ANCA and normal CRP levels. All developed the lesions against treatment with prednisolone (PSL), PGE1 and two of them with IV-CY. They were refractory to PSL in the dosage 0.4 mg/kg for at least 4 weeks prior treatment with TNF blockers. TNF blockers (1 infliximab, 2 etanercept) were administered. **RESULTS:** All patients achieved a rapid clinical remission of the skin ulcers after TNF blockers therapy with a successful PSL reduction till 5mg a day. **CONCLUSIONS:** TNF blockers seem to be very effective for skin ulcers in patients with cutaneous vasculitis.

W107-1

Observational study of Japanese AAV patients (RemIT-JAV) (Preliminary report)

Ken-ei Sada¹, Hirofumi Makino¹, Yoshihiro Arimura^{1,2}, Ministry of Health, Labor, and Welfare intractable vasculitis research group¹

¹Ministry of Health, Labor, and Welfare intractable vasculitis research group, ²First Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan

Objective: To estimate a usefulness of the Ministry of Health, Labor, and Welfare (MHLW) criteria for the ANCA-associated vasculitides (AAV). **Methods:** We analyzed the data of the cohort study in MHLW intractable vasculitis research group. **Results:** Of 128 patients, 34 and 99 patients fulfilled MHLW criteria for definite and possible microscopic polyangiitis (MPA). Similarly, 13 and 109 patients fulfilled MHLW criteria for definite and possible Wegener's granulomatosis (WG). While the definite MPA and WG criteria had high specificity (91.8%, 94.9%) and high positive likelihood ratio (4.63, 5.24), the possible MPA and WG criteria had a high sensitivity (94.9%, 90.0%) and low negative likelihood ratio (0.10, 0.12). **Conclusion:** These criteria may be useful for the diagnosis of MPA or WG.

W107-2

An association study between BLK and ANCA-associated vasculitis in Japanese.

Naoyuki Tsuchiya¹, Ikue Ito¹, Hiroshi Furukawa², Shigeto Tohma², Shigeto Kobayashi³, Hiroshi Hashimoto⁴, Hidehiro Yamada⁵, Shoichi Ozaki⁶, Nobuyuki Miyasaka⁶, Masayoshi Harigai⁷, Hirofumi Makino⁸

¹Doctoral Program in Life System Medical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan, ²Clinical Research Center for Allergy and Rheumatology, National Hospital Organization, Sagami National Hospital, Sagami, Japan., ³Department of Medicine, Juntendo University Koshigaya Hospital, Koshigaya, Japan., ⁴School of Medicine, Juntendo University, Tokyo, Japan., ⁵Division of Rheumatology and Allergology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan., ⁶Department of Medicine and Rheumatology, Tokyo Medical and Dental University, Tokyo, Japan., ⁷Department of Pharmacovigilance, Tokyo Medical and Dental University Graduate School of Medicine, Tokyo, Japan., ⁸Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine Dentistry and Pharmaceutical Sciences, Okayama, Japan.

Objective: Susceptibility genes to autoimmune rheumatic diseases such as systemic lupus erythematosus, rheumatoid arthritis and systemic sclerosis are substantially overlapping. In this study, we examined whether B lymphoid tyrosine kinase (*BLK*) gene, previously associated with these diseases, is also associated with ANCA-associated vasculitis.

Methods: A case-control association study was performed on 98 patients with microscopic polyangiitis (MPA), 18 with Wegener's granulomatosis (WG), 10 with Churg-Strauss syndrome (CSS) and 511 healthy controls.

Results: The A allele of rs13277113 was increased in MPA under the recessive model (odds ratio 1.56, $P=0.044$). A tendency towards increase was also observed in CSS, but not in WG.

Conclusion: *BLK* was suggested to be a susceptibility gene to MPA.

W107-3

Relapse in patients with MPO-ANCA-positive microscopic polyangiitis

Kiyoki Kitagawa, Yasuyuki Shinozaki, Tadashi Toyama, Akinori Hara, Kengo Furuichi, Takashi Wada
Kanazawa University Hospital, Division of Nephrology

Clinicopathological characteristics were examined in patients with MPO-ANCA-positive microscopic polyangiitis (MPA) with relapse. A total of 12 patients who were diagnosed as MPA in Kanazawa University Hospital from 2005 to 2009 was examined in this study. Four patients were relapsed during the follow-up period (relapse group: female 4, male 0. non-relapse group: female 5, male 3). Neither clinical findings (BVAS, urinalysis, eGFR, CRP and MPO-ANCA level) nor pathologic findings at initial treatment had statistical difference between both groups. On the other hand, the level of vasculitis damage index (VDI) at remission was higher in relapse group (5.5 ± 1.0 vs. 3.0 ± 0.5 , $p=0.03$). In conclusion, the level of VDI at remission may be a useful predictive factor of relapse in patients with MPA.

W107-4

Longitudinal efficacy of intravenous cyclophosphamide for vasculitis syndrome

Yusaku Kanetsuka, Tetsuya Horita, Kotaro Otomo, Michihito Kohno, Yuka Shimizu, Takashi Kurita, Toshio Odani, Yuichiro Fujieda, Masaru Kato, Shinji Fukaya, Shinsuke Yasuda, Tatsuya Atsumi, Takao Koike

Department of Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Aim: To evaluate the longitudinal efficacy of IVCY. Method: This study comprised 38 patients treated with IVCY and 13 patients without. The clinical outcome of those patients was evaluated retrospectively. The endpoint was defined by relapse, major complications and death. Results: 49 patients (96%) had clinical remission. The median follow-up period was 19.5 [3-119] months, and the Event Free Survival Analysis showed significant benefits in IVCY (Log Rank test: $p=0.025$). Multi-regression analysis revealed that length between the disease onset and the initiation of IVCY affected relapse ration (COX regression analysis: HR (95%CI)=1.026 (1.003-1.049), $p=0.028$). Conclusion: IVCY contributes to the better longitudinal outcome for patients with vasculitis syndrome.

W107-5

Cardiac manifestations of microscopic polyangiitis

Atsuko Murota, Junko Maruyama, Misato Kawakami, Yasunobu Takizawa, Keigo Setoguchi

Rheumatology Division Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital

Background: Cardiac manifestation in Wegener's granulomatosis is well known, but that in microscopic polyangiitis (MPA) is unclear.

Objective / method: We retrospectively evaluated the frequency, the risk factors and the prognostic factors of cardiac manifestations of 27 MPA patients, who were admitted to our hospital from June 1993 to June 2010 and undergone ECG and transthoracic echocardiogram before treatment.

Result: Abnormalities in ECG were observed in 17 patients. Birmingham Vasculitis Activity Score tended to be higher in LVH, cardiac effusion and RVSP ≥ 40 mmHg, although not statistically sig-

nificant ($p=0.11$). There was no direct relationship between cardiac manifestation and death.

Conclusion: Cardiac manifestation occurs highly in MPA and should be evaluated regularly.

W107-6

Plasma levels of FDP in ANCA-associated vasculitis

Kuninobu Wakabayashi, Kumiko Otsuka, Michihito Sato, Ryo Takahashi, Tsuyoshi Odai, Takeo Isozaki, Nobuyuki Yajima, Yusuke Miwa, Masao Negishi, Hirotsugu Ide, Tsuyoshi Kasama
Division of Rheumatology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

Purpose: We examined plasma levels of FDP in ANCA-associated vasculitis patients. Methods: Plasma levels of FDP were measured in 21 patients with ANCA-associated vasculitis in active and inactive disease states, and the relationships between plasma FDP and serum CRP levels, ESR, MPO- and PR3-ANCA values, BVAS were discussed. Results: A statistically significant positive correlation was observed between plasma FDP levels and serum CRP levels ($rs:0.69$ $p<0.001$), ESR ($rs=0.57$ $p<0.02$), BVAS ($rs:0.65$ $p<0.002$). There is no correlation in plasma FDP levels and MPO- and PR3-ANCA values. Plasma FDP levels decreased significantly after treatment ($p<0.001$). Conclusion: It is suggested that plasma FDP levels may be useful marker of disease activity in ANCA-associated vasculitis.

W108-1

Assessment of disease activity in 314 patients with SLE: A cross-sectional study

Yuko Okamoto, Yasuhiro Katsumata, Yasushi Kawaguchi, Sayumi Baba, Takahisa Gono, Masanori Hanaoka, Masako Hara, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Objective. To assess the disease activity in Japanese patients with SLE.

Methods. A cross-sectional study was conducted on 428 patients with SLE. Participants completed the systemic lupus activity questionnaire (SLAQ) and underwent clinical and laboratory examination to evaluate disease activity.

Results. A total of 314 patients returned the questionnaire. Median duration of disease was 10 years. Median current dose of prednisolone was 10 mg/day. Median SLEDAI and SLAQ score were 2 and 5, respectively. There was no significant correlation among disease duration, current dose of steroids, or SLEDAI.

Conclusion. The large cross-sectional study revealed the disease activity and its characteristics in Japanese patients with SLE. Disease duration and activity were not significantly correlated.

W108-2

Long term efficacy of plasmapheresis therapy for SLE & Lupus Nephritis

Kaoru Sugimoto¹, Ruka Hishinuma¹, Risa Yamada¹, Takuya Nemoto¹, Katsura Houtatsu¹, Keisuke Oda¹, Michiaki Kageyama¹, Toshio Kawamoto¹, Shin Onuma¹, Makio Kusaoi¹, Takayuki Kon¹, Fumio Sekiya¹, Kazuo Kempe¹, Michihiro Ogasawara¹, Ken Yamaji¹, Hiroshi Tsuda², Yoshinari Takasaki¹

¹Department of Rheumatology and Internal Medicine, Juntendo University School of Medicine, Tokyo, Japan, ²Department of Geri-

atric General Medicine, Juntendo Tokyo Koto Geriatric Medical Center, Juntendo Medical School of Medicine, Tokyo, Japan

Plasmapheresis is one of the effective therapies especially for steroid-resistant Systemic Lupus Erythematosus (SLE) and Lupus Nephritis (LN). Nevertheless the long-term efficacy of plasmapheresis for SLE and LN was still unclear. In this study, we analyzed serological data and steroid dosage from 25 SLE cases (containing 12 LN cases) who received plasmapheresis therapy in our hospital for more than 7 years. In the half of LN cases, plasmapheresis was started after the recurrence of LN. The result showed that 10 cases out of 12 LN cases achieved complete response and one case had incomplete response. The complete response rate was more than 80%. We considered that the long-term plasmapheresis for LN is effective to induce a response, and moreover, helpful to maintain good response.

W108-3

Long-term efficacy of treatment of rituximab in patients with refractory SLE

Shigeru Iwata, Kazuyoshi Saito, Mikiko Tokunaga, Kunihiro Yamaoka, Masao Nawata, Yoshiya Tanaka

The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

Twenty patients with refractory SLE were treated with anti-CD20 antibody. We assessed the efficacy of rituximab (RTX) and alteration of surface function molecule on lymphocyte at 4 years. Nineteen female and one male had systemic manifestation including 13 NPSLE, 11 nephritis and 2 AIHA. Four patients were re-tried with RTX and 4 patients were received IV-CY, among 8 relapsed patients. In relapsing patients, CD80+ memory B cells re-appeared, while CD69+ or ICOS+ memory CD4+ T cells was increased. The mean SLEDAI and BILAG score remain fallen significantly at 4 years. The dose of corticosteroid was decreased and all patients had no severe adverse effect. These results imply us that RTX is an excellent therapy for induction and long-term remission in refractory SLE.

W108-4

Impact of absorption profiling on efficacy of CsA therapy in patients with CVD

Hiroki Hayashi¹, Sho Sendo², Daisuke Sugiyama³, Shimpei Kasagi³, Goh Tsuji², Jun Saegusa³, Kunihiro Nishimura³, Seiji Kawano³, Akio Morinobu³, Shunichi Kumagai², Yukio Yuzawa¹

¹Department of Nephrology, Fujita Health University School of Medicine, ²Shinko Hospital, Department of Rheumatic Disease, ³Department of Clinical Pathology and Immunology, Kobe University Graduate School of Medicine

The pharmacokinetics of CsA has rarely been studied in patients with collagen vascular diseases (CVD). In this study, we calculated the area under the blood concentration-time curve (AUC) of CsA microemulsion at once daily, given 15min before breakfast, in 42 patients with CVD, and analyzed its correlation with CsA levels at blood sampling time points to investigate the optimum monitoring and dosing regimen. Adjustments were made to achieve the predefined target AUC: AUC 0-4h: 2000 ng/h/ml. The highest correlation between AUC0-4 and blood level of CsA was observed C1 and C2 at two time points ($AUC0-4=73.47+0.95\times C1+1.92\times C2, R^2=0.98$) and C2 at one time point ($AUC0-4=638.33+2.55\times C2, R^2=0.77$). It is

suggested that preprandial, once daily administration of CsA is beneficial in patients with CVD.

W108-5

New osteonecrosis lesion associated with SLE recurrence

Junichi Nakamura¹, Tomonori Shigemura¹, Yoshitada Harada², Koh Shimizu³, Satoshi Iida⁵, Koya Kamikawa⁷, Munenori Takeshita¹, Masahiko Suzuki⁸

¹Department of Orthopaedic Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan, ²Chibaken Saiseikai Narashino Hospital, Narashino, Japan, ³Chiba Rosai Hospital, Ichihara, Japan, ⁴Chiba Kaihin Municipal Hospital, Chiba, Japan, ⁵Matsudo City Hospital, Matsudo, Japan, ⁶Funabashi Orthopaedic Hospital, Funabashi, Japan, ⁷Teikyo University Chiba Medical Center, Ichihara, Japan, ⁸Chiba University Research Center for Frontier Medical Engineering

Objective: To clarify the incidence of new osteonecrosis associated with SLE recurrence.

Methods: We prospectively studied 291 joints (134 hips and 157 knees) in 106 SLE patients without osteonecrosis after initial corticosteroid therapy, with follow-up period of 14 years and follow-up rate of 71%. SLE recurrence occurred in 131 joints (45%), while SLE was well controlled in 160 joints (55%). Osteonecrosis was evaluated with MRI.

Results: New osteonecrosis developed in 6 joints (2%) only after SLE recurrence. Time from SLE recurrence to of new lesion was 6.2 months.

Conclusion: We suggest that with respect to long-term effects, total cumulative dose and duration of corticosteroid therapy do not contribute to osteonecrosis. However, SLE recurrence is a risk factor for new osteonecrosis.

W108-6

Investigation of actual conditions of limitation at labor in patients with SLE

Mutsuhito Ui^{1,2}, Shoji Sugii¹, Kota Shimada¹, Naoto Yokogawa¹, Katsuaki Shioto¹, Takahiro Nunokawa¹, Yoshiki Nagai¹, Naofumi Chinen¹, Satoshi Watanuki¹, Shinichi Inada¹

¹Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center, Tokyo, Japan, ²Department of Public Health, Juntendo University Graduate School of Medicine, Tokyo, Japan

【Objective】We examined the realities of labor as an index of SLE patient's QOL. **【Methods】**We investigated change of the working hour and the income after the SLE contraction, person who influences for labor form change etc. about 35 SLE patients by using the questionnaire. **【Results】**The reduction of working hours and income were admitted by 13 people of 35. the person who influenced most for the labor form change were the patient was 6, the boss at the office was 5, and the doctor was 2. **【Conclusion】**Working hours and income decreased after SLE contraction, and judgment of the patient or the boss tends to be given to priority more than the doctor. It was suggested that the limitation of labor was admitted by various reasons other than the condition, and patient's QOL have decreased.

W109-1

Antiribosomal P protein antibodies enhance the in vitro IL-17 production of PBMC

Tatsuo Nagai, Satoko Tejima, Toshihiro Tono, Shunsei Hirohata

We have recently disclosed that autoantibodies to ribosomal P proteins (anti-P) enhance the production of TNF- α and IL-6 of activated monocytes and induce Th1 responses by up-regulating their production of IL-12. The current study was undertaken to explore the effects of anti-P on the induction of Th17 responses. IgG anti-P were affinity-purified from sera of anti-P positive lupus patients. Peripheral blood mononuclear cells from healthy donors were cultured with anti-P or control IgG for 5 days. The concentrations of IL-17 in the culture supernatants were measured using ELISA. Anti-P significantly enhanced the production of IL-17 by PBMC. These results indicate that anti-P play an important role in the pathogenesis of SLE through promotion of Th17 responses.

W109-2

Increased concentration of serum soluble LAG3 in systemic lupus erythematosus

Yu Seri, Keishi Fujio, Hirofumi Shoda, Tomohisa Okamura, Akiko Okamoto, Shuji Sumitomo, Mihoko Shibuya, Yukiko Iwasaki, Kazuhiko Yamamoto

Department of Allergy and Rheumatology, Graduate School of Medicine, the University of Tokyo

In SLE, type I interferon and plasmacytoid DCs are supposed to play important roles in SLE. Plasmacytoid DCs are reported to produce soluble LAG3 (sLAG3) upon activation in mice. Therefore, serum sLAG3 concentration was examined in SLE and other autoimmune diseases. The ratio of sLAG3 concentration in RA to control was 0.77 \pm 0.14, PM/DM to control was 1.04 \pm 0.08, and SLE to control was 3.10 \pm 1.05. In addition, sLAG3 concentrations showed a significant correlation with SLEDAI. Interestingly, elevation of sLAG3 was observed in patients with SLEDAI=0. These results suggested that sLAG3 is a specific marker for SLE. The association between elevated sLAG3 and activation of pDCs should be investigated further.

W109-3

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

Shun-ichiro Ota¹, Hiroaki Niiri¹, Siamak Jabbarzadeh Tabrizi¹, Kumiko Noda¹, Naoyasu Ueda¹, Atsushi Tanaka¹, Kentaro To¹, Yasushi Inoue¹, Yojiro Arinobu^{1,2}, Hiroshi Tsukamoto¹, Takahiko Horiuchi¹, Koichi Akashi^{1,2}

¹Department of Clinical Immunology, Rheumatology, and Infectious Diseases, Kyushu University Hospital, Fukuoka, Japan, ²Center for Cellular and Molecular Medicine, Kyushu University Hospital, Fukuoka, Japan

B-cell depletion therapy occasionally leads to exacerbation of autoimmune diseases, suggesting the existence of regulatory B cells (Bregs). In rodents Bregs exert their regulatory function via production of IL-10. In this study we sought to clarify which stimulations are pivotal for Breg induction in normal subjects and SLE patients. Among various stimuli tested, CD40 was the most potent for IL-10 production in normal B cells, while CD40 as well as several cytokines was comparably potent for IL-10 production in SLE patients. We are now testing whether such a difference in IL-10 production is the case with B cell subsets of normal subjects and SLE patients,

and also whether Breg induction in SLE patients is influenced by disease activity.

W109-4

Microalbuminuria in patients with systemic lupus erythematosus

Hidetoshi Kagawa¹, Tsutomu Hiromasa¹, Takayuki Hara¹, Ken-ei Sada², Hirofumi Makino²

¹Department of Internal Medicine, Himeji Red Cross Hospital, Himeji, Japan, ²Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan

We examined the risk factors of CVD in patients with SLE. (1) The levels of microalbuminuria (MA) were higher in patients with SLE, SLE without lupus nephritis (LN), RA, MPA, and SSc than that of HC. (2) Risk factors in 142 SLE patients were as follows: history of CVD: 12.7%, BMI: 21.6, history of smoking: 23.2%, diabetes mellitus: 11.3%, hypertension: 35.2%, dyslipidemia: 32.4%, history of LN: 42.2%, proteinuria (PU): 12.7%, MA: 35.2%, eGFR: 80.4, and APS: 29.6%. The history of CVD was correlated with ages, hypertension, PU, and eGFR. The presence of MA and/or PU was correlated with the number of traditional risk factors, eGFR, and SLEDAI. (3) The levels of MA were decreased than that of 1 year ago. Our results suggest that MA is possibly a modifiable risk factor of CVD in SLE.

W109-5

Prevalence of HBs and HBc antibody and safety of immunosuppressant in SLE

Ryu Watanabe, Kyohei Nakamura, Tsuyoshi Shirai, Yumi Tajima, Hiroshi Fujii, Naruhiko Takasawa, Tomonori Ishii, Hideo Harigae
Tohoku University Graduate School of Medicine, Sendai, Japan

Reactivation of HBV associated with immunosuppressive therapy has been reported in those who are negative for HBsAg and positive for HBsAb and/or HBcAb. To clarify the prevalence of HBsAb and HBcAb and safety of immunosuppressant in SLE, HBsAg, HBsAb, and HBcAb were evaluated in 248 patients. If patients were positive for HBsAb and/or HBcAb, we examined HBV DNA level by real-time PCR. 41 patients (16.5%) were positive for at least one antibody, and mean age of these patients was higher than that of the patients who were negative for both antibodies. 7 and 16 patients were positive for HBsAb and HBcAb, respectively. 18 patients were positive for both antibodies. Among 40 patients whose HBV DNA level was assessed, RT-PCR was positive in 1 case.

W109-6

DNase1 activity in patients with systemic lupus erythematosus (SLE)

Miyuki Miki, Takuji Nakamura, Haruka Iwao, Akio Nakajima, Tomoyuki Sakai, Toshioki Sawaki, Yoshimasa Fujita, Yasufumi Masaki, Toshihiro Fukushima, Hisanori Umehara

Department of Hematology and Immunology Kanazawa Medical University

Introduction: This study examined the following two hypotheses: first, the serum DNase1 activity is correlated with disease activity of SLE patients; second, polymorphism of DNase1 is a hereditary risk factor. **Methods:** Serum DNase1 activity was measured by single radial enzyme-diffusion (SRED) method. DNase1 has polymorphism based on SNP. There are three phenotypes in DNase1,

classified as type 1, 1-2 and 2 by codominance alleles (*DNASE1*1*, *DNASE1*2*). **Result:** We found that the serum DNaseI activity was significantly correlated with SLE disease activity determined by SLEDAI. Concerning DNaseI genetic polymorphism, type2 of DNaseI was significantly increased in SLE patients. **Conclusion:** DNaseI activity is a good marker for disease activity and may be involved in pathogenesis of SLE.

W110-1

The usefulness of biomarkers in knee osteoarthritis in mass cohort study of Japan

Mitsuhiro Morita¹, Harumoto Yamada¹, Hideki Date¹, Noriko Yoshimura², Shigeyuki Muraki², Hiroshi Kawaguchi³, Kozo Nakamura³

¹Department of Orthopaedic Surgery, Fujita Health University, Toyoake, Japan, ²2nd Century Medical and Research Center, University of Tokyo Hospital, Tokyo, Japan, ³Sensory and Motor System Medicine, Faculty of Medicine, University of Tokyo, Postgraduate school of Medicine, Tokyo, Japan

(Objective) The aim of this study is to evaluate the usefulness of some serum or urine biomarkers in OA in the large population cohort study of Japan. (Methods) Totally 1690 peoples (864 peoples at the farmers' area of Miyama-mura and 826 peoples at the fishermen's area of Taiji-cho :Wakayama prefecture) and K-L grade of knee OA. Serum levels of COMP, HA, MMP-3, urinary levels of CTX-I and CTX-II were measured and analysed to evaluate the correlation of knee OA. (Results) Prevalence of knee OA was 44.0 to 45.4%. Serum levels of COMP, HA and urine levels of CTX-II were positively correlated with the clinical stage of knee OA in ANCOVA. There were partially correlation in serum levels of MMP-3, CII and urinary levels of CTX-I, and the radiological severity of knee OA. There was no correlation between COMP or HA and gender. (Discussion) Serum levels of COMP, HA and urinary levels of CTX-II were useful to evaluate the clinical stage of knee OA.

W110-2

The analysis of oxidative stress in the synovial fluid of osteoarthritis

Sanshiro Hashimoto^{1,2}, Kenji Takahashi², Hiroshi Nakamura²

¹Hashimoto Clinic, ²Department of Rheumatology, Nippon Medical School, Tokyo, Japan

Oxidative stress has important roles for cartilage degeneration and cell death. We examined oxidative stress and biological antioxidant stress in the synovial fluid from osteoarthritic knees. Oxidative stress (d-ROM) and biological antioxidant stress (BAP) were measured using FRAS4 (free radical analytical system4, Diacrom, Italy). The samples of synovial fluid were collected from 29 OA patients and 8 simple synovitis which were no abnormality in X-rays and MRI. It was also determined the influence after intra-articular injection of hyaluronan. BAP level was significantly lower in OA synovial fluid than in simple synovitis, and d-ROM level was not significant difference. After hyaluronan injection, BAP level was significantly increased and d-ROM level was decreased.

W110-3

The expression of periostin in tissues derived from osteoarthritis patients

Yasuo Kunugiza¹, Tetsuya Tomita², Masakazu Fujii³, Hiroyuki Nakaya³, Hideki Yoshikawa¹

¹Department of Orthopedic Surgery, Osaka University Graduate School of Medicine, ²Division of Orthopedic biomaterial Science, Osaka University Graduate School of Medicine, ³Department of Orthopedic Surgery, Grathia Hospital

Purpose: Periostin was found as osteoblast specific factor and it is related to bone formation, calcification, cell adhesion, release, and remodeling. We analyzed the expression of periostin in the joint tissue derived from osteoarthritis patients. Method: We extracted the RNA from synovial tissue, bone, osteophyte, bone marrow, and examined the expression of periostin in those tissues. We analyzed the correlation of osteophyte formation and periostin expression in synovial tissue. Results: Strong expression of periostin was observed in synovial tissue and osteophyte. The significant correlation of osteophyte formation and expression of periostin in synovial tissue was observed. Conclusion: There would be relationship between osteophyte formation and expression of periostin.

W110-4

Involvement of synovium-derived ADAMTS-4,5 in the development of osteoarthritis

Taiichi Kosaka, Yasunobu Sawaji, Kengo Yamamoto

Department of Orthopedic Surgery, Tokyo Medical University, Tokyo, Japan

Objective: Roles of ADAMTS-4 and 5 for the development of osteoarthritis (OA) were investigated. **Method:** The synovial fibroblasts were isolated from the synovial tissue after total knee replacement surgery of OA (n=8) and rheumatoid arthritis (RA) (n=3). Confluent cells were stimulated with either interleukin (IL)-1b (10 ng/ml) or tumor necrosis factor (TNF) a (10 ng/ml) for 24 hours in a serum-free condition and the expressions of ADAMTS-4 and -5 and their endogenous inhibitor, TIMP-3, were quantified by real-time-PCR. **Results:** Expression of ADAMTS-4 was higher in cells from the patients who underwent surgery within a year from the complaint of joint pain. **Conclusion:** Synovial cells of patients with comparatively early disease progression may participate in the development of OA.

W110-5

The distribution of subchondral bone marrow lesions in knee osteoarthritis

Daisuke Hamada, Tomohiro Goto, Hiroshi Egawa, Natsuo Yasui

Department of Orthopedics, Tokushima University School of Medicine, Tokushima, Japan

Objective: Bone marrow edema can be detected only on MRI. Although bone marrow edema in rheumatoid arthritis is well known, bone marrow abnormality in knee osteoarthritis (OA) is not well understood. In this paper we report the distribution of the bone marrow lesions in knee OA.

Patients and Methods: Eleven knees in 9 patients who underwent TKA were recruited. Subchondral bone marrow abnormality was evaluated with MRI preoperatively. Bone marrow lesions were defined as poorly marginated high intensity areas on fat-suppressed T2 weighted images.

Results: All knees showed bone marrow abnormalities. These lesions were located especially in medial femorotibial joint and beneath the tibial spine.

Discussion: Bone marrow lesions detected on MRI are suggested to be involved in the pathogenesis of OA.

W110-6

Anatomical study of the patello-femoral joint change in cadavers

Naoyuki Okada

Medical Education Center (Orthopedics), Faculty of Health Sciences
Ryotokuji University

We anatomically observed the patello-femoral joint articular cartilage change in cadavers. The average age was 84.0 years old (67- 103). The degenerative change of articular cartilage was evaluated by International Cartilage Repair Society grade. The articular cartilage change observed 43 knees, and the average age in change of both knees was 86.5 years old. Patella was thin and patella groove depth was shallow in cases having articular cartilage change. The result indicates a relation between patello-femoral structures and that articular cartilage change.

W111-1

Evaluation of diagnostic criteria for Sjögren's syndrome in childhood

Minako Tomiita¹, Kimiyuki Saito², Takayasu Arima¹, Yuzaburo Inoue¹, Yoshinori Morita¹, Taiji Nakano¹, Naoki Shimojo¹, Yoichi Kohno¹

¹Department of Pediatrics, Graduate School of Medicine, Chiba University, ²Sunrise Children's Clinic

Pediatric patients with Sjögren's syndrome (SS) may be thought of as prototype of early stage of SS. However, there were no criteria for early diagnosis of SS. As SICCA criteria have declared, we compared the sensitivity for diagnosis of childhood SS between three criteria: revised Japanese criteria, European-American revised classification criteria, and SICCA criteria. Pediatric patients who has hyper-IgG, or RF or ANA or anti-SS-A antibody or anti-SS-B antibody, and focus score ≥ 1 in labial biopsy specimen or sialography stage ≥ 1 were enrolled. As dry-eye are mild in children, we only evaluated serum examinations and salivary gland damages. The sensitivity of these criteria was 60.7%, 42.9%, 50%, respectively. The new diagnostic criteria for childhood SS are needed.

W111-2

Serum IgG4 and cytokine levels in Juvenile Onset Sjögren's Syndrome

Yoshinori Morita, Minako Tomiita, Taiji Nakano, Yuzaburo Inoue, Takayasu Arima, Kimiyuki Saito, Naoki Shimojo, Yoichi Kohno
Department of Pediatrics, Graduate School of Medicine, Chiba University, Chiba Japan

[Background] Recently, a new clinical entity "IgG4-related disease" comes under the spotlight. Mikulicz disease, which has been considered part of primary Sjögren's syndrome (SS), is now considered to belong to IgG4-related disease. However there is no report about IgG4-related disease in pediatric field.

[Objective] Our object was to assess the relationship between SS patients and IgG4-related disease.

[Material & methods] 21 juvenile onset primary SS patients were included. We analyzed serum IgG4 levels, cytokines.

[Results] There were 2 patients whose IgG4 levels were higher than 135mg/dl. In one case, only low titer of ANA was positive, and anti-SS-A and SS-B antibodies were negative.

[Conclusion] We should check serum IgG4 levels in patients suspected SS in children.

W111-3

Analysis of 15 male patients with primary Sjogren syndrome

Satoshi Hara¹, Kazunori Yamada¹, Shinichiro Tsunoda², Rika Kawamura¹, Yasushi Kakuchi¹, Ryoko Hamano¹, Hiroshi Fujii¹, Masami Matsumura¹, Mitsuhiro Kawano¹

¹Department of Rheumatology, Kanazawa University Hospital, Kanazawa, Japan., ²Department of Internal Medicine, KKR Hokuriku Hospital, Kanazawa, Japan.

Previous reports described the features of primary Sjogren syndrome (pSS) in men, however there has been some controversies due to ethnic differences. Hence we studied the features of Japanese male patients with pSS. We analyzed retrospectively the clinical features, complications and immunological tests of 15 male and 91 female patients with pSS. The prevalence of sarcoidosis was significantly higher in men than in women (male 2/15, female 0/91). However there was no significant difference in the clinical features and immunological tests. There was a difference in the complication between Japanese men and women with pSS, therefore it is important to focus on gender differences in patients with pSS.

W111-4

Pathophysiology of anti-centromere antibody positive primary Sjögren's syndrome

Masahiro Sekiguchi¹, Naoaki Hashimoto¹, Kazuyuki Fujita¹, Mika Okabe¹, Takuya Hino¹, Mai Morimoto¹, Aki Nishioka¹, Ryota Okazaki¹, Naoto Azuma¹, Masayasu Kitano¹, Kiyoshi Matsui¹, Tsuyoshi Iwasaki², Hajime Sano¹

¹Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan, ²Department of Pharmacy, Hyogo university of Health Sciences, Hyogo, Japan

Objective: The purpose of this study is to examine the clinical feature of anti-centromere antibody (ACA) positive primary Sjögren's syndrome (pSS) with using thermography. **Methods:** 19 ACA positive pSS patients, 22 ACA negative pSS patients, and 21 SSc patients were examined cold challenge test using thermography and the involvement of gastrointestinal tract (GI) and lungs diseases. **Results:** The recovery rate of fingers skin temperature of ACA positive pSS patients were similar to that of SSc patients and significantly lower than that of ACA negative pSS patients ($P < 0.05$). However, the involvement rate of lungs and GI tract was higher in SSc patients than that in ACA positive pSS patients. **Conclusion:** Our results indicated that ACA affected to the peripheral circulation disorders.

W111-5

Clinical characteristics of Sjogren's syndrome with anticentromere antibody

Hisako Inoue¹, Yoshifumi Tada¹, Syuichi Koarada¹, Rie Suematsu¹, Sachiko Soejima¹, Akihide Ohta², Kohei Nagasawa¹

¹Department of Internal Medicine, Saga Medical School, Saga, Japan, ²Department of Clinical Nursing, Saga Medical School, Saga, Japan

Objective: To examine clinical characteristics of primary Sjogren's syndrome with anticentromere antibody (ACA) in 23 patients. **Results:** There were 22 female and a male patients aged from 43 to 75 years old. Thirteen patients had ACA alone and 10 patients had both ACA and anti-SSA/Ro antibody. All patients had sicca syndrome. Raynaud's phenomenon (RP) was seen in 20 patients. Sicca syndrome and RP developed independently of the presence of anti-SSA/Ro antibody. Of interest, the prevalence of rheumatoid

factor, leukocytopenia and hypergammaglobulinemia was lower in patients with ACA alone. Conclusion: Our data suggests that there is an intermediate group between Sjogren's syndrome and Systemic sclerosis (SSc). That group doesn't show tendency to evolve SSc.

W111-6

Treatment of pulmonary artery hypertension associated with primary SS.

Kyohei Nakamura, Tomonori Ishii, Yumi Tajima, Tsuyoshi Shirai, Ryu Watanabe, Hiroshi Fujii, Naruhiko Takasawa, Hideo Harigae
Department of Hematology and Rheumatology, Tohoku Graduate School of Medicine, Sendai, Japan

Immunosuppressive therapy is often effective in connective tissue diseases-associated pulmonary artery hypertension (PAH). In primary Sjogren syndrome (SS), however, PAH is reported only sporadically, and therapeutic strategy is yet to be established. We analyzed the efficacy of immunosuppressive therapy in three SS-PAH cases. Five episodes of PAH exacerbation were observed in three cases, although disease activity remained stable in four episodes. Prednisolone was administered in all episodes in addition to immunosuppressive drug; intravenous cyclophosphamide in four episodes and azathioprine in one episode. Immunosuppressive therapy improved symptoms and reduced pulmonary vascular resistance in all episodes, and it should be considered in SS-PAH regardless of the disease activity of SS.

W112-1

A crucial role of M3R reactive T cells in Sjögren's syndrome like sialadenitis

Mana Iizuka¹, Hiroto Tsuboi¹, Yumi Nakamura^{1,2}, Naomi Matsuo¹, Isao Matsumoto¹, Takayuki Sumida¹

¹Division of Clinical Immunology, Major of Clinical Science, Graduated School of Comprehensive Human Science, University of Tsukuba, ²Japan Society for the Promotion of Science

OBJECTIVE To clarify the pathological role of M3R reactive T cells in SS like autoimmune sialadenitis. **METHODS** 1) M3R^{-/-} and IFN- γ ^{-/-}/M3R^{-/-} mice were immunized with M3R peptides and their splenocytes were transferred to Rag1^{-/-} mice (M3R^{-/-}→Rag1^{-/-} and IFN- γ ^{-/-}/M3R^{-/-}→Rag1^{-/-}). 2) CD3⁺ cells from M3R immunized M3R^{-/-} mice were transferred to Rag1^{-/-} (M3R^{-/-}/CD3⁺→Rag1^{-/-}). **RESULTS** 1) In M3R^{-/-}→Rag1^{-/-}, CD4⁺ T cells infiltrated into salivary glands. IL17 and IFN γ were highly produced in splenocytes and salivary glands. In IFN- γ ^{-/-}/M3R^{-/-}→Rag1^{-/-}, the sialadenitis was reduced compared with M3R^{-/-}→Rag1^{-/-}. 2) The sialadenitis was also observed in M3R^{-/-}/CD3⁺→Rag1^{-/-}. **Conclusion** M3R reactive T cells should play a crucial role in the generation of autoimmune sialadenitis such as SS.

W112-2

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

Naomi Matsuo¹, Hiroto Tsuboi¹, Mana Iizuka¹, Yumi Nakamura^{1,2}, Isao Matsumoto¹, Takayuki Sumida¹

¹Division of Clinical Immunology, Doctoral Programs in Clinical Sciences, Graduate School of Comprehensive Human Science, University of Tsukuba, Tsukuba, Japan, ²Research Fellow of the Japan Society for the Promotion of Science, Tokyo, Japan

Purpose: To clarify the epitope of M3R reactive T cells in M3R induced autoimmune sialadenitis (MIS).

Methods: 1) Splenocytes of M3R^{-/-} mice immunized with M3R peptides mixture (N-terminal, 1st, 2nd, 3rd extracellular loops) were cultured with each M3R peptide. The cytokine production was 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 Rag1^{-/-} mice. After transfer, saliva flow and anti-M3R antibodies were measured and salivary glands were histologically examined.

Results: 1) IL-17 and IFN- γ against 1st loop were produced higher than the other domains of M3R. 2) Under examination.

Conclusion: We concluded that one of T cell epitopes in MIS might be 1st loop of M3R.

W112-3

Autoimmunity to REG in patients with primary Sjögren's syndrome

Kiyomi Yoshimoto^{1,2,3}, Takashi Fujimoto³

¹Department of Biochemistry, Nara Medical University, ²Sonil village national health insurance clinic, ³Department of General Medicine, Nara Medical University, ⁴Department of Diagnostic Pathology, Nara Medical University

The regenerating gene product (REG) acts as an autocrine/paracrine growth factor for regeneration of many tissues including pancreatic beta-cells. We have recently found a correlation between anti-REG autoantibodies (a-REG) and saliva secretion in primary Sjögren's syndrome (pSS) patients. In the present study, we analyzed REG expression in the minor salivary gland (MSG) by immunohistochemistry. Of 54 SS patients, 11 patients (20%) tested positive for a-REG, and 29 patients (54%) over-expressed REG protein in ductal epithelial cells. All the 11 samples showed REG expression in a-REG positive group whereas only 42% showed REG expression in a-REG negative group (P=0.00056). These results suggest that autoimmunity to REG is associated with the tissue injury of MSG in at least some pSS patients.

W112-4

Histopathological analysis in Lptm5 transgenic mouse as dry mouth model

Masako Inagaki¹, Noboru Kitamura², Takamasa Nozaki², Hidetaka Shiraiwa², Masaaki Shiozaki², Hirotake Inomata², Hiromi Karasawa², Natsumi Ikumi², Yoshikazu Kuwana², Shigemasa Sawada², Masami Takei²

¹Resident Center, Nihon University School of Medicine, Tokyo, Japan, ²Division of Hematology and Rheumatology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan

The Lptm5 is highly expressed on the salivary glands of the two model mice, and patients with Sjögren's syndrome. We compare the extra-salivary gland (ESG) tissues of the transgenic mouse induced Lptm5 (Lptm5 TGM) with those of the wild mouse (WdM). We hybridized Lptm5 TGM and use the first passage number TGM. The TGM are fixed with 10% formaldehyde and made as tissue section, compared with the WdM. On both of the ESG (lung tissues) and salivary gland, lymphocytes infiltrate bronchial epithelial cells focally and there is not a significant difference pathologically between the TGM and the WdM in ESG. Salivary secretions of Lptm5 TGM are decreasing in compared with WdM and the TGM is not tissue-destructive in both salivary glands and ESG. We need to investigate the influences of the Lptm5.

W112-5

Regulatory mechanism of TLR3-mediated cell death in primary Sjögren's syndrome

Hideki Nakamura, Akitomo Okada, Takahisa Suzuki, Mami Tamai, Satoshi Yamasaki, Atsushi Kawakami

Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences

Objective: To investigate regulatory mechanism for toll-like receptor (TLR)3-mediated apoptosis of salivary glands epithelial cells (SGECs) in primary Sjögren's syndrome (pSS). **Methods:** Poly IC induced apoptosis was determined by Hoechst and TUNEL staining. Expression of TLR3 and pAkt was examined by IF or WB. **Results:** Expression of TLR2/3 with pAkt was observed in the stimulation with PGN and poly IC. Poly IC stimulation induced nuclear fragmentation in pSS and control ($p < 0.01$). Co-expression of TLR3 and pAkt accorded with nuclear fragmentation, which was confirmed as apoptosis by TUNEL staining. TUNEL positivity and caspase-3 cleavage were significantly inhibited by PI3K inhibitor. **Conclusion:** Innate immunity-mediated mechanism for SGEC damage was elucidated and further study is in progress.

W112-6

Diagnostic Value of Salivary β_2 Microglobulin and Na^+ Levels in Sjögren Syndrome

Hiromitsu Asashima, Shigeko Inokuma, Shinichiro Nakachi, Yoshimi Matsuo, Ryo Rokutanda, Kiyofumi Hagiwara, Shoko Kobayashi

Department of Allergy and Rheumatology, Japanese Red Cross Medical Center, Tokyo, Japan

Objectives. To find the cutoff levels of salivary β_2 microglobulin (β_2 MG) and Na^+ differentiating Sjögren Syndrome (SjS).

Methods. Salivary β_2 MG and Na^+ levels were measured in 98 SjS patients (55.9 \pm 14.2 years old) and 122 controls (60.8 \pm 15.6). Area under the receiver-operating characteristic (ROC) curve (AUC) was employed to evaluate the diagnostic value of salivary β_2 microglobulin and Na^+ levels.

Results. When setting the cutoff value for β_2 MG level at 2.3mg/L, the specificity of 81% and the sensitivity of 79% were obtained; for Na^+ level, the cutoff level of 23mEq/L resulted in those of 91% to 68%, respectively. ROC curves for both of β_2 MG and Na^+ levels showed the good performer (AUC=0.87).

Conclusion. Salivary β_2 MG and Na^+ levels could show high diagnostic accuracies for SjS.

W113-1

Clinical characteristics of collagen disease patients with CMV antigenemia

Hidetake Nagahara, Masataka Kohno, Amane Nakabayashi, Takashi Kida, Wataru Fujii, Ken Murakami, Kaoru Nakamura, Takahiro Seno, Aihiro Yamamoto, Hidetaka Ishino, Yutaka Kawahito
Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine

To clarify the clinical characteristics of collagen disease patients with cytomegalovirus (CMV) antigenemia, we evaluated 52 inpatients of our hospital, who were suspected of CMV infection and tested on C7HRP assay. We classified the patients by the number of C7HRP-positive cells (Group A: C7HRP \geq 5/100000, n=11; Group B: C7HRP<5/100000, n=41). The dose of oral prednisolone when

C7HRP was measured was 0.84mg/kg of body weight (A) vs. 0.37 (B), lymphocyte count was 844/ml (A) vs. 1240 (B), and IgG count was 1083mg/dl (A) vs. 1458 (B). Nine of 11 patients in group A (82%) had been treated with pulsed methylprednisolone before C7HRP was tested, 3 of 41 in group B (7.3%). Immunosuppression by high dose of steroids, especially by pulsed therapy, may be a risk factor of CMV antigenemia.

W113-2

Cytomegalovirus (CMV) enterocolitis associated with anti-TNF treatment

Yuichi Izumi, Hideki Ito, Ryuta Endo, Ayako Hirata, Takehisa Ogura, Takehiko Ogawa

Division of Rheumatology, Toho University Ohashi Medical Center

OBJECTIVE: We reported previously CMV enterocolitis in patients receiving anti-TNF agents. To determine the predictors of CMV infections and the extent to which specific anti-TNF treatments increase CMV infection risk.

METHODS: Data from 4 patients with CMV enterocolitis and from 30 patients without CMV infection receiving anti-TNF therapy were reviewed retrospectively.

RESULTS: Four patients with CMV infection included 2 RA, one adult-onset Still's disease and one Behcet disease. Infliximab use was significantly more common in patients with CMV enterocolitis than those without CMV infection. Prednisolone use modestly increased the risk of CMV infection. No increase in risk was found for decreased lymphocytes, lower serum protein levels or lower serum IgG levels.

W113-3

Cytomegalovirus infection in patients with connective tissue diseases

Kazuyoshi Ishigaki¹, Noboru Hagino¹, Yasunobu Takizawa², Junko Maruyama², Atsuko Murota², Keigo Setoguchi²

¹Department of Allergy and Rheumatology, Graduate School of Medicine, the University of Tokyo, ²Department of Allergy and Immunological Diseases, Tokyo Metropolitan Komagome Hospital

To elucidate the feature of cytomegalovirus (CMV) infection complicated in cases with connective tissue diseases (CTDs), we reviewed the medical records from Tokyo Metropolitan Komagome Hospital and the University of Tokyo Hospital. We detected 4 cases of definite CMV infection with pathological evidences and 9 cases of probable CMV infection from 2006 to 2010. Out of 13 cases, 10 cases had gastrointestinal infection and 4 cases had infection in the same organ as that impaired by the underlying CTDs. Six patients had vasculitis, 4 patients had SLE and 3 patients had others as primary CTDs. These data suggest the importance of suspecting CMV infection when we encounter cases with unexplained colitis or refractory exacerbations of underlying CTDs, especially cases with vasculitis and SLE.

W113-4

Examination of clinical utility of Procalcitonin in this hospital

Motokazu Kai, Shigenori Tamaki

National Hospital Organization Mie Chuo Medical Center

Procalcitonin (PCT) is generated as a precursor protein of the calcitonin in C cell of the thyroid. It becomes an insurance adjustment in 2006, and clinical is applied. Uniqueness is high compared with the infectious disease, especially the bacteremia, and it is useful

for differential diagnosis of heat patient and the severity of symptoms judgment of the sepsis. The heat patient such as the infectious disease, the collagen diseases, and FUO has been inspected in the this hospital since 2008, and the number of accumulations is 146 cases, and 160 counts. When the case diagnosed as the bacteremia in an actual clinical diagnosis was identified to non-bacteremia or the cutoff value was assumed to be 0.4ng/ml with serum PCT, it was sensitivity 45%, and the specificity 95%.

W113-5

Usefulness of Procalcitonin for patients with connective tissue diseases (CTD)

Shinya Hagiwara, Hiroto Tsuboi, Tomoya Hirota, Hiroshi Ogishima, Yuya Kondo, Masanobu Horikoshi, Naoto Umeda, Yusuke Chino, Makoto Sugihara, Takeshi Suzuki, Taichi Hayashi, Isao Matsumoto, Takayuki Sumida

Division of Clinical Immunology, Doctoral Program in Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba

<Objective> To clarify usefulness of Procalcitonin (PCT) for patients with CTD in differential diagnosis for fever. <Methods> 65 patients with CTD, who were admitted because of fever and were examined in PCT and blood culture from Dec 2009 to Sep 2010, were enrolled in this study. We analyzed CTD, PCT, blood culture, and final clinical diagnosis for fever. <Results> CTD: SLE 16, RA 12, MPA 7, PN 3, DM 3, AOSD 3, MRA 2, WG 2, BD 2, overlap 8, and the others 7 cases. PCT: positive (+) 25/negative (-) 40 cases. Blood culture: + 8/- 57 cases. Final clinical diagnosis was infection in 45 patients. The sensitivity of PCT for infection was 51.1%, and the specificity was 90.0%. <Conclusion> These results indicated PCT might be prospective marker for infection in CTD patients.

W114-1

Risk factor of infection in elderly patients with connective tissue disorders

Waka Yokoyama, Naoshi Kanda, Takahiko Sugihara
Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan

(Purpose) To establish scoring system to predict infections in elderly patients during an immunosuppressive therapy. (Method) 63 elderly patients with a mean age of 76 years who received more than 0.5mg/kg of PSL were retrospectively analyzed. (Result) 24 patients experienced infections within 3 months after the treatment. Scoring of risk factors was established with age, BMI, ALB, Basic activity of daily living score, past history of infections or lung disease and aspiration disorder. The scores, but not the doses of PSL were significantly higher in patients with infections than those without infections. Treatment of PSL \geq 0.5mg/kg significantly increased frequency of infections in high risk group compared to low risk group. (Conclusion) This scoring system could well predict infections.

W114-2

Infections in the patients with connective tissue disease

Tepei Kamikawa¹, Yuichi Handa¹, Teruchika Yamada²

¹Saitama Red Cross Hospital, Saitama, Japan, ²Oomiya Clinic

OBJECTIVE: To evaluate the clinical features of infections in patient of connective tissue disease. METHOD: We conducted a retrospective, clinical evaluation of 94 hospitalized patients who had developed infections from 2003 to 2009. RESULTS: The mean age 63, female 62 cases, 32 cases of men, RA is 52 cases, SLE is 16,

polymyositis (PM) / dermatomyositis (DM) is 9. 83 cases received corticosteroid, 51 cases received immunosuppressive agents, 16 cases received biologics agent. The most common sites are lung, kidney, intestines, pelvis, skin, and systemic infections. The 78 patients recovered, 11 patient died. 10 patients died from pneumonia. CONCLUSION: We need keeping in mind the risk of developing respiratory infections when following patients with connective tissue disease.

W114-3

Effect of H1N1pdm influenza vaccine on the patients with rheumatoid arthritis

Tomomi Tsuru¹, Midori Suzuki¹, Yumi Kobayashi¹, Misato Nakagawa¹, Hitoshi Nakashima², Inoue Yasushi¹

¹Med.Co.LTA PS Clinic, ²Fukuoka University Hospital

We studied about immunogenicity of H1N1pdm influenza vaccine on the patients with rheumatoid arthritis. Object and method: 59 patients treated with conventional DMARDs therapy, 27 patients treated with infliximab, 18 patients treated with etanercept, and 22 patients treated with tocilizumab were enrolled in this study. A split-virion H1N1pdm influenza vaccine was administered subcutaneously to all patients in September to October of 2009. Vaccine was administered twice. The interval was 3 weeks. Antibody titer for H1N1pdm influenza were measured before vaccination, before second vaccination and 4 weeks after second vaccination. Result: Effect of the vaccination were less in aged group and Infliximab group, other parameters were not affected to the immune response to vaccination.

W114-4

Retrospective study of HBV infection in autoimmune disease in Tohoku area

Tomonori Ishii¹, Hiroko Kobayashi², Yukitomo Urata³, Hiromasa Ohira², Hideo Harigae¹, Takeshi Sasaki⁴

¹Department of Rheumatology and Hematology, Tohoku University School of Medicine, Sendai, Miyagi, Japan, ²Department of Gastroenterology and Rheumatology Fukushima Medical University School of Medicine, Fukushima, Fukushima, Japan, ³Department of Rheumatology, Seihoku Central Hospital, Goshogawara, Japan, ⁴Department of Rheumatology, Tohoku Medical Center NTT EC

HBV reactivation in autoimmune disease has drawn attention. HBIRTH has initiated retrospective and prospective studies to examine the actual HBV infection status in patients (pts) on immunosuppressant therapy. [Methods] HBs antigen, HBs antibody and HBc antibody positivity rates, number of pts with HBV reactivation, and number of pts with de novo hepatitis were retrospectively reviewed. [Results] Number of responses (facilities) was 68 (collection rate, 20.73%); number of RA pts, 7031 (including 1337 pts given biologics); and number of SLE pts, 795. HBs antigen, HBs antibody and HBc antibody positivity rates in RA pts (on biologics) were 1.09% (0.2%); 18.3% (12.8%), and 25.8% (26.6%), respectively; corresponding rates in SLE pts were 0.2%, 12.8% and 26.6%.

W114-5

HBV reactivation in the immunosuppressed patients with rheumatic diseases

Toshihide Mimura¹, Kazuhiko Yamamoto², Yoshihisa Nojima³, Keiju Hiromura³, Nobuyuki Miyasaka⁴, Shunichi Shiozawa⁵, Akira Hashiramoto⁵, Tsuneyo Mimori⁶, Naoichiro Yukawa⁶, Masataka

Kuwana⁷, Takayuki Sumida⁸, Taichi Hayashi⁸, Tomoki Origuchi⁹, Takao Koike¹⁰, Yuji Akiyama¹, Satoru Mochida¹
¹Saitama Medical University, Saitama, Japan, ²University of Tokyo, Tokyo, Japan, ³Gunma University, Gunma, Japan, ⁴Tokyo Medical and Dental University, Tokyo, Japan, ⁵Kobe University, Hyogo, Japan, ⁶Kyoto University, Kyoto, Japan, ⁷Keio University, Tokyo, Japan, ⁸University of Tsukuba, Ibaraki, Japan, ⁹Nagasaki University, Nagasaki, Japan, ¹⁰Hokkaido University, Hokkaido, Japan

Reactivation of hepatitis B virus (HBV) has been seen in the patients receiving immunosuppressants, glucocorticoids, anti-cancer drugs or anti-rheumatic biologics. We have organized this prospective study to evaluate HBV reactivation in the rheumatic patients by support of the Ministry of Health, Labor and Welfare of Japan. Enrolled in this study were the patients positive in HBsAg, HBsAb or HBcAb under informed consent. Blood samples from the patients were analyzed for HBV DNA every month after initiation of the immunosuppression. Prophylactic anti-HBV was administered for HBV DNA-positive patients. In 52 patients, three were HBV-carriers and HBV reactivation was detected in 2 patients. HBV reactivation may be observed in patients with rheumatic diseases receiving immunosuppression.

W114-6

Introduction of biologics to patients with rheumatoid arthritis of HBV carrier.

Tetsuo Takanashi¹, Masayuki Matsuda², Hideshi Yamazaki¹, Yukio Nakatsuchi³

¹Center for Rheumatic Diseases, Houseikai Marunouchi Hospital, Nagano, Japan, ²Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, Nagano, Japan, ³Department of Orthopaedic Surgery, Houseikai Marunouchi Hospital, Nagano, Japan

Though the therapeutic gain of biologics to rheumatoid arthritis (RA) is high, there is the risk of HBV reactivation, or de novo hepatitis. As for de novo hepatitis, the rate of fulminant hepatitis and the fatality rate both are high. Therefore it is necessary to screen the serological profile of HBV infection before introduction of biologics. And then the patients should be closely monitored not to miss the clinical and laboratory signs and symptoms of active HBV infection during the therapy. We have four cases administered Etanercept with Entecavir. Their RA activity have been good controlled, and the signs of HBV reactivation have not been found. It is necessary to make the guideline to administer not only biologics but also other immunosuppressants for RA patients with HBV.

W115-1

Analysis of rheumatoid arthritis operation receiving biologic agent treatment

Kensuke Koyama, Michitomo Sakuma, Yoshihiro Takayama, Hirotaka Haro
 Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi

We investigated patients with rheumatoid arthritis used of biologic agents operated from August, 2007 to September, 2010. Twenty one RA patients were treated with various biologic agents (INF 9, ETN 11 and TCZ 1). Discontinuation of biologic agents, surgical site infection and delay of wound healing were surveyed. INF was discontinued 29.4 days before and was resumed 27.2 days after the day of operation, and ETN was discontinued 13 days before and was

resumed 15.7 days after the day of operation. Surgical site infection was not seen. Two cases had experience of late wound healing, and one INF case had an acute exacerbation of rheumatoid arthritis. Prevention of surgical site infection is most important in patients with RA treated with biological agents.

W115-2

Operation of rheumatoid arthritis analyze in saitama medical university

Hiroyuki Yoshioka, Hiromi Oda, Yoon Taek Kim, Shinya Tanaka, Hirohito Tanaka
 Saitama Medical University, Department of Orthopaedic surgery, Saitama, Japan

(purpose)Biological medicine make change treatment of rheumatoid arthritis.Operation of make frequent use of biological medicine is increasing.It was for that purpose that we analyze operation of rheumatoid arthritis in saitamamedical university, (method)Operation of rheumatoid arthritis in saitama medical university analyze between2007 and2009,cases 196.196cases divide used of biological medicine and not biological medicine. (result)Used of biological medicine is 61 cases whole 30%.The last few years is no change.But use of biological medicine 4cases recognized after operation wound infection.No use of biological medicine does not recognized wound infection. (conclusion)It is possible that operation of use of biological medicine is after operation wound infection.

W115-3

Joint surgeries for RA with biologics and non-biologics

Yoichi Toyoshima, Hajime Ishikawa, Akira Murasawa, Kiyoshi Nakazono, Asami Abe, Hiroshi Otani, Satoshi Ito, Hiroe Sato
 Niigata Rheumatic Center

To compare the outcome of joint surgeries in RA patients with biologics and that without biologics. Patients who underwent joint surgery (TEA:2, TKA:11, knee joint synovectomy:2, and ankle arthrodesis:4) between 2005 and 2010 were matched for age, gender, and disease duration, and classified into two groups of 20 patients, either with biologics or not. They were evaluated regarding DAS28, the oral PSL dose, mHAQ, VAS-GH, and infection. The follow-up period was 6 mos. DAS28 improved significantly in both groups. Postoperative mHAQ and VAS-GH improved significantly in the biologics group. No patients in either group showed infection and delayed wound healing. Surgery was performed safely.

W115-4

Surgical Procedures to Rheumatoid Arthritis under the Biologics Treatment

Hiroshi Jojima¹, Akira Maeyama², Tomoko Nagano², Hitoshi Nakashima³, Katsuhisa Miyake³, Masatoshi Naito², Yozo Shibata³
¹Department of Orthopaedic Surgery, Chikushi Hospital, Fukuoka University, ²Department of Orthopaedic Surgery, School of Medicine, Fukuoka University, ³Division of Nephrology and Rheumatology, Department of Internal Medicine, School of Medicine, Fukuoka University

【Introduction】Biologic agents (Bio) plays an important role in the treatment of rheumatoid arthritis (RA). However, a few arthritis sometime exist even under the treatment. Clinical results of joint surgery to the arthritis under the Bio were reported. 【Cases】In RA patients treated with Bio, 11 synovectomies and 6 joint reconstructions were performed. In the synovectomy group, 9 cases were set-

tled, one recurrence and an exacerbation case after the operation were observed. In the joint reconstruction group (2 THA and 4 TKA), no postoperative infections were observed. **【Discussion】**A synovectomy were performed to remaining arthritis under the treatment. Joint reconstructions were safely done during discontinuation period. Both procedures are very safe and effective under the Bio treatment.

W115-5

Arthroscopic synovectomy for rheumatoid patients with anti-TNF blockade

Yukio Shigeyama, Masaaki Usui, Keiya Yamana

Department of Orthopaedic Surgery, Okayama City Hospital, Okayama, Japan

We performed arthroscopic synovectomy of three knees and one shoulder in four rheumatoid patients who had been having anti-TNF therapy. After several times of administration of anti-TNF blocker, they still had a swollen and tender joint. We observed hypertrophic synovial tissues in the all four joints and excised these tissues arthroscopically. After arthroscopic synovectomy, anti-TNF therapy was continued. Joint function was preserved well, and there was no swelling and no tenderness in the treated joints in four RA patients. We did not see any radiological progression in Larsen grade. Arthroscopic synovectomy might be a useful treatment for swollen and tender joints in rheumatoid patients who had been having anti-TNF therapy, to preserve the joint function in the joints.

W115-6

Analysis of perioperative condition of RA in treatment with biologic agents

Masao Sato¹, Ryuki Shinohe², Katsuji Shimizu¹

¹Department of Orthopaedic Surgery, Gifu University Graduate School of Medicine, Gifu, Japan, ²Department of Orthopaedic Surgery, Nishimino Welfare Hospital, Gifu, Japan

It is said that joint surgeries in RA patients treated with biologic agents have demonstrated no increase in the incidence of perioperative adverse events. But besides orthopaedic surgeries, it is not clear whether there might be another complications on surgeries underwent in the course of biologics therapy. We analyzed 11 RA patients who underwent non-orthopaedic surgeries in the course of biologics therapy. The causes of operations included gastric cancer, lung cancer, renal cancer, colon cancer, cerebral aneurysm, hemorrhoid, tonsillitis, ileus and rectovesical fistula. A case of ileus died because of peritonitis after the operation. Further investigations might be needed to establish the safety on perioperative treatment in terms of non-orthopaedic surgeries.

W116-1

Clinical results of Surgeries in RA Patients treated with (Etanercept)

Toshiharu Okuda

Okuda Orthopedic Clinic

Thirty-nine surgeries were performed on 21 RA patients. Surgical treatment were including 19 arthroplasty of fingers, 7 synovectomy of the wrist, 4 endoscopic synovectomy of the knee, 10 synovectomy in the elbow, 6 arthroplasty of the toes and 1 TAA. In 3 of the patients using Etanercept the RA flared up again while the drug was discontinued, but improved after readministration of the preparation.

Complications like postsurgical infections or poor wound healing

were not observed. Local swelling or pain remained in some synovectomy patients, but the arthritis was alleviated in all cases and RA activity improved. The RA was well controlled, while in patients who underwent reconstructive surgery for deformity and disorder of fingers and toes, appearance and function improved.

W116-2

Examination of surgery in RA patients undergoing treatment with Abatacept.

Masamichi Tahara¹, Ryutaro Matsumura²

¹Department of Orthopaedic Surgery, National Hospital Organization Chiba-East Hospital, Chiba, Japan, ²Division of Rheumatology, Allergy and Nephrology, Clinical Research Center, National Hospital Organization Chiba-East Hospital, Chiba, Japan

Aim: We examined administration methods for rheumatoid arthritis patients using Abatacept during perioperative period.

Patients and Methods: 3 RA patients undergoing treatment with Abatacept were recruited. They were two men and one woman. The mean age of the patients was 59.7 years. The RA patients underwent surgical treatments such as total knee arthroplasty and Darrach procedure. We examined the administration methods of Abatacept for these patients during perioperative period.

Results: In this study, serious complications of wound healing and surgical site infection were not observed. Flare up of RA activities did not experience during 8 weeks of the drug discontinuation period.

Conclusions: RA patients treated with Abatacept can be received operations safely under proper management.

W116-3

Perioperative infection and flare-up in RA patients with etanercept therapy.

Ryuichi Nakahara

department of Orthopaedic Surgery, Okayama University Medical School, Okayama, Japan

Objective: To investigate the incidence of the infection and delayed wound healing after orthopaedic surgery in patients with rheumatoid arthritis (RA) who were receiving etanercept (ETN). **Method:** Surgical procedures were recorded in 51 patients with RA (50 woman), with mean age of 51.5 years, mean disease duration of 16.8 years. The mean discontinuation period of ETN before surgery was 10.1 days. **Results:** No infectious and healing complications were recorded. Flare-up of the disease was found in three patients after more than 12 days' discontinuation of ETN before surgery. All flare up was developed more than three weeks after discontinuation of ETN. **Conclusion:** Our data may suggest useful information for discontinuation period of ETN before surgery.

W116-4

Risk factors for forefoot surgery in rheumatoid arthritis

Koichiro Yano, Katsunori Ikari, Atsuo Taniguchi, Hisashi Yamanaka, Shigeki Momohara

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

The risk factors for forefoot surgery were assessed in a cohort of RA patients recruited and followed prospectively for 9 years. Baseline routine clinical and laboratory assessments were recorded. The data were analyzed using the multivariate Cox regression model that included potential risk factors for forefoot surgery such as gender,

age, disease duration, BMI, VAS generated by physicians, a patient-reported VAS for pain, DAS28, J-HAQ, RF, CRP and past history of surgery. Of the 9,150 patients registered at baseline, 187 (2.04%) had surgery on one or both forefoot joints. The variables with positive coefficients were gender, long RA duration, J-HAQ, RF positive and past history of surgery.

W116-5

Wound healing and perioperative complications of forefoot operation for RA

Koichi Okamura¹, Yukio Yonemoto¹, Takeo Sakurai², Tsuyoshi Ichinose^{1,2}, Yasuyuki Tamura², Yoshihiro Yamashina², Kimihiko Takeuchi^{1,4}, Tsutomu Kobayashi¹, Takenobu Iso³, Hiroshi Inoue^{2,3}, Kenji Takagishi¹

¹Department of Orthopaedic Surgery, Gunma University Graduate School of Medicine, Maebashi, Japan, ²Inoue Hospital, Takasaki, Gunma, Japan, ³Gunma RA clinic, ⁴Department of Orthopaedic Surgery, Isesaki Fukushima Hospital, Isesaki, Gunma, Japan

We studied wound healing and perioperative complications of forefoot operations for rheumatoid arthritis. 84 patients (7 men and 77 women, the average age: 63.3) who had forefoot operations in our hospitals from April /2005 to November/2010, were investigated. 35 patients had bilateral foot operations. The biological products, anti-TNF drugs, were administered to 17 patients (IFX=7, ETN=9, Ada=1). The average days necessary for wound healing of patient who were undergoing anti-TNF therapies were not significantly different from others. Much more perioperative complication had not occurred after anti-TNF therapies. We considered that biological treatment might not increase the risk of forefoot operations.

W116-6

About the influence over the perioperative trouble of the biological agent

Kouhei Kamito¹, Chikara Miyamoto¹, Makoto Osaki¹, Toshiyuki Tsurumoto², Tomoko Matsumoto³, Hiroyuki Shindo¹

¹Department of Orthopaedics, Nagasaki University, ²Department of Anatomy, Nagasaki University School of Medical, ³Ajisai clinic

"First" It reviewed the example which was experienced in this department to original about whether or not the difference occurred to the perioperative trouble with the use or not use the biological agent. "Object" The patient 70 example which is diagnosed as being the arthrorheumatism (RA) which operated in our hospital. The example which was using biological agent was 18 pieces. As the evaluation, we choice The healing of wound, surface infection, depth infection, other complications, period from beginning biological agent, drug withdrawal period, period from RA. "Result" The occurrence example of the perioperative trouble was 4 pieces of example in use example of the biological agent, and 8 pieces of example in the non-use example. It decides to review in the future.

W117-1

Differentiation of systemic-JIA from other autoinflammatory diseases.

Yuichi Yamasaki, Tomohiro Kubota, Yukiko Nonaka, Harumi Akaike, Yasuhito Nerome, Tomoko Takezaki, Hiroyuki Imanaka, Suyji Takei

Kagoshima university hospital pediatrics, Kagoshima, Japan

s-JIA comes to be regarded as autoinflammatory disease, recently. On the other hand, there are a lot of examples that the other au-

toinflammatory diseases such as FMF and EOS were initially diagnosed as s-JIA due to the clinical similarity. Serum S100A12 and VEGF levels of sJIA (12 cases /82 specimens) patients were compared with genetically diagnosed patients with FMF (1c/8s) and EOS (5c/14s). In CRP \geq 1mg/dl, there were significant increase in S100A12 in both patients with FMF and sJIA than that with EOS. Serum VEGF levels of sJIA patients significantly differ from that of patients with FMF and EOS. In CRP<1mg/dl, high levels of S100A12 was observed only in FMF. S100A12 and VEGF may be useful in differentiation of sJIA patients from FMF and EOS.

W117-2

The role of heme oxygenase-1 in s-JIA-associated macrophage activation syndrome

Masaki Shimizu, Tadafumi Yokoyama

Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University

We evaluated the role of heme oxygenase-1 (HO-1) in s-JIA associated MAS. Serum concentrations of HO-1 and cytokines (IL-18, IL-6, sTNFRI,II, neopterin) from patients with s-JIA, EBVHLH and Kawasaki disease were analyzed by ELISA. Serum concentrations of HO-1 in MAS/s-JIA were significantly higher than those in other diseases and remained elevated in the inactive phase of disease, whereas clinical parameters and other cytokines normalized. Serum concentrations of HO-1 correlated positively with the markers of disease activity (CRP, AST, LDH, ferritin) and inflammatory cytokines, particularly IL-18. In conclusion, HO-1 may be an important mediator in s-JIA as well as IL-18 and serum concentrations of HO-1 may be a promising indicator of the disease activity.

W117-3

Preliminary criteria for initiating anti-TNF to JIA after initial EBV infection

Ken-ichi Yamaguchi, Yuri Ohara, Yasuhiro Suyama, Hisanori Shimizu, Atsushi Nomura, Eishi Uechi, Yukio Matsui, Mitsumasa Kishimoto, Masato Okada

St Luke's International Hospital

Safety of anti-TNF agent (anti-TNF) to adult patients who were infected with Epstein-Barr Virus (EBV) previously were reported, but children are at high risk of initial infection of EBV. We made preliminary criteria for initiation of anti-TNF after initial infection of EBV. (1. Improvement of liver function test. 2. Positive anti Epstein-Barr virus nuclear antigen antibody test. 3. Negative of EBV DNA in quantitative polymerase chain reaction. 4. No mosquito allergy.) A 7 year old girl who was refractory poly JIA treated with MTX was infected EBV and developed infectious mononucleosis. After she satisfied the criteria on 129th day, Adalimumab was administered, and she was in remission without reactivation of EBV. We need to accumulate experience to prove the validity of this criteria.

W117-4

Anti-MDA5 antibody predicts complication of interstitial lung disease in JDM

Ichiro Kobayashi¹, Yasuhiro Yamazaki¹, Shunichiro Takezaki¹, Yuka Okura¹, Masataka Kuwana²

¹Department of Pediatrics, Hokkaido University Graduate School of Medicine, ²Department of Rheumatology, Keio University School of Medicine

Interstitial lung disease (ILD) is a life-threatening complication of both adult dermatomyositis (DM) and juvenile dermatomyositis (JDM). We evaluated anti-melanoma differentiation-associated gene (MDA) 5 antibody, a recently identified marker for DM-associated ILD, in 13 cases of JDM including 6 cases with ILD. Five of the six cases with ILD were positive for the anti-MDA5 antibody. Three cases with rapidly progressive ILD showed extremely high levels of the antibody. In two cases, the antibody was detected before the development of ILD. All of the 7 cases without ILD were negative for the antibody. In conclusion, anti-MDA-5 autoantibody is not only a disease marker for ILD associated with JDM but also a predictive marker for the complication regardless of the muscle weakness

W117-5

Two girls with systemic lupus erythematosus complicated with pulmonary embolism

Utako Kaneko^{1,2}, Masako Kikuchi², Takako Miyamae², Tomoyuki Imagawa², Shumpei Yokota²

¹Department of Pediatrics, Niitaga University School of Medicine, Niigata, Japan, ²Department of Pediatrics, Yokohama City University School of Medicine, Yokohama, Japan

We report two adolescent girls with SLE complicated with pulmonary thromboembolism. Both patients showed chest pain and abnormal findings of lung on chest radiograph and CT scan in early phase of the disease. Complication of anti-phospholipid syndrome was not observed, but thrombocytopenia and hyperfibrinolysis were persistently observed. After renal biopsy or methylprednisolone pulse therapy, abnormal shadow on chest CT scan worsened and deep venous thrombosis was revealed, that led to the diagnosis of pulmonary thromboembolism.

In early phase of the disease, SLE patients usually receive renal biopsy and methylprednisolone pulse therapy, which would worsen thrombosis. We should carefully investigate thromboembolism in SLE patients with chest pain and pulmonary shadow.

W117-6

SLE in which effects of drug were predicted by lymphocyte stimulating test

Yasuyuki Wada

Department of Pediatrics, The Jikei University Kashiwa Hospital, Chiba, Japan

Active use of immunosuppressants has greatly improved prognosis of collagen disease. We examined the sensitivity of various immunosuppressants mitogen-induced proliferation of peripheral lymphocytes in collagen disease patients. We report a case in which sensitivity test was useful. [Case] A 20-year-old woman developed SLE at age 12 and was treated with prednisolone (PSL), and mizoribine (MZR). Symptoms relapsed and laboratory findings became worse with tapering of the drugs. Switching MZR to tacrolimus (TAC) and cyclosporine (Cy-A) induced fever and cytopenia, progressively. The patient showed low sensitivity to TAC and Cy-A; thus, these drugs may be obstacles to the clinical course.

International Workshop

IW1-1

Study of Efficacy and Safety of Imatinib in the Treatment of Systemic Sclerosis with or without Diffuse Parenchymal Lung Disease

Md. Abu Shahin, Syed Atiqul Haq, Sakina Anowar, Shamim Ahmed

Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

Aims and Objectives

To evaluate the efficacy and safety of Imatinib in the treatment of systemic sclerosis with or without diffuse parenchymal lung disease.

Materials and Methods

Study Design - Open, controlled clinical trial study. **Study period** - January 08 to December 09 **Place of study** - Outpatient department of Rheumatology wing and in patients department of Medicine, BSMMU. **Study Population** - Subjects affected with systemic sclerosis aged ≥ 18 . **Sample Size** - A total of 32 patients were

Follow Up - Clinical and laboratory evaluation including primary and secondary outcome variables were done during 6 months follow up period.

Statistical Analysis

All collected data were entered into a predesigned data collection form and analyzed using computer based SPSS programme and expressed as mean (\pm SD) or in frequency or percentage unless mentioned otherwise. Level of significance was expressed as P value. P value < 0.05 was considered as a level of significance.

Treatment response in imatinib group after 6 months: After the end of six months of treatment 8 (100%) patients responded favorably according to TSS(MRSS) and none (0%) showed unfavorable response.

Treatment response in MTX group after 6 months: After completion of six months of treatment 5 patients responded favorably and 11 patients showed unfavorable response according to TSS in MTX group.

Changes in outcome variables of both groups: There are significant changes in outcome variables of both groups.

Discussion: As fibrosis is clearly a major cause of both disability and mortality in SSc. Many drugs have been used to decrease fibrosis. In the present, we have setup our study design partially following the guidelines for clinical trial in SSc by www.clinicaltrial.gov. Despite smaller sample size and short duration of study it appeared that the efficacy of imatinib is better than MTx in the treatment of systemic sclerosis.

Recommendation : This study has shown that imatinib can be used in systemic sclerosis but a long term randomized double-blind placebo controlled clinical trial with larger sample has to be carried out to establish the safety and efficacy of imatinib in SSc patient.

IW1-2

To Study the Effects of Anti TNF Alpha Agents on Bone Health and Disease Activity in Ankylosing Spondylitis Patient

Shefali K Sharma, Sandeep Mohanan, S.K. Sharma

Department of Medicine, All India Institute of Medical Sciences, New Delhi, India

Background: Ankylosing spondylitis (AS) shows the paradox of abnormal new bone formation coexisting with reduced bone mass and increased fracture risk. Tumor necrosis factor-alpha (TNF α) plays a prominent role in the inflammatory process and bone resorption. Osteoporosis has an incidence between 18.7% and 62% in AS. In this study, we evaluate the relationship between bone mineral density (BMD) with disease activity in AS patients on Anti TNF α

agents.

Aims and Objectives:

1. To study the effect of Anti TNF agents in the improvement of bone mineral density of lumbar spine and hip in AS patients
2. To study the effect of anti TNF α agents in the over all bone metabolism in AS patients.

Methods: 42 patients of AS were recruited of which 23 were started on Anti TNF therapy in accordance to the Assessment of Ankylosing Spondylitis International Society(ASAS) guidelines (19 on Infliximab and 4 on Etanercept). Detailed assessment of disease activity was done in terms of Erythrocyte Sedimentation rate(ESR), Bath Ankylosing Spondylitis Disease Activity Index(BASDAI), Bath Ankylosing Spondylitis Functional Index(BASFI), Bath Ankylosing Spondylitis Metrological Index (BASMI), Modified Stokes Ankylosing Spondylitis Spinal Score (mSASSS) and Ankylosing Spondylitis Quality of Life Questionnaire (AsQOL) at baseline, 6 months and 1 year. Baseline serum Vitamin D and PTH (chemiluminescence assay) were done to rule out hyperparathyroidism. Bone mineral density of the Lumbar spine and Hip was done. After ethical clearance study was started on Aug 2009.

Results: Osteoporosis was present in 39% (n=9) and osteopenia in another 34.8% (n=8) of the study population at baseline, as per the WHO criteria. Data analysis was done for 10 patients who completed the 6 month follow up. At baseline the mean BASDAI was 6.48, BASFI 6.55, BASMI 3.9, mSASS 25.9, AsQOL 12.1 and ESR 50.9. Significant improvements were seen for BASDAI ($P<0.01$), BASFI ($P<0.01$), BASMI ($P=0.019$), AsQOL (<0.01) and these correlated with a decrease in ESR($P=0.01$) at 6 months. An overall trend for improvement was seen for BMD values with in 6 months - Lumbar spine AP (mean change of +0.023, $P=0.052$), Lumbar spine Lateral (mean change of +0.014, $P=0.68$), Hip NOF (mean change of +0.034, $P=0.093$).

Conclusion: Anti TNF α agents significantly decrease disease activity in AS patients. It correspondingly has a beneficial effect on bone metabolism resulting in improved bone formation.

IW1-3

Efficacy of anti-TNF therapy in patients with refractory entero-Behcet's disease

Ippei Miyagawa, Kazuyoshi Saito, Shigeru Iwata, Kunihiro Yamaoka, Shintaro Hirata, Shizuyo Tsujimura, Masao Nawata, Yoshiya Tanaka

The First Department of Internal Medicine, University of Occupational & Environmental Health, School of Medicine, Kitakyushu, Japan

Entero-Behcet's disease (BD) is one of the serious pathological conditions that determine prognosis in BD patients. Although high dose of corticosteroid (CS) and immunosuppressants are widely used for treatment, refractory entero-BD is difficult to manage and effective treatment remains elusive. We assessed the efficacy of anti-TNF therapy, in 17 patients with entero-BD who failed to respond to conventional therapy. The patients including 4 men and 13 women were enrolled. The mean age was 40.7 years and mean duration of Entero-BD was 34.5 months. 13 patients showed improvement of gastrointestinal symptoms and disease-associated complications. Furthermore, the dose of CS was significantly reduced. The results suggest that ant-TNF therapy is an effective treatment for Entero-BD patients.

IW1-4

Discontinuation of adalimumab in RA patients after attaining clinical remission

Shintaro Hirata, Kazuyoshi Saito, Ippei Miyagawa, Satoshi Kubo, Koshiro Sonomoto, Shunsuke Fukuyo, Kentaro Hanami, Sonosuke Yukawa, Shigeru Iwata, Masao Nawata, Shizuyo Tsujimura, Mikiko Tokunaga, Kunihiro Yamaoka, Yoshiya Tanaka

The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health Japan, Kitakyushu, Japan

To elucidate the ability of ADA-free remission, we discontinued ADA for 30 RA patients, maintained DAS28 <2.6 for ≥ 24 wks without NSAIDs and glucocorticoids, in 121 patients, initiated ADA ≥ 1 yr before. Median age 62.5yr, female 80%, duration 25.5mo, stage I+II in 70%, dosing period of ADA 52 wks. Discontinued group had shorter duration and earlier stage. Mean DAS28 were 5.1 at starting ADA, and 1.9 at termination. Data at 24 and 52 wks after terminating ADA were available in 11 and 5 cases. Nine (82%) at 24 wks and 5 (100%) at 52 wks stayed in DAS28 <3.2 . HAQ ≤ 0.5 was achieved in 26 (87%) at termination, 10 (91%) at 24 wks after, and 5 (100%) at 52 wks. All of 5 cases kept structural remission for 52 wks. These results suggest that ADA could be discontinued with preferred maintenance effect.

IW1-5

Reduced dose rituximab in rheumatoid arthritis: efficacy depends on degree of B cell depletion

Edward M Vital¹, Shouvik Dass¹, Karen Henshaw¹, Julie Madden¹, Andrew C Rawstron², Paul Emery¹, Dennis McGonagle¹

¹Academic Unit of Musculoskeletal Disease, University of Leeds and Chapel Allerton Hospital, United Kingdom, ²Haematological Malignancy Diagnostic Service, St. James's Institute of Oncology, Leeds, UK.

Aim. Studies comparing 500mg and 1000mg rituximab doses in RA have yielded conflicting data on clinical outcomes but in all a subgroup of patients had excellent responses at the lower dose. Historically it was considered that rituximab uniformly depleted B cells at both doses. We have previously shown, using highly sensitive assays, that B cell depletion is variable and predictive of clinical response. We therefore used the same techniques to test the hypothesis that the level of B cell depletion, rather than the rituximab dose determines clinical response.

Methods. 21 patients were treated with 2x500mg rituximab (RTX500) and 73 patients with 2x1000mg (RTX1000). Highly sensitive flow cytometry was performed at 0,2,6,14 and 26 weeks. EULAR criteria at 6 months were compared between patients with complete and incomplete depletion at each dose.

Results. Median B cell count was numerically higher at all time points following therapy in the RTX500 group. 25% of RTX500 patients demonstrated complete depletion at 2 weeks, compared to 48% of RTX1000. Complete depletion at 2 weeks after RTX500 was associated with lower baseline plasmablast cell counts ($p=0.047$), suggesting that complete depletion at the lower dose may be predicted at baseline. Most patients responded after either dose, but response was related to B cell depletion. Notably, in the RTX500 group all patients with complete depletion had a EULAR-Good response ($p=0.011$). All 5 patients with EULAR non-response had incomplete depletion ($p=0.099$).

Conclusions. This pilot study suggests that the degree of B cell depletion rather than the dose of rituximab determines clinical response. It may be possible to predict which patients may respond to

lower dose RTX, which has may allow more cost effective treatment.

IW1-6

Effect of Pneumococcal Vaccination in patients treated with TNF inhibitors

Satoshi Kubo, Kazuyoshi Saito, Kunihiro Yamaoka, Shintaro Hirata, Shizuyo Tsujimura, Masao Nawata, Takayuki Katsuyama, Yoshiya Tanaka

The first department of internal medicine, University of Occupational and Environmental Health, Japan.

Higher incidence of bacterial pneumonia in rheumatoid arthritis patients treated with TNF inhibitors (TNF-I) is known. However, the effect of pneumococcal vaccine (PPV) remains unclear. The post marketing survey of TNF-I in Japan have shown that pulmonary disease, diabetes mellitus, oral glucocorticoid (GC) and age over 65 were the risk factors for pneumonia. Therefore, patients with more than 3 risk factors were vaccinated since 2008 (group A). On the other hand, our data before 2008 indicated that pulmonary disease and oral GC were the risk factors and patients with this factor were vaccinated since 2009 (group B). The incidence of pneumonia was 1.7 (/100 person-year) compared with 2.9 in group A. In conclusion, **PPV is recommended in patients with coexisting pulmonary disease or oral GC.**

IW1-7

Prophylaxis using TMP - SMX for PCP in RA patients with biologics

Takayuki Katsuyama, Kazuyoshi Saito, Kunihiro Yamaoka, Shintaro Hirata, Shizuyo Tsujimura, Masao Nawata, Ippei Miyagawa, Satoshi Kubo, Maiko Yoshikawa, Eri Hirakawa, Yoshiya Tanaka

First department of Internal Medicine, University of Occupational and Environmental Health

We analyzed 702 RA patients treated with biologics (IFX, ETN, ADA, TCZ) to identify risk factors for PCP. 9 patients developed PCP, and NNT led the conclusion that patients with at least two of three risk factors (age ≥ 65 , coexisting pulmonary disease and usage of glucocorticoids) benefit from primary prophylaxis against PCP. We investigated the efficacy and safety of this procedure for 231 RA patients started biologics after Oct. 2009. The prophylaxis was administered in 103 patients (44.6%). 14 patients received inhaled pentamidine because of renal dysfunction, and TMP - SMX prophylaxis was administered in 89. Liver dysfunction (4 patients), cytopenia (2), skin rash (1), were identified in TMP - SMX group. No patient developed PCP in this study, to prove the efficacy of this procedure.

IW1-8

Influencing factors of Quality of life (QOL) in Korean Rheumatoid Arthritis (RA) patients

Soo-Kyung Cho, Dam Kim, Yoon-Kyoung Sung, Sang-Cheol Bae
Department of Rheumatology, The Hospital for Rheumatic Diseases, Hanyang University, Seoul, Korea

Objective: To determine the influencing factors of health related quality of life (HR-QOL) in Korean RA patients

Methods: Two hundred twenty five RA patients diagnosed with the 1987 American College of Rheumatology criteria were recruited from the Hospital for Rheumatic Disease in Hanyang University,

Seoul, Korea (from Hanyang University Medical center Arthritis Network, HUMAN). Data on demographics, disease activity (DAS28-ESR), pain visual analogue scale (VAS), functional disability (Health Assessment Questionnaire, HAQ), anemic state (male $<12\text{mg/dL}$, female $<11\text{mg/dL}$), co-morbidity, operational history and European Quality of Life-5 Dimensions (EQ-5D) were collected. Logistic regressions were used to explore determinants of responses in the EQ-5D dimensions, and linear regression was used to explore determinants of the EQ-5D score.

Results: The mean utility observed for Korean RA patients was 0.60(-0.29~1.0) for the EQ-5D. The EQ-5D scored 12.8% of patients as less than 0.25; 8% of the RA group were scored less than 0 (state defined as worse than death). The EQ-5D scores were highly correlated with the HAQ ($r=-0.715$) and shows moderate correlation with the pain VAS ($r=-0.499$), GH VAS ($r=-0.411$), DAS28 ($r=-0.409$) and physician VAS ($r=-0.323$). However, number of co-morbidity, disease duration show no or low correlation with EQ-5D score. HAQ ($p<0.001$), DAS28 ($p=0.003$) and patient assessed pain-VAS ($p=0.013$) were significant predictors of EQ-5D utility in multiple stepwise regression models. For patients who are remission or low disease activity, alternative medicine ($p=0.014$), physician VAS ($p=0.011$) and HAQ ($p=0.002$) were significant predictors of EQ-5D utility, and for patients who are moderate to severe disease activity, only pain VAS ($p=0.002$) was predictors of EQ-5D utility.

Conclusion: The strongest determinants of reduced HRQoL in Korean RA patients were presence of functional disability, higher physician's global assessment of disease activity and patient assessed pain-VAS. The EQ-5D dimensions and the EQ-5D seem capable of capturing the consequences of RA functional disability, and it may have substantial impact on several dimensions of health-related quality of life (HRQoL).

IW1-9

Prediction of ongoing joint destruction in RA clinical remission by US

Ryusuke Yoshimi, Kaoru Takase, Maasa Hama, Kouji Kobayashi, Kayo Terauchi, Toshiyuki Watanabe, Reikou Watanabe, Sei Samukawa, Hiroshi Kobayashi, Atsushi Ihata, Atsuhisa Ueda, Mitsuhiro Takeno, Yoshiaki Ishigatsubo

Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine

Objective: To assess whether ultrasonography (US) predicts joint destruction during clinical remission of rheumatoid arthritis (RA). **Methods:** Hand X-ray and power Doppler (PD) US were monitored in 20 RA patients who had been in clinical remission for two years. The association between radiological joint destruction and total PD score in US was analyzed. **Results:** Progressive radiological destruction in any joints was found in some patients having more than 2 of total PD score in US at the entry, but not those having one or zero, during the 2 year observation. **Conclusion:** The results suggest that PDUS detects latent synovitis which causes joint destruction even in the clinical remission of RA patients. Thus, imaging remission in US is essential to reach "true remission" of RA.

IW1-10

Spontaneous repair of steroid-associated osteonecrosis in SLE patients

Junichi Nakamura¹, Tomonori Shigemura¹, Yoshitada Harada², Koh Shimizu³, Satoshi Iida⁵, Koya Kamikawa⁷, Munenori Takeshita¹, Masahiko Suzuki⁸

¹Department of Orthopaedic Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan, ²Chibaken Saiseikai Narashino Hospital, Narashino, Japan, ³Chiba Rosai Hospital, Ichihara, Japan, ⁴Chiba Kaihin Municipal Hospital, Chiba, Japan, ⁵Matsudo City Hospital, Matsudo, Japan, ⁶Funabashi Orthopaedic Hospital, Funabashi, Japan, ⁷Teikyo University Chiba Medical Center, Ichihara, Japan, ⁸Chiba University Research Center for Frontier Medical Engineering

Objective: To clarify spontaneous repair of osteonecrosis in SLE.

Methods: 537 joints (251 hips and 286 knees) in 144 SLE patients were included with follow-up period of 14 years. Osteonecrosis developed in of 537 joints (44%). After initial therapy, SLE was well maintained in 159 joints but recurred in 79 joints. Spontaneous repair was evaluated with MRI.

Results and Conclusion: Spontaneous repair was observed in 117 joints (49%); for osteonecrosis of the femoral head, 48% of type C2 hips, 50% of C1 hips, 71% of B hips, and 100% of A hips. Spontaneous repair was observed in 57% without SLE recurrence and 34% with recurrence. Cox regression analysis indicated that type A hips had a 2.5 times and non-recurrence group had a 2.3 times higher likelihood of repair.

IW1-11

Evaluation of the American College of Rheumatology 2010 criteria for the diagnosis of rheumatoid arthritis in Chinese Patients

Juan Zhao, Jing Xu, Xiaohui Zhang, Guangtao Li, Zhuoli Zhang
Department of Rheumatology and Clinical Immunology, Peking University First Hospital

[OBJECTIVE] To evaluate the ability of American College of Rheumatology (ACR) 2010 classification criteria to diagnose rheumatoid arthritis (RA) compared with widely used ACR 1987 criteria in Chinese patients.

[METHODS] Four hundred and four patients from rheumatology department who suffered from arthritic problems were included in the study. Among these patients, 221 were diagnosed as RA and 183 were diagnosed as other rheumatic diseases by experienced rheumatologists. The patients were further subdivided into three groups according to their disease duration within one year, between one to two years and over two years. The diagnostic value of ACR 2010 criteria for RA was evaluated by comparing its sensitivity and specificity with those of ACR 1987 criteria in these patients.

[RESULTS] The sensitivity and specificity of the ACR 2010 criteria for diagnosing RA were 95% and 92.9%, respectively. In contrast, the sensitivity and specificity of the ACR 1987 criteria were 81.4% and 92.9%, respectively. Compared to the 1987 criteria, the ACR 2010 criteria enhanced the sensitivity while conserved the specificity. The efficacy of the ACR 2010 criteria was superior to the 1987 criteria by comparing the area under the curves (AUC) (0.940 vs 0.872, $p < 0.05$). The accuracy rating of the ACR 2010 criteria was higher than 1987 criteria (94.5% vs 86.6%, $p < 0.05$). Interrater analysis showed that agreement of the two criteria was substantial (Kappa=0.744, $p < 0.001$). For patients with disease duration within one year, between one to two years and over two years, the sensitivities of the ACR 1987 criteria were 69.2%, 81.3% and 89.9%, while the specificities were 94.4%, 90.6% and 92%, respectively. The corresponding sensitivities of the ACR 2010 criteria in these patients were 91%, 93.8% and 98.2%, while the corresponding specificities were 94.4%, 96.6% and 89.3%, respectively. The advantage of the ACR 2010 criteria in higher sensitivity was dramatic particularly in patients with disease duration within one year ($p < 0.001$).

[CONCLUSION] The accuracy rating of the ACR 2010 criteria

was much higher than the ACR 1987 criteria due to its enhancing sensitivity while conserving the specificity, especially in patients with disease duration within one year. The ACR 2010 criteria may serve as new diagnostic tools in clinical daily practice for Chinese patients.

IW1-12

Reliability and Agreement of the proposed 2010 ACR/EULAR classification criteria comparing to 1987 ACR classification criteria for RA in Korea; usual practice setting

Yoon-Kyoung Sung, Dam Kim, Soo-Kyung Cho, Sang-Cheol Bae
Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea

Objective. To examine the reliability and agreement of the proposed 2010 American College of Rheumatology (ACR) / EULAR (European League Against Rheumatism) classification criteria for Rheumatoid arthritis(RA) and 1987 ACR classification criteria in Korea

Methods. Total of 203 patients who firstly visited Rheumatology department in a university hospital from MAY 2010 to AUG 2010 were retrospectively enrolled. Among them, 143 patients who satisfied our inclusion criteria (aged ≥ 20 , having arthralgia, and who was performed X-ray and laboratory tests including inflammatory markers and antibodies) were analyzed. We defined RA patients as a gold standard who finally diagnosed RA by two rheumatologists with starting methotrexate therapy within 3 months after first visit. To examine the reliability, we estimated sensitivity, specificity, and accuracy of both 1987 ACR criteria and 2010 ACR/EULAR classification criteria for RA. Agreement between the two criteria was evaluated with using Cohen's kappa coefficient.

Results The sensitivity of the 2010 ACR/EULAR classification criteria was 64.3%, specificity was 98.3%, positive predictive value was 90%, and negative predictive value was 91.9%, respectively. The sensitivity of the 1987 ACR classification criteria was 25%, specificity was 100%, positive predictive value was 100%, and negative predictive value was 84.6%, respectively. Cohen's kappa coefficient between the 1987 ACR criteria and 2010 ACR/EULAR criteria was 0.481

Conclusion and Discussion

2010 ACR/EULAR classification criteria has higher reliability than 1987 ACR classification criteria for RA. However, 1987 ACR classification criteria for RA show very low sensitivity and high specificity. It indicates that 1987 ACR criteria are useful in confirmatory diagnosis for RA and rheumatologists in Korea has already been practiced based on laboratory data such as anti-ccp antibody, rheumatoid factor, and inflammatory markers which included in 2010 ACR/EULAR criteria before exposure of new classification criteria. (This abstract shows preliminary results and further enrollment with subgroup analyses are ongoing)

IW1-13

The incidence of MTX lymphoproliferative disorders in RA patients

Yuji Yoshida, Yuko Takahashi, Hiroyuki Yamashita, Hiroshi Kaneko, Akio Mimori

Division of Rheumatic Diseases, National Center for Global Health and Medicine

The incidence of methotrexate lymphoproliferative disorders (MTX-LPD) in RA patients was estimated. Patients: Our complete database of 586 RA patients registered between 1990 and 2010 was used. Result: 403 patients had received MTX, with administration

totaling 2379 person-years. 4 patients developed MTX-LPD during the observation period (2 diffuse large B-cell, 1 Hodgkin, and 1 T-cell type). The incidence of MTX-LPD was 0.00168/year. The mean MTX dose was 7.4 ± 1.9 mg/week, for a total of 1142 ± 871 mg per patient. After MTX withdrawal, spontaneous tumor regression was seen in one patient, and transient regression and relapse in another, with the latter requiring chemotherapy. The incidence of lymphoma in RA patients who received MTX was 9.9 times higher than that in the general population.

IW1-14

Clinical features of pregnant patients with antiphospholipid syndrome

Yuko Matsuki¹, Kentaro Matsuoka², Koshi Yamaguchi¹, Atsuko Murashima¹

¹Division of Rheumatology, Department of Women's Health, National Center for Child Health and Development, Tokyo, Japan, ²Department of Pathology, National Center for Child Health and Development, Tokyo, Japan

Objective: To investigate clinical features and placental pathology of pregnant patients with antiphospholipid syndrome (APS). **Methods:** Clinical records were reviewed for pregnant patients with APS, and we studied 16 patients who met the Sapporo Criteria. **Results:** All patients were treated with heparin and low dose aspirin. They were divided into two groups: the mild group was well controlled with the above treatment, and the severe group required further treatment. Severe cases tended to be lupus anticoagulant positive or have multiple types of antiphospholipid antibodies (aPLs). Not all cases showed thrombosis in the placenta. **Conclusions:** When APS patients desire pregnancy, it is important to determine the type and titer of aPLs, and the pregnancy and delivery must be carefully managed.

IW2-1

TIARP regulates autoimmune arthritis via suppression of inflammatory cytokines.

Asuka Inoue^{1,2}, Isao Matsumoto¹, Yoko Tanaka¹, Naoto Umeda¹, Yuki Tanaka¹, Takayuki Sumida¹

¹Division of Clinical Immunology, Doctoral Program in Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, ²JSPS Research Fellow

[Objective] To explore the role of TIARP in experimental autoimmune arthritis.

[Methods] 1) TIARP^{-/-} mice in B6 background were generated, and were immunized with 200µg type II collagen (C II) on day 0, 21. The severity of arthritis was monitored.

2) C II-specific T cell response and autoantibodies were assessed.

3) The expression of inflammatory cytokines in serum and joints on day60 were examined.

[Results] 1) The severity of arthritis in TIARP^{-/-} mice was higher than that in WT.

2) C II-specific T cell responses and anti-C II Abs in TIARP^{-/-} were comparable with those in WT.

3) Serum IL-6 and TNFα, IL-6 mRNA expression in joints were significantly increased in TIARP^{-/-} compared with WT.

[Conclusion] TIARP should be a negative regulator against autoimmune arthritis via suppression of inflammatory cytokines.

IW2-2

The role and source of IL-17 in antibody-induced arthritis

Masaki Katayama, Koichiro Ohmura, Chikashi Terao, Naoichiro Yukawa, Hajime Yoshifuji, Daisuke Kawabata, Takao Fujii, Tsuneyo Mimori

Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

IL-17 producing T cells have important roles in a number of mouse models for rheumatoid arthritis, but it was not known how IL-17 works in the effector phase of arthritis. Now, when K/BxN serum-induced arthritis, which is useful to analyze this phase, was introduced in IL-17 knock out (KO) mice, arthritis was significantly suppressed in comparison with that in the wild type mice. K/BxN serum-induced arthritis exacerbated when IL-17^{+/+} neutrophils, but not CD4⁺ T cells or IL-17^{-/-} neutrophils, were injected into IL-17 KO mice at day0 and day2. Moreover, in vitro experiments, neutrophils secreted IL-17 by stimulating with immune complex (IC). In summary, IL-17 has a proinflammatory role even in the arthritis effector phase and neutrophil stimulated by IC is a major source of IL-17.

IW2-3

Expressions of BAFF/BAFF-R and their correlation with disease activity in systemic lupus erythematosus

Yang Li¹, Li-dan Zhao¹, Michael F. Smith, Jr.², Jing-song Wang², Fu-lin Tang¹, Xin-ping Tian¹, Feng-chun Zhang¹, Xuan Zhang¹

¹Department of Rheumatology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, ²Discovery Translational Medicine, Wyeth Research, USA

Objective

BAFF is essential for B-cell survival and function through interaction with its receptors BR3, BCMA and/or TACI, though the latter two can also bind to APRIL. We evaluate the correlation of the expressions of these ligands/receptors with different clinical manifestations of SLE (Systemic Lupus Erythematosus).

Methods

Levels of BAFF and APRIL in plasma from 73 SLE patients were determined by ELISA. Expressions of BR3, TACI and BCMA on CD19⁺ B cells were detected by flow cytometry. Clinical data were collected and disease activity was evaluated using SLEDAI-2000.

Results

SLE patients had elevated BAFF and APRIL levels in their plasma. BAFF levels correlated positively with SLEDAI while negatively with the BR3 protein expression on CD19⁺ B cells ($p < 0.05$). The detected BR3 protein expression in SLE patients was reduced on CD19+IgD+CD27-, CD19+IgD+CD27+ as well as CD19+IgD-CD27+ B cells compared to the counterparts of health controls ($p < 0.001$), whereas SLE patients did not differ from health controls on BR3 mRNA level. In untreated newly-onset patients, the expression rate of BR3 on CD19⁺ B cells correlated negatively with SLEDAI ($p < 0.05$). Elevation of BAFF and reduction of BR3 on CD19⁺ B cells were more obvious in those with lupus nephritis (LN) ($p < 0.05$). TACI expression on CD19⁺ B cells was up-regulated only in those subjects with LN ($p < 0.05$).

Conclusion

Elevated plasma BAFF and reduced BR3 protein expression on peripheral B cells could act as biomarkers for active disease in SLE patients. High expression of TACI may indicate the occurrence of LN.

IW2-4

A novel point mutation causing proteasome dysfunction in NNS

Kazuhiko Arima¹, Hiroaki Ida², Tomoki Origuchi³, Nobuo Kanazawa⁴, Katsumi Eguchi⁵

¹Nagasaki University Graduate School of Biomedical Sciences, Department of Medical Gene Technology, Nagasaki, Japan, ²First Department of Internal Medicine, Kurume University, Kurume, Japan, ³Nagasaki University School of Health Sciences, Nagasaki, Japan, ⁴Department of Dermatology, Wakayama Medical University, Wakayama, Japan, ⁵Sasebo City hospital, Sasebo, Japan

Background: Nakajo-Nishimura syndrome (NNS) is a systemic inflammatory disorder that segregates in an autosomal recessive fashion.

Objective: To identify the causative mutation of NNS.

Methods: Genomic DNA samples collected from 5 patients and 3 unaffected sibs of the patients were analyzed. The extracts from immortalized cell lines were assayed for 3 different peptidase activities of the proteasome.

Results: A novel mutation was identified in a gene encoding a proteasome subunit in all NNS patients. The proteasome activities were reduced with a gene dosage effect.

Conclusion: This is the first direct evidence of proteasome dysfunction causing a human disease. This provides a new insight into the pathogenesis of other persistent inflammatory diseases.

IW2-5

The Role of Reactive Oxygen Species and Caspase-3 in Cytotoxic T Lymphocyte Mediated Cell Death in Systemic Lupus Erythematosus

Dilip Shah¹, Ravi Kiran², Archana Bhatnagar², Ajay Wanchu³

¹Department of Biochemistry, Basic Medical Science, Kathmandu Medical College, Kathmandu, Nepal, ²Department of Biochemistry, Basic Medical Sciences Block, Panjab University, Chandigarh, India, ³Division of Arthritis and Rheumatic Diseases, Portland, OR

Cytotoxic T lymphocyte (CTL)-mediated cell death through granzyme B has recently been proposed to be a preferential and selective source of autoantigens in systemic lupus erythematosus (SLE). The reactive oxygen species (ROS) are considered to be the universal factors involved in the development of various clinical features seen in SLE. The aim of this study was to study role of ROS and caspase-3 in CTL mediated cell death in 40 SLE patients and controls. The ROS levels were measured using the dye 2', 7'-dichlorofluorescein diacetate by flow cytometry. Cytotoxic T lymphocyte activity of CD8⁺ T cells was detected by measuring the intracellular expression of perforin and granzyme B on CD8⁺ T cells by three colour flow cytometry. The disease activity was determined by using SLE Disease Activity Index (SLEDAI) score. The level of ROS was found to be significantly elevated in SLE patients and positive correlation existed with disease activity in SLE patients. The expression of perforin, granzyme B independently and perforin/granzyme B together on CD8⁺ T cells were significantly increased in SLE patients and correlated with the disease in SLE patients. Furthermore, the expression of granzyme B and perforin/granzyme B on CD8⁺ T lymphocyte positively correlated with caspase-3 expression in these cells and with ROS levels in SLE patients. The increased levels of caspase-3 and ROS production demonstrate that CTL mediated cell death occurs by caspase-3 dependent pathway and this amplification get enhanced by production of ROS in SLE patients.

Keywords: reactive oxygen species, caspase-3, cytotoxic T lymphocyte, systemic lupus erythematosus

IW2-6

IL-33 contributes to joint inflammation via mast cell immune function

Shinjiro Kaieda

Division of Respiratory, Neurology and Rheumatology, Kurume University School of Medicine

Mast cells (MCs) have been recognized as potential participants in inflammatory arthritis. Recent studies have highlighted potent effects of the synovial fibroblast-derived IL-33 on the phenotype of MCs. We explored the importance of this axis in the K/BxN serum transfer model of arthritis. Compared with littermate controls, ST-2 KO mice exhibited a reduced intensity of arthritis. Since activation of MCs in this model proceeds via Fc γ receptors, we examined the implications of IL-33 exposure to IgG-mediated activation of MCs. Pre-incubation with IL-33 markedly enhanced production of pro-inflammatory cytokines such as IL-1 β and MIP-2. These findings define a novel role of IL-33 in the priming of MCs for immune complex-mediated inflammation and demonstrate a key role for IL-33 in arthritis.

IW2-7

SIRT1 Acts as a Negative Regulator of Human Pulmonary Arterial Smooth Muscle Cells Proliferation: A Novel Target of Pulmonary Arterial Hypertension Therapy

Shuang Zhou¹, Meng-Tao Li², Xiao-Feng Zeng²

¹Department of Internal Medicine, Peking Union Medical College Hospital, Beijing, China, ²Department of Rheumatology, Peking Union Medical College Hospital, Beijing, China

Background: Pulmonary arterial hypertension (PAH) is one major cause of death in patients with rheumatic diseases. Proliferation of pulmonary arterial smooth muscle cells (PASMCs) is cytological basis of vascular remodeling, which could lead to PAH. SIRT1, a class I histone deacetylase, has been implicated as a key regulator of angiogenesis, but its effects on pulmonary arteries remain poorly defined. Recently, a small-molecule activator of SIRT1, resveratrol, has been shown to inhibit PASMCs proliferation.

Objectives: To investigate the role of SIRT1, in the regulation of human PASMCs (HPASMCs) cell cycle and whether SIRT1 mediates the inhibition effect of resveratrol on HPASMCs proliferation.

Methods: With realtime-PCR and western blot, we measured the expression of SIRT1 in HPASMCs stimulated with PDGF-BB. FCM was applied to detect the effects of SIRT1 on HPASMCs cell cycle progression in vitro. After over-expression or RNAi to SIRT1, expression of cell cycle protein which functions in G1 state were examined by western blot. HPASMCs were treated with resveratrol after RNAi to SIRT1, cell cycle protein were examined by western blot.

Results: We found that expression of SIRT1 and p21 (G1 phase negatively regulatory protein) decreased but the expression of CyclinD1&CyclinE (G1 phase positively regulatory proteins) increased in HPASMCs after PDGF-BB stimulation. Adenoviral overexpression of SIRT1 led to an arrest of the HPASMCs in phase G1 and inhibited HPASMCs proliferation induced by PDGF-BB. In addition, Adenoviral overexpression of SIRT1 decreased the expression of CyclinD1&CyclinE, but increased expression of p21. However, Adenoviral RNAi to SIRT1 had the reverse effects. Resveratrol increased SIRT1 and p21 expression but decrease CyclinD1&CyclinE expression in HPASMCs. The regulation of CyclinD1, CyclinE and

p21 by resveratrol was reversed by knockdown of SIRT1 in HPASMCs.

Conclusion: SIRT1 could inhibit proliferation of HPASMCs by affecting expression of cell cycle regulatory protein. SIRT1 mediates phase G1 arrest effect of resveratrol on HPASMCs. Activation of SIRT1 might be novel target of PAH therapy in the future.

Key words: pulmonary arterial hypertension, pulmonary arterial smooth muscle cells, SIRT1, cell cycle, proliferation

IW2-8

Attenuation of T cell receptor signaling causes autoimmune disease

Shinji Maeda¹, Satoshi Tanaka¹, Shuji Akizuki¹, Motomu Hashimoto¹, Shimon Sakaguchi¹

¹Department of Experimental Pathology, Institute for Frontier medical Sciences, Kyoto University, Kyoto, Japan, ²Department of Medical Oncology and Immunology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

We have gradationally expressed the zeta-associated protein-70 (ZAP-70) in normal mice by tetracycline-inducible genetic control, and examined whether TCR signal alteration is able to cause autoimmune disease. We show that developing T cells expressing lower amounts of ZAP-70 are less sensitive to thymic negative selection than those expressing normal levels of ZAP-70, which results in thymic production of pathogenic self-reactive T cells and occurrence of autoimmune disease, such as autoimmune arthritis. This indicates that genetic anomalies or variations attenuating TCR-proximal signaling enhance the production of pathogenic autoimmune T cells and make the host succumb or susceptible to autoimmune disease.

IW2-9

Shared Epitope Alleles Remain As Risk Factor for Anti-Citrullinated Proteins Antibody (ACPA) - positive Rheumatoid Arthritis in Three Asian Ethnic Groups

Chun-Lai Too^{1,2}, Leonid Padyukov¹, Jasbir Singh Dhaliwal², Lars Klareskog¹, Lars Alfredsson³, Per Larsson¹, Shahnaz Murad²

¹Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, ²Institute for Medical Research, Kuala Lumpur, Malaysia, ³Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

Introduction: Our knowledge on disease pathology and risk assignment in rheumatoid arthritis is mainly based on studies of Caucasian population. Investigations on different ethnic groups are, however, relatively rare and have not followed the rapidly increasing understanding of the genetic heterogeneity of rheumatoid arthritis (RA).

Objective: To investigate the associations between HLA-DRB1 shared epitope (SE) alleles and RA in subsets of RA defined by autoantibodies in three Asian populations from Malaysia.

Methods: 1,149 RA patients (515 Malays, 255 Chinese and 379 Indians) and 1,524 healthy controls (1029 Malays, 208 Chinese and 287 Indians) were included in the study. Levels of antibodies to citrullinated proteins (ACPA:s) and rheumatoid factors (RF:s) were assessed and the PCR-SSO method was used for HLA-DRB1 genotyping.

Results: The ACPA-positivity was noted to be significantly associated with RA in all the three ethnic groups (Malay odds ratio (OR) 95% confidence interval (95% CI)=61.66 (39.21-97.65), p value=7.88 x 10⁻¹⁵⁰; Chinese OR (95%CI)=56.43 (24.39-137.12), p=9.5 x 10⁻⁴⁴ and Indian OR (95% CI) =96.31 (40.12-246.67), p=2.64 x 10⁻⁶⁵). We also found that SE was highly associated with ACPA-

positive among all the three ethnic groups (Malay OR (95% CI)=5.63 (4.22-7.50), p= 8.6 x 10⁻³⁶; Chinese OR (95% CI)=6.00 (3.60-9.99), p=3.6 x 10⁻¹³ and Indian OR (95%CI)=3.03 (2.13-4.32), p=4.6 x 10⁻¹⁰). Presence of two SE gene copies (double SE alleles) conferred a higher risk than presence of single SE allele in all three populations for the development of RA. There was no association between SE alleles and ACPA- negative RA in any of the three Asian ethnic groups.

Conclusion: The HLA-DRB1 SE alleles increase the risk of ACPA positive RA in all three Asian populations from Malaysia.

IW2-10

A crucial role of M3R reactive T cells in Sjögren's syndrome like sialadenitis

Mana Iizuka¹, Hiroto Tsuboi¹, Yumi Nakamura^{1,2}, Naomi Matsuo¹, Isao Matsumoto¹, Takayuki Sumida¹

¹Division of Clinical Immunology, Major of Clinical Science, Graduated School of Comprehensive Human Science, University of Tsukuba, ²Japan Society for the Promotion of Science

OBJECTIVE To clarify the pathological role of M3R reactive T cells in SS like autoimmune sialadenitis. **METHODS** 1) M3R^{-/-} and IFN- γ ^{-/-}/M3R^{-/-} mice were immunized with M3R peptides and their splenocytes were transferred to Rag1^{-/-} mice (M3R^{-/-}→Rag1^{-/-} and IFN- γ ^{-/-}/M3R^{-/-}→Rag1^{-/-}). 2) CD3⁺ cells from M3R immunized M3R^{-/-} mice were transferred to Rag1^{-/-} (M3R^{-/-}CD3⁺→Rag1^{-/-}). **RESULTS** 1) In M3R^{-/-}→Rag1^{-/-}, CD4⁺ T cells infiltrated into salivary glands. IL17 and IFN γ were highly produced in splenocytes and salivary glands. In IFN- γ ^{-/-}/M3R^{-/-}→Rag1^{-/-}, the sialadenitis was reduced compared with M3R^{-/-}→Rag1^{-/-}. 2) The sialadenitis was also observed in M3R^{-/-}CD3⁺→Rag1^{-/-}. **Conclusion** M3R reactive T cells should play a crucial role in the generation of autoimmune sialadenitis such as SS.

IW2-11

The Differential Effect of HLA-DRB1 *0901 allele from Shared Epitope on the Development of RA

So-Young Bang¹, Hye-Soon Lee¹, Kyung Wha Lee², Sang-Cheol Bae¹

¹Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, ²Kyung Wha Lee, PhD: Hallym Institute for Genome Application, Hallym University Sacred Heart Hospital, Anyang, South Korea

Objectives. Smoking is associated with rheumatoid arthritis (RA) in individuals with the HLA-DRB1 shared epitope (SE) alleles encoding conserved amino acid sequence (*0101, *0404, *0405, *0410 [70QRRAA⁷⁴], *0401 [70QKRAA⁷⁴], *1001 [70RRRAA⁷⁴]). The HLA-DRB1*0901 [70RRRAE⁷⁴], non-SE allele, is significantly associated with RA in Asian, but it is rare in Caucasian. We aimed to investigate interactions between HLA-DRB1 susceptible alleles and smoking, to examine the quantitative effects of these alleles on anti-CCP titers, and to study which distinct HLA-DRB1 alleles involve for developing anti-CCP-positive/negative RA in Korean populations with RA.

Methods. All RA patients (n=1482) and controls (n=1119) were Korean. Four-digit HLA-DRB1 typing was performed by a conventional PCR-SBT method. Information about smoking history was obtained through a questionnaire by interviewers.

Results. The combination of smoking and SE alleles (OR 15.68) / *0901 allele (OR 7.73) increased the risk for RA. The attributable proportions was 0.45 (0.19-0.72) for smoking and SE alleles, but 0.17 (-0.44-0.79) for smoking and *0901 allele. Smoking interacted

with SE alleles, but no significant interaction was found between *0901 allele and smoking. The SE alleles and smoking were associated with markedly increased titers of anti-CCP. But *0901 allele was significantly associated with reduced median titer of anti-CCP. In addition, DRB1*0405/*0901 heterozygote dramatically increased the risk in anti-CCP-positive RA smokers (OR 120.29 [12.83-1127.63]) and anti-CCP-negative RA smokers (OR 37.96 [2.06-693.47]) compared with nonsmokers without HLA-DRB1 risk alleles.

Conclusions. Gene-environment interaction of HLA-DRB1 *0901 allele is differ from SE alleles. The DRB1*0405/*0901 heterozygote enhances the susceptibility to both anti-CCP-positive and anti-CCP-negative RA.

IW2-12

Histone deacetylase inhibitor (HDAi) ameliorates arthritis via dendritic cells

Kenta Misaki¹, Akio Morinobu¹, Jun Saegusa¹, Shimpei Kasagi¹, Shunichi Kumagai²

¹Department of Clinical Pathology and Immunology, Kobe University, Kobe, Japan, ²Center of Rheumatology, Shinko Hospital, Kobe, Japan

Purpose; To elucidate the effects of HDAi on dendritic cells (DC) and on arthritis (AR) in SKG mice. **Methods & Results;** AR was induced in SKG mice by Zymosan A (ZyA) injection. Trichostatin A (TSA), a HDAi, was administered and its effects on AR was evaluated by joint swelling. TSA ,when administered both before and after the onset of AR ,prevented SKG mice from AR. TSA reduced IL-17 production by lymph node cells, but not Treg cells by splenic CD4 T cells, TSA treatment also decreased CD80, CD86 expression on splenic DC *in vivo*. *In vitro* TSA markedly suppressed ZyA-induced IL-12, IL-6 production, T cell stimulation and up-regulated indoleamine 2,3-dioxygenase expression by bone marrow derived DC. **Conclusion;** HDAi changes DC to a tolerogenic phenotype and ameliorates arthritis in SKG mice.

IW2-13

The phenotype of CD4+ T cells which recognize an autoantigen BiP-derived epitope

Hirofumi Shoda, Keishi Fujio, Kazuhiko Yamamoto

Dept. of Allergy and Rheumatology, Graduate School of medicine, the Univ. of Tokyo, Tokyo, Japan

< Introduction > We identified an autoantigen-derived HLA-DR4 epitope, BiP336-355.

< Methods > The phenotypes of BiP336-355-HLA-DR4-tetramer (BiP-Tet)+ CD4+ T cells from healthy volunteers (HV) and rheumatoid arthritis (RA) were analyzed by FACS and RT-PCR. The proliferation of PBMCs in response to BiP336-355 was examined by ³H-thymidine uptake.

< Results > BiP-Tet+ CD4+ T cells existed 0.23% in HV and 0.52% in RA. BiP-Tet+ cells consisted of naive and memory T cells, not Treg cells. BiP-Tet+ T cells in HV showed Th1 phenotypes, whereas those in RA highly produced IL-17 in peripheral blood and synovium. PBMCs from HV showed less proliferation than those from RA.

< Discussion > Induction of IL-17-producing BiP-Tet+ T cells is a key step in the pathogenesis of RA.

IW2-14

Identification of FLRT2 as a novel autoantigen for AECA using retrovirus vector

Tsuyoshi Shirai, Hiroshi Fujii, Kyohei Nakamura, Ryu Watanabe, Yumi Tajima, Naruhiko Takasawa, Tomonori Ishii, Hideo Harigae
Department of Hematology and Rheumatology, Tohoku University Graduate School of Medicine, Sendai, Japan

Objective: Most reported antigens of AECA are intracellular proteins. The aim is to identify autoantigen expressed on cell surface. **Methods:** Sera were screened for AECA activity with human umbilical vein endothelial cell (HUVEC) by FACS. cDNA library of HUVEC was inserted into retroviral vector and stably transfected to rat myeloma cells. cDNA expressing cells were FACS sorted with AECA IgG and cloned. **Results:** By FACS sorting with IgG from lupus patient that had AECA activity, 2 clones were isolated and both have fibronectin leucine-rich transmembrane 2 (FLRT2). HUVEC expressed FLRT2 and IgG of this patient bound to FLRT2 expressing cells. **Conclusion:** We identified membrane protein FLRT2 as a novel autoantigen for AECA. This system is useful for identification of cell surface autoantigen.

New Generation Workshop

NGW1-1

Does serum MMP-3 level reflect real synovitis?

Tadashi Okano¹, Masahiro Tada¹, Yuko Sugioka¹, Shigeyuki Wakitani¹, Kenji Mamoto¹, Tatsuya Koike²

¹Department of Orthopedic Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan, ²Department of Rheumatology, Osaka City University Graduate School of Medicine, Osaka, Japan

Background: We investigated the relationship between the values of serum MMP-3 and synovial tissue expression of MMP-3. **Methods:** 84 cases (RA: 73, OA: 11) were analyzed. Synovial tissue was taken during surgery. We performed immunostaining of MMP-3, and classified into four grades (0-3). We examined the relationship between the grade and the value of preoperative serum MMP-3, DAS28-ESR. **Results:** Mean serum MMP-3 values are higher in Grade3, but the differences between grades was not significant ($P = 0.748$), and not correlated ($P = 0.384$, $r = 0.105$). DAS28-ESR had also no significant difference among grades ($P = 0.669$). **Conclusions:** There is a possibility serum MMP-3 doesn't correlate to MMP-3 expression of synovial tissue. This result suggests caution in the interpretation of clinical data.

NGW1-2

Our research on anti-peroxiredoxin2 antibodies in patients with Kawasaki disease

Rie Karasawa, Kazuo Yudo

Institute of Medical Science, St. Marianna University School of Medicine, Kawasaki, Japan

Purpose: We investigated clinical importance of antibodies (Abs) to peroxiredoxin2 (Prx2), a target protein of AECA, in Kawasaki disease patients (KD). **Methods:** Sera samples were obtained from 30 KD and 15 healthy controls. Anti-Prx2 Abs were measured by ELISA. **Results:** We detected IgG anti-Prx2 Abs in 60% of KD, but not in healthy controls. They were detected in all the tested KD with CAL. Anti-Prx2 Abs increased especially G-CSF secretion by HCAEC. In all 7 tested KD treated by IVIG, the IgG anti-Prx2 Abs titers on the posttreatment was higher than them on pretreatment. Whereas in the IgG anti-Prx2 Abs titers/total IgG, it's the opposite. The effects of therapy with IVIG may result in increased titers of IgG anti-Prx2 Abs. **Conclusions:** IgG anti-Prx2 Abs would be a useful marker for KD.

NGW1-3

A case of JIA treated with tocilizumab after administration of infliximab

Yasuo Nakagishi, Shingo Abe, Kazuko Kasai, Mari Miyoshi
Department of Rheumatology, Hyogo Prefectural Kobe Children's Hospital, Kobe, Japan

We report a 20-year-old female patient with polyarticular juvenile idiopathic arthritis. She was diagnosed at the age of 7. She was managed in our hospital at the age of 11. After administration of prednisolone and methotrexate (MTX), but we could not control disease activity. We started Infliximab (IFX) in 2007. Her disease activity scale (DAS) 28 was 4.30 at the start of IFX. But her disease activity gradually got worse and acute infusion reactions occurred in 14th administration of IFX. We decided to switch IFX to tocilizumab (TCZ). Her DAS 28 was 3.58 at the start of TCZ. Her disease activity decreased immediately after administration of TCZ. The pa-

tient is now under the treatment of MTX only and DAS 28 is decreased to 1.74.

NGW1-4

A suspected case of polyarteritis nodosa under the treatment with TCZ for sJIA.

Hiroaki Umebayashi
Miyagi Children's Hospital

A 11-year-old boy had developed fever, leg pain, and rash in 2007. Laboratory findings showed high serum level of CRP, and autoantibodies were negative. He was diagnosed systemic on-set juvenile idiopathic arthritis and treated with steroid, MTX and cyclosporine. But he could not reduce steroid, so he consulted our hospital. We started tocilizumab in 2008, and then he was improved and reduced steroid. But he was admitted to our hospital because of subarachnoid hemorrhage in 2009. We detected multiple cerebral infarction by MRI, so we suspected polyarteritis nodosa. We performed cerebral angiography and biopsy of kidney, and then could detect renal infarction but could not detect microaneurysm. Now he has been treated with steroid and azathioprine for suspected case of polyarteritis nodosa.

NGW1-5

Expression of Fos protein after acute arthritis: using transgenic rats

Toru Ishikura^{1,2}, Hitoshi Suzuki^{1,2}, Hideo Ohnishi², Yoichi Ueta¹

¹Department of Physiology, School of Medicine, University of Occupational and Environmental Health, ²Department of Orthopedics, School of Medicine, University of Occupational and Environmental Health

The expression of the *c-fos* gene has been widely used as a marker of neuronal activity. Recently, we generated transgenic rats expressing the *c-fos* and monomeric red fluorescent protein (mRFP) fusion gene. Details are uncertain though expression pattern and kinetics of the mRFP fluorescence may be similar to those of Fos protein. Thus, we observed mRFP fluorescence and Fos protein in the spinal cord and hypothalamus after acute arthritis caused by subcutaneous (s.c.) injection of formalin or saline in both hind paws of the *c-fos*-mRFP transgenic rats and Wistar rats. Next, we tried to compare these in time course of 90 min, 3 h and 6 h after s.c. injections. This *c-fos*-mRFP transgenic rat is a useful animal to study the central response in acute arthritis model.

NGW1-6

A novel cell population with features of mesenchymal and hematopoietic lineages

Masanobu Ohishi^{1,2,3}, Hisaaki Miyahara², Yukihide Iwamoto¹, Ernestina Schipani³

¹Department of Orthopaedic Surgery, Kyushu University Graduate School of Medicine, ²Department of Orthopaedic Surgery and Rheumatology, National Hospital Organization Kyushu Medical Center, ³Endocrine unit, Massachusetts General Hospital-Harvard Medical School

By crossing a mouse line expressing constitutively active PTH/PTHrP receptor (PPR*Tg) and a mouse line expressing GFP (WT/GFP) under the control of a 2.3kb fragment of type1 collagen promoter respectively, a double mutant was generated (PPR*Tg/GFP). Confocal microscopy analysis revealed the presence of GFP(+) fibroblastoid cells that were also CD45(+) in PPR*Tg/GFP bone mar-

row (BM). Mature osteoblasts were GFP(+) but were CD45(-). Osteoclasts were GFP(-). The presence of GFP(+)CD45(+) cells in BM was confirmed by flow cytometry analysis also in WT/GFP. This population was significantly expanded in PPR*Tg/GFP BM. Majority of these cells was CD11b(+) and both native PPR and RANK were also detectable, indicating that these cells had features of both mesenchymal and hematopoietic lineages.

NGW1-7

Screening of bioactive molecules that promote induction of human tolerogenic DCs

Takuya Matsumoto, Hitoshi Hasegawa, Rai Kin, Sachiko Onishi, Koichiro Suemori, Masaki Yasukawa
Department of Bioregulatory Medicine, Ehime University Graduate School of Medicine, Ehime, Japan.

[purpose] Dendritic cells (DCs) play an important role in a pathogenesis of the autoimmune diseases such as RA. We screened the molecules which enhanced induction of human tolerogenic DCs (tDCs) from the library of the nuclear receptor ligands and the lipids. **[methods]** DCs were prepared from human monocytes by treatments of GM-CSF, IL-4 and TNF- α . We screened the molecules that suppressed the appearance of CD80, CD83 and CD86 on mature DCs. And, we examined the roles of these molecules in antigen presenting and induction of regulatory T cells (Tregs). **[results]** We screened the 14 kinds of bioactive molecules such as dexamethazone and 15dPJ2. **[conclusion]** There are some bioactive molecules that promote the induction of both human tDCs and Tregs, and its clinical application would be expected.

NGW1-8

Role of NK1.1⁺ γ δ T cells in IL-2 plus IL-18 induced interstitial lung disease

Seiji Segawa, Daisuke Goto, Masanobu Horikoshi, Isao Matsumoto, Takayuki Sumida
Graduate School of Comprehensive Human Science, University of Tsukuba

[Purpose] The purpose of this study is to clarify the involvement of NK1.1⁺ γ δ T cells in the pathogenesis of IL-2+IL-18 induced interstitial lung disease (ILD). **[Methods]** 1) The TCR repertoire of NK1.1⁺ γ δ T cells and their cytokines were examined. 2) NK cells were examined in TCR δ KO mice transferred with NK1.1⁺ γ δ T cells after injection of IL-2+IL-18. **[Results]** 1) NK1.1⁺ γ δ T cells showed polyclonal TCR repertoire and IL-18/IL-2-stimulated NK1.1⁺ γ δ T cells produced higher levels of IFN- γ than NK1.1⁻ γ δ T cells. 2) The expansion of NK cells was expanded and IFN- γ mRNA was increased in the lung by IL-2+IL-18 injection. **[Conclusion]** NK1.1⁺ γ δ T cells might play a crucial role in the generation of IL-2+IL-18 induced ILD.

NGW1-9

Effect of IL-6 on ADAMTS-4, -5 expression in RAFLS and the signaling pathway

Yoshikuni Mimata¹, Akihisa Kamataki², Shinya Oikawa^{3,4}, Kenya Murakami^{2,4}, Tadashi Shimamura⁴, Takashi Sawai²

¹Department of Orthopaedic Surgery, Iwate prefectural Kuji hospital, Kuji, Japan, ²Department of Pathology, Iwate Medical University School of Medicine, Morioka, Japan, ³Department of Orthopaedic Surgery, Hachinohe red cross hospital, Hachinohe, Japan, ⁴Depart-

ment of Orthopaedic Surgery, Iwate Medical University School of Medicine, Morioka, Japan

[Purpose] The aim of this study is to examine the effect of IL-6 on the expression of ADAMTS-4, -5 in RAFLS and the signaling pathway in this process. **[Methods]** Expression of ADAMTS-4, -5 in FLS after IL-6 stimulation was analyzed using real-time PCR. Furthermore, the effect of anti-IL-6 receptor antibody, STAT3 inhibitor parthenolide or MEK1/2 inhibitor U0126 was analyzed. **[Results]** IL-6 upregulated ADAMTS-4 and downregulated ADAMTS-5 in FLS. Anti-IL-6 receptor antibody inhibited the effect of IL-6 on ADAMTS-4, -5 expression. U0126 inhibited the effect of IL-6 on ADAMTS-4, -5 expression in FLS. Parthenolide suppressed ADAMTS-4 expression. **[Conclusions]** These results suggest IL-6 may induce ADAMTS-4 in synovium and both STAT3 and MEK1/2 signaling pathway may participate in this process.

NGW1-10

Disease activities and Th17 subset, and IL-17 expression in RA synovial tissues

Arata Nakajima¹, Koichi Nakagawa¹, Masato Sonobe¹, Yoshifumi Shibata¹, Yasuchika Aoki¹, Yu Sasaki¹, Shintaro Tsuge¹, Manabu Fujino¹, Teruo Furufu¹, Toru Suguro²

¹Department of Orthopedic Surgery, Toho University Sakura Medical Center, ²Department of Orthopedic Surgery, Toho University Omori Medical Center

[Introduction] Recently, role of Th17 and IL-17 in joint destruction has been pointed out. Using synovial tissues from RA patients, we investigated relationship between disease activities and Th17 subset, and IL-17 expression. **[Patients and Methods]** Synovial tissues from 10 joints in 10 RA patients were included in this study. Th17 cells were immunostained using an anti-CCR6 antibody then the number of CCR6⁺IL-17⁺ cells was counted. Expression of IL-17 mRNA was analyzed by real-time PCR. **[Results and Perspective]** Among all disease activities, there were no apparent differences in the percentage of CCR6⁺IL-17⁺ cells and in expression levels of IL-17 mRNA. Increasing number of cases will reveal the relationship between inflammation through the Th17-IL-17 axis and disease activities.

NGW2-1

Clinical results of total knee arthroplasty in patients with RA for young people

Yoshiyasu Miyazaki¹, Kazuaki Tsuchiya¹, Masayuki Sekiguchi¹, Hiroshi Takahashi¹, Takashi Nakamura¹, Hideyuki Aoki¹, Ayako Kubota¹, Hideko Torihata¹, Muneki Saito¹, Maki Ishii¹, Toshiyuki Tsutsui², Wataru Shishikura², Toru Suguro¹

¹Department of Orthopaedic Surgery, Toho University School of Medicine, ²Sagamihara Chou hospital

TKA is a surgical patient at our university is growing, we study cases were traceable from the knee in January 2002 was 804. Age 91-21 years, average 71.2 years. By lap 546 the OA disease (67.9%), RA 240 knees (29.9%) had other knee 18. Of these 50 patients were younger than 31 is a knee in RA and other diseases were 29 knees with the majority. Preoperative range of motion of the knee extension 804 -9.1 °, flexion 116.2 °, 182.1 ° femorotibial angle is that many in knee and under the age of 50 RA patients with the extension of -13.9 °, flexion 123.2 °, femorotibial 171.4 °. Led to the re-replacement surgery patients were not seeing results from a rela-

tively satisfactory. In some cases highly active, however, further observation is probably more vital than sensitive.

NGW2-2

Prognostic factors for surgical intervention after AVN

Ryo Hiroshima, Katsunori Ikari, Kosei Kawakami, Ikuko Masuda, Shigeki Momohara
Institute of Rheumatology, Tokyo Women's Medical University

BACKGROUND: We evaluated the prognostic value of the MRI classification in patients undergoing surgical intervention after AVN patients.

METHODS: We applied the MRI classification in 195 hips (136 patients) with AVN.

RESULTS: The results of the multivariate logistic regression analysis indicate that types C1 and C2 of the MRI classification ($P=3.3 \times 10^{-5}$) and bilateral cases ($P=0.005$) were associated with future surgical intervention after AVN.

CONCLUSIONS: Type C (C1 and C2) on the MRI classification at the time of diagnosis of AVN and bilateral AVN cases are the risks for future surgical intervention after diagnosis of AVN.

NGW2-3

Surgical Treatment for Thoracic Spinal Fractures in Ankylosing Spinal Disorder.

Yasuchika Aoki^{1,2,3}, Teruo Furufu¹, Koichi Nakagawa¹, Arata Nakajima¹, Yoshifumi Shibata¹, Manabu Fujino¹, Masato Sonobe¹, Toru Suguro⁴

¹Toho University Sakura Medical Center, ²Chiba Rosai Hospital, ³Graduate School of Medicine, Chiba University, ⁴Toho University Omori Medical Center

Ankylosing spinal disorder (ASD) is at high risk for complications such as spinal cord injury and pseudoarthrosis. We report 3 patients with thoracic spine fracture in ASD: case 1, T9-T10; case 2, T11; case 3, T12. In cases 1 and 2, fractured spine was completely ankylosing as bamboo-like, and had severe back pain. In the patients, posterior spinal fusion was performed with 3-above 3-below way. In case 3, fractured spine was hyperostotic but bamboo-like, had moderate back pain and can sit in a wheel chair. In the patient, decompression without spinal fusion was performed. Surgical results are favorable in all patients, suggesting a possibility that spinal fusion could be avoided in some cases, however, long posterior fusion is the safer way to treat patients with significant instability.

NGW2-4

Rate of collapse and surgery in steroid-associated osteonecrosis

Tomonori Shigemura¹, Junichi Nakamura¹, Yoshitada Harada², Koh Shimizu³, Satoshi Iida⁵, Koya Kamikawa⁷, Munenori Takeshita¹, Masahiko Suzuki⁸

¹Department of Orthopaedic Surgery, Graduate school of Medicine, Chiba University, Chiba, Japan, ²Chibaken Saiseikai Narashino Hospital, Narashino, Japan, ³Chiba Rosai Hospital, Ichihara, Japan, ⁴Chiba Kaihin Municipal Hospital, Chiba, Japan, ⁵Matsudo City Hospital, Matsudo, Japan, ⁶Funabashi Orthopaedic Hospital, Funabashi, Japan, ⁷Teikyo University Chiba Medical Center, Ichihara, Japan, ⁸Chiba University Research Center for Frontier Medical Engineering

Objective: To clarify the rate of collapse and surgery in steroid-associated osteonecrosis of the femoral head and the knee with MRI prospective study. **Methods:** We prospectively performed MRI screening of bilateral hip and knee in 1239 joints 312 collagen dis-

ease patients at initial corticosteroid therapy. Rate of osteonecrosis was 30% (370 joints). We compared the rate of collapse and surgery with 191 osteonecrosis of the femoral head and 179 osteonecrosis of the knee, using Kaplan-Meier test. Results: Rate of collapse was significantly higher in the femoral head than in the knee (43% versus 6%, 10-year cumulative rate). Rate of surgery was significantly higher in the femoral head than in the knee joint (78% versus 31%, 10-year cumulative rate).

NGW2-5

Mid-term results of cementless TKA in RA - A comparison of a X ray in RA and OA

Chikara Miyamoto¹, Kouhei Kamito¹, Makoto Osaki¹, Toshiyuki Tsurumoto², Tomoko Matsumoto³, Hiroyuki Shindo¹

¹Department of Orthopaedic Surgery, Nagasaki University School of Medicine, Nagasaki, Japan, ²Department of Anatomy, Nagasaki University School of Medicine, Nagasaki, Japan, ³Ajisai clinic

OBJECTIVE: To report the medium term outcomes of cementless TKA in treatment of RA. **METHODS:** A total of 16 cementless TKAs were performed in 13 patients (1 man, 12 women) with RA. An average age was 64.6 years (41 to 79) at the time of operation. An average disease course was 16 years (1 to 31). All had Larsen grade 3 (8 knees) or 4 (8 knees) rheumatoid changes on X-ray. The mean follow-up was 5.3 years (3 to 9.6). Additionally, we compared radiographic outcomes to 13 knees (11 patients) with OA. **RESULTS:** In OA, clear zone occurred in 1 case, sinking occurred 4 cases. In RA, on the contrary, clear zone and sinking didn't occur. **CONCLUSION:** In treatment of RA with mild osteoarthritic changes and a good bony substance, we don't think cementless TKA would be a bad choice.

NGW2-6

Expression of DGK ζ and TLR4, 9 in aseptic periprosthetic loosening/osteolysis

Yasunobu Tamaki¹, Tomoyuki Hirayama¹, Yuya Takakubo^{1,2}, Hiroshi Hasegawa¹, Kan Sasaki¹, Akiko Sasaki¹, Suran Yang¹, Kiyoshi Iwazaki¹, Masaji Ishii³, Toshihiko Ogino¹, Michiaki Takagi¹

¹Department of Orthopaedic Surgery, Yamagata University School of Medicine, ²Institute of Biomedicine, Department of Anatomy, University of Helsinki, Helsinki, Finland, ³Department of Orthopaedic Surgery, Saiseikai Yamagata Saisei Hospital

【Introduction】 This study was designed to evaluate expression of diacylglycerol kinase ζ (DGK ζ) and toll-like receptor (TLR) 4, 9 in granuomatous interfacial membrane of loose hip joint. **【Methods】** Interfacial membranes around loosened total hip prosthesis of six cases were stained with double-immunofluorescent method with CD68, DGK ζ and TLR4, 9. **【Results】** Focal localization of CD68-positive macrophages were detected. Immunoreactivities of CD68 were co-localized with DGK ζ , and TLR4, 9. **【Discussion】** In periprosthetic osteolysis due to particle wear from implant, macrophages play a critical role of its pathogenesis. DGK ζ , innate immune system TLRs may contribute to inflammatory reaction leading to periprosthetic osteolysis.

NGW2-7

Histological assessment of cruciate ligament in RA treated with biologics

Ken Kumagai, Yutaka Inaba, Akiko Nagaoka, Yuichiro Yamaguchi, Kosuke Matsuo, Tomoyuki Saito

Cruciate ligaments were obtained from rheumatoid arthritis patients treated with or without biological therapy during surgery of total knee arthroplasty. Cell migration, blood vessel formation and disruption were histologically assessed in ACL and PCL. Biological therapy group exhibited significant decrease in cell migration and blood vessel formation. There was no significant differences in disruption between biological therapy group and non biological therapy group. This study suggested biological therapy inhibits inflammation of cruciate ligament in patient with rheumatoid arthritis.

NGW2-8

Down regulation of TLR4 expression of macrophage after LPS/particle stimulation

Tomoyuki Hirayama, Michiaki Takagi, Yasunobu Tamaki, Yuya Takakubo, Toshihiko Ogino

Department of Orthopaedic Surgery, Yamagata University School of Medicine, Yamagata, Japan

Background: Macrophages can phagocytose wear debris from prosthetic implants. It is recognized that adherent LPS of wear particles stimulate macrophages activation via TLR4. However the precise mechanism is still unclear.

Methods: We analyzed mRNA and protein levels of cytokines, TLR4 and adaptor molecules expression of macrophages derived from bone marrow after titanium particle stimulation with or without LPS.

Results: LPS-adhered particles induced elevated production of TNF- α and IL-1 β . However, mRNA level of TLR4, MyD88, IRAK1 and IRAK4 expressions and protein levels of TLR4 and IRAK4 tended to decrease.

Discussion: Macrophages after LPS-coated particle stimulation might equip preventative mechanism to regulate harmful host responses and injury to innocent bystander cells/tissues.

NGW2-9

Wear debris-driven osteolysis in Diacylglycerol kinase ζ (DGK ζ) deficient mice

Kiyoshi Iwazaki^{1,2}, Michiaki Takagi¹, Yasunobu Tamaki¹, Toshihiko Ogino¹

¹Department of Orthopaedic Surgery, Yamagata University School of Medicine, Yamagata, Japan, ²Department of Anatomy and Cell Biology, Yamagata University School of Medicine, Yamagata, Japan

[Objective]

Diacylglycerol kinase (DGK) consists of a family of isozymes that convert a second messenger diacylglycerol to phosphatidic acid, and some isoforms are shown to be identified in macrophages. In the present study, we examined whether DGK ζ is involved in osteolytic process in vivo using DGK ζ -KO mice.

[Method]

We employed a mouse calvaria osteolysis model of Merkel. In brief, PMMA particles are put onto the calvaria, which is extracted after 1 week. Then TRAP staining is performed on sagittal sections of the calvaria and the areas of bone absorption were calculated.

[Result]

In DGK ζ -KO mice osteolysis is accelerated 50% compared with wild type mice. Many osteoclasts are seen in sections of DGK ζ -KO mice.

[Conclusion]

DGK ζ may serve as a negative regulator of osteolysis.

NGW2-10

Histological analysis of synovium of rheumatoid arthritis with biologics

Yuichiro Yamaguchi, Yutaka Inaba, Akiko Nagaoka, Ken Kumagai, Kosuke Matsuo, Tomoyuki Saito

Department of orthopaedic surgery, Yokohama-city university, Yokohama, Kanagawa, Japan

Objective: We evaluated histological features of synovium in rheumatoid arthritis patients treated with biologics. Materials and methods: Twenty-two patients were included in this study and divided into two groups. Thirteen patients treated with biological drugs (biologics group) were compared with 9 patients treated with non-biological drugs (non-biologics group). In biologics group, etanercept, infliximab and tocilizumab were administered to 7, 3 and 3 patients respectively. Synovium were obtained during surgeries and assessed using scoring system by Rooney. Results: The scores in biologics group were significantly lower than those in non-biologics group. Conclusion: The data suggested that biologics have suppressive effects on inflammation in synovium of rheumatoid arthritis patients.

NGW3-1

The cytokine effect for introduction of anti U1RNP Ab into cells.

Tatsuki Okuyama¹, Koichiro Komai¹, Yuka Kosugi¹, Kazuko Shiozawa², Akira Hashimoto^{1,3}, Shunichi Shiozawa^{1,3}

¹Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan, ²Rheumatic Diseases Center, Konan Kakogawa Hosp., Kakogawa, Japan, ³Department of Medicine, Kobe University Graduate School of Medicine, Kobe, Japan/ The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

OBJECTIVE: We found that Angiopoietin-1 splice variant (*Ang-1/ins*) was induced in the serum of the patients with MCTD. We also found that *Ang-1/ins* is induced with TNF α and IL-6 when anti U1RNP Ab is introduced into Human Pulmonary Artery Smooth Muscle Cells (HPASMC). Here we examined the cytokine effect for introduction of Ab into HPASMC.

METHODS: Anti-U1A, U1C, and U1-70K antibodies were labeled using Alexa Fluor 488 and introduced into HPASMC using protein delivery reagent and cultivated with TNF α and IL-6. We determined the rate of Ab introduction using FACS.

RESULTS: Abs were introduced into cells equally with or without cytokine.

CONCLUSION: It is suggested that the induction of *Ang-1/ins* with anti U1RNP Ab *via* cytokine is not due to the enhancement of Ab uptake.

NGW3-2

Atorvastatin ameliorates the pro-fibrotic effects of TGF- β in systemic sclerosis

Yuko Ota, Yasushi Kawaguchi, Manabu Kawamoto, Kae Takagi, Akiko Tochimoto, Yasuhiro Katsumata, Takahisa Gono, Chikako Fukazawa, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University

Objectives. Atorvastatin was reported to be beneficial in treating vascular involvements of SSc. The aim of this study was to investi-

gate the antifibrotic effect of atorvastatin on skin fibroblasts of patients with SSc. *Methods.* Skin fibroblasts derived from 4 patients with SSc were incubated with TGF- β and various concentrations of atorvastatin. After fibroblasts were cultured for 24, 48, and 72 hours, the supernatants were collected. Procollagen type I was measured using a commercial ELISA kit. *Results.* In the supernatants of cultured fibroblasts with atorvastatin, procollagen type I production was significantly suppressed. *Conclusions.* Our results suggest atorvastatin ameliorated the pro-fibrotic effects with TGF- β in skin fibroblasts and might be a target for antifibrotic therapies.

NGW3-3

Evaluation of Kim-1 in patients of lupus nephritis

Kazuya Kishimoto, Shoichi Hino, Tomohiro Yano, Yasuaki Nagare, Hideki Shimazu, Yuji Nozaki, Masafumi Sugiyama, Shinya Ikoma, Shigeo Irimajiri, Koji Kinoshita, Masanori Funauchi
Department of Nephrology and Rheumatology, Kinki University School of Medicine, Osaka-Sayama, Osaka, Japan

Kim-1 is featured for urinary biomarker of early acute kidney injury. To evaluate the impact of Kim-1 in patients of lupus nephritis, we investigated the Kim-1 expression in these patients. We studied 15 cases lupus nephritis patients and other kidney disease patients. We investigated GFR, BUN, serum creatinine, proteinuria, urinary NAG and SLEDAI in these patients. We also performed the immunohistochemistry of Kim-1, CD3 and macrophage in the kidney, and determined urinary Kim-1 with ELISA. The expressions of Kim-1 in renal tubules and urine in patients with lupus nephritis were increased. Furthermore, the level of Kim-1 expression in them was correlated with the activity of lupus nephritis. The urinary Kim-1 expression might become one of the criteria of therapeutic effect.

NGW3-4

Prevalence of serum autoantibodies to KIR in patients with collagen diseases

Yasuo Nagafuchi¹, Hideaki Kawada², Yuko Takahashi¹, Rika Kuwabara¹, Yukihito Ishizaka², Akio Mimori¹

¹Division of Rheumatic Diseases, National Center for Global Health and Medicine, Tokyo, Japan, ²Department of Intractable Diseases, Research Institute, National Center for Global Health and Medicine

Backgrounds: We found autoantibodies to killer cell immunoglobulin-like receptor (KIR)-3DL1 (a subtype different from those reported by Matsui et al. 2001) in patients with rheumatic disease, and their prevalence was further examined. **Methods:** Recombinant KIR-3DL1 was prepared for use as an ELISA antigen. The baseline ELISA score was determined using serum from 28 healthy subjects. **Results:** Positive ELISA scores were obtained in 31/34 (91%) patients with SLE, 6/6 (100%) with myositis, and 1/7 with SSc. One SSc patient with a positive result had lethal pulmonary arterial hypertension, whereas in the remaining 6 SSc patients, the disease was inactive. **Conclusion:** The clinical significance of autoantibodies to KIR-3DL1 across different disease entities merits further study.

NGW3-5

Abnormal expressions of immune response-related genes in RA bone marrow cells

Hooi-Ming Lee¹, Hidehiko Sugino¹, Chieko Aoki², Yasunori Shimaoka³, Kensuke Ochi⁴, Takahiro Ochi⁵, Norihiro Nishimoto^{1,2}

¹Graduate School of Frontier Biosciences, Osaka University, Osaka, Japan, ²Laboratory of Immune Regulation, Wakayama Medical Uni-

versity, Wakayama, Japan, ³Yukioka Hospital, Osaka, Japan, ⁴Kawasaki Hospital, Kawasaki, Japan, ⁵Osaka Police Hospital, Osaka, Japan

Abnormalities in bone marrow (BM) are reported contributing to rheumatoid arthritis (RA) pathogenesis. Gene expression profiles (GEPs) of BM mononuclear cells were therefore compared between 9 RA and 10 osteoarthritis patients by using DNA microarray followed by bioinformatics analysis. Upregulated genes over-represented the functional abnormalities in immune response which mainly included interferon inducible genes and MHC class I genes (HLA-C, HLA-E, HLA-F, and HLA-G). Network pathway analysis showed that these genes were highly relevant to antigen presentation pathway and interferon signaling. However, these immunological abnormalities were not found in the peripheral blood cells of RA. Our results suggest that activation of immune response in BM is involved in RA pathogenesis.

NGW3-6

Identification of anti citrullinated GPI peptide antibodies in patients with RA

Naoto Umeda, Isao Matsumoto, Yoko Tanaka, Asuka Inoue, Kayo Yamamoto, Yuki Tanaka, Shinya Hagiwara, Tomoya Hirota, Yuya Kondo, Masanobu Horikoshi, Hiroto Tsuboi, Makoto Sugihara, Hiroshi Ogishima, Takeshi Suzuki, Taichi Hayashi, Takayuki Sumida

Division of Clinical Immunology, Major of Advanced Biochemical Applications, Graduate School of Comprehensive Human Science, University of Tsukuba, Tsukuba, Japan

Objective: To identify anti-citrullinated (Cit) GPI Abs in patients with RA. **Methods:** 1) Abs against GPI proteins in serum with RA and healthy subjects were measured by ELISA. 2) We selected peptides bearing Arginine in GPI protein and constructed Cit and circulated peptides (CCG). AutoAbs against these peptides were evaluated by ELISA. 3) Anti-CEP-1 and CCP Abs were also screened and compared with anti-CCG. **Results:** 1) The positivity of anti-GPI Abs in RA was 13.8%. 2) The positivity of anti-CCGs in RA was 40.3% (specificity 95.4%). 3) The positivity of anti-CEP and anti-CCP were 46.9%, 86.2%, respectively. Anti-CCG was correlated with anti-CEP-1 and anti-CCP Abs. **Conclusion:** We identified anti-CCG Abs in patients with RA. Further examination will be necessary to clarify the role of anti-CCG Abs in RA.

NGW3-7

Histone methylation is associated with MMPs gene expressions in RA synoviocytes

Yasuto Araki¹, Kazuhiro Yokota¹, Fumihiko Miyoshi¹, Kojiro Sato¹, Yoon Taek Kim², Hiromi Oda², Toshihide Mimura¹

¹Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University, Saitama, Japan, ²Department of Orthopaedic Surgery, Faculty of Medicine, Saitama Medical University, Saitama, Japan

Rheumatoid arthritis (RA) is a chronic inflammatory synovitis by autoimmune mechanisms. RA synovial fibroblasts (RASFs) proliferate aberrantly and produce inflammatory mediators and matrix-degrading enzymes. Recently epigenetic mechanisms are considered to be important regulators in gene transcriptions. We hypothesized that epigenetic abnormalities might cause pathological activation of RASFs. We found that histone methylation was higher in some of matrix metalloproteases (MMPs) gene in RASFs than in osteoarthritis.

tis (OA) SFs whereas histone acetylation was comparable in RASFs and OASFs. MMPs gene expressions were higher at rest and after TNF α or IL-1 β stimulation in RASFs than in OASFs. These results suggest that elevated histone methylation is related to MMPs gene expressions in RASFs.

NGW3-8

TNF α modulates the expression of circadian clock genes in RA synovial cells

Kohsuke Yoshida¹, Akira Hashiramoto^{2,3}, Nao Shibamura^{3,4}, Kazuko Shiozawa⁵, Shunichi Shiozawa^{1,2,3}

¹Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan, ²Department of Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, ³The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan, ⁴Department of Orthopaedic Surgery, Kobe Kaisei Hospital, Kobe, Japan, ⁵Rheumatic Diseases Center, Konan Kakogawa Hospital, Kakogawa, Japan

Objective: We previously showed that the expression of circadian clock gene was disturbed in the synovium of experimental arthritis in mice, and circadian clock gene *Cry* and TNF α regulated their expressions each other. In this study, we examined the effect of TNF α on the expression of clock genes in primary cultured human rheumatoid synovial cells.

Methods: Total RNA was extracted from TNF α -stimulated synovial cells to analyze quantitative expression of clock genes (*Bmal1*, *Clock*, *Per1/2*, *Cry1/2*, *Dbp*) by real-time PCR.

Results: TNF α significantly enhanced the expression of *Cry1*, *Bmal1* mRNA and inhibited those of *Per2*, *Dbp* in synovial cells ($P < 0.05$).

Conclusion: TNF α can contribute to the pathogenesis of RA by modulating the expression of circadian clock genes in synovial cells.

NGW3-9

Critical role of T_{FH} in antinuclear antibody production during lymphopenia

Takeyuki Kanzaki¹, Kimito Kawahata¹, Mitsuru Imamura^{1,2}, Risa Akahira¹, Kazuya Michishita¹, Makoto Dohi¹, Kazuhiko Yamamoto¹

¹Department of Allergy and Rheumatology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan, ²Division for Health Service Promotion, University of Tokyo, Tokyo, Japan

Lymphopenic mouse transfer model is a well known model for autoimmune diseases, in which various autoantibodies are observed in T-cell-deficient recipients injected with regulatory T cells (T_{reg})-depleted CD4⁺ T cells. Using this mouse model, we investigated the mechanisms of antinuclear autoantibody production. As a result, we elucidated the development of IL-21-producing T follicular-helper cells (T_{FH}) characterized as PD-1⁺CXCR5⁺CD4⁺T cells under lymphopenic conditions. In recipients with injection of CD4⁺ T cells including T_{reg}, the numbers of CXCR5⁺T_{FH} and titers of autoantibodies were reduced. These results suggest that T_{reg} maintain B-cell tolerance and inhibit autoantibody production in T-cell homeostasis by preventing lymphopenia-induced CXCR5⁺T_{FH} development.

Basic Science

BS1-1

Analysis of CD4⁺CD25⁺LAG3⁺ regulatory T cells in NZB/W F₁ lupus model mice

Akiko Okamoto, Keishi Fujio, Tomohisa Okamura, Kazuhiko Yamamoto

Department of Allergy and Rheumatology, Graduate School of Medicine, the University of Tokyo

We have previously identified a novel regulatory T cell subset, CD4⁺CD25⁺LAG3⁺ Treg (LAG3⁺ Treg), in mice. LAG3⁺ Tregs exhibit suppressive activity, anergic phenotype, and IL-10 production capacity. LAG-3 and IL-10 expression levels in LAG3⁺ Treg are regulated by a transcription factor Egr2. T cell-specific Egr2 deficient mice exhibit lupus-like disease. In this study, we examined the role of LAG3⁺ Treg in lupus-prone mice. The frequencies of LAG3⁺ Treg were decreased in the spleens of young NZB/W F₁ mice and NZW mice (the parental strain), compared to C57BL/6(B6) mice. The gene expression levels of Egr2, LAG3 and IL-10 in LAG3⁺ Treg were similar between B6 and NZB/W F₁ mice. Our results suggest that the number of LAG3⁺ Treg is genetically determined in lupus-prone mice.

BS1-2

The role and source of IL-17 in antibody-induced arthritis

Masaki Katayama, Koichiro Ohmura, Chikashi Terao, Naoichiro Yukawa, Hajime Yoshifuji, Daisuke Kawabata, Takao Fujii, Tsuneyo Mimori

Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

IL-17 producing T cells have important roles in a number of mouse models for rheumatoid arthritis, but it was not known how IL-17 works in the effector phase of arthritis. Now, when K/BxN serum-induced arthritis, which is useful to analyze this phase, was introduced in IL-17 knock out (KO) mice, arthritis was significantly suppressed in comparison with that in the wild type mice. K/BxN serum-induced arthritis exacerbated when IL-17^{+/+} neutrophils, but not CD4⁺ T cells or IL-17^{-/-} neutrophils, were injected into IL-17 KO mice at day0 and day2. Moreover, in vitro experiments, neutrophils secreted IL-17 by stimulating with immune complex (IC). In summary, IL-17 has a proinflammatory role even in the arthritis effector phase and neutrophil stimulated by IC is a major source of IL-17.

BS1-3

Prophylactic and therapeutic effects of anti-IL-17 antibody on the animal model of ankylosis

Shin Ebihara, Masao Ono

Department of Pathology, Tohoku University Graduate School of Medicine, Sendai, Japan

Objective: The aim of this study is evaluation of anti-IL-17 therapy on a spontaneous ankylosing arthropathy previously characterized in mice. **Methods:** The onset of ankylosis in DBA/1 mice was assessed by gross findings of foot joint swelling and partly histopathological examination. IL-17 concentration and Th17 were determined by ELISA and intracellular staining, respectively. Anti-IL-17 antibody was administered to male DBA/1 mice since before or after the ankylosis onset. Pathology and various mRNA were analyzed for joints and skins at the end point. **Results:** Circulating IL-17 and Th17 in draining lymph nodes were increased with aging. These

mice developed psoriasis-like dermatitis with ankylosis. Prophylactic administration of anti-IL-17 antibody dramatically inhibited the development of ankylosis and dermatitis, while therapeutic administration effected on the joint manifestation. Conclusion: These results indicated that IL-17 is new therapeutic target of ankylosis and psoriasis.

BS1-4

TIARP regulates autoimmune arthritis via suppression of inflammatory cytokines.

Asuka Inoue^{1,2}, Isao Matsumoto¹, Yoko Tanaka¹, Naoto Umeda¹, Yuki Tanaka¹, Takayuki Sumida¹

¹Division of Clinical Immunology, Doctoral Program in Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, ²JSPS Research Fellow

[Objective] To explore the role of TIARP in experimental autoimmune arthritis.

[Methods] 1) TIARP^{-/-} mice in B6 background were generated, and were immunized with 200µg type II collagen (C II) on day0, 21. The severity of arthritis was monitored.

2) C II-specific T cell response and autoantibodies were assessed.

3) The expression of inflammatory cytokines in serum and joints on day60 were examined.

[Results] 1) The severity of arthritis in TIARP^{-/-} mice was higher than that in WT.

2) C II-specific T cell responses and anti-C II Abs in TIARP^{-/-} were comparable with those in WT.

3) Serum IL-6 and TNFα, IL-6 mRNA expression in joints were significantly increased in TIARP^{-/-} compared with WT.

[Conclusion] TIARP should be a negative regulator against autoimmune arthritis via suppression of inflammatory cytokines.

BS1-5

Similarity of bone marrow abnormalities in RA patients and DNaseII KO mice

Masashi Wada¹, Hooi-Ming Lee², Chieko Aoki¹, Hidehiko Sugino², Miho Murakami¹, Takaji Matsutani¹, Takahiro Ochi⁴, Norihiro Nishimoto^{1,2}

¹Laboratory of Immune Regulation, Wakayama Medical University,

²Graduate School of Frontier Biosciences, Osaka University, ³Graduate School of Medicine, Kyoto University, ⁴Osaka Police Hospital

Abnormalities in bone marrow (BM) play important roles in the pathogenesis of RA. Meanwhile, DNase II KO mice develop a polyarthritis that resembles RA. In BM of the mice, activated macrophages which carry undigested DNA were observed. In this study, using DNA chip analysis, we compare the gene expression profiles (GEPs) of BMs between RA patients and DNase II KO mice to know whether there are similar functional abnormalities in BM.

GEPs of BM from DNase II KO mice showed that IFN-stimulated genes and antigen presenting genes including MHC class I genes were up-regulated, indicating acceleration of immune response. These immunological abnormalities are similar to those of RA patients.

These results show that immunological abnormalities in BM may contribute to the development of arthritis.

BS2-1

Reduced TLR- and IC-induced cytokine production by DC from IRF5^{-/-} MRL/lpr mice

Yoshifumi Tada¹, Seiji Kondo², Syuichi Koarada¹, Hisako Inoue¹, Rie Suematsu¹, Sachiko Soejima¹, Akihide Ohta³, Kohei Nagasawa¹

¹Department of Rheumatology, Faculty of Medicine, Saga University, ²Department of Hematology, Saga Prefectural Hospital Koseikan,

³Department of Clinical Nursing, Faculty of Medicine, Saga University

It has been shown that polymorphisms of IRF5, a transcription factor, are associated with increased or decreased risk of SLE. We have demonstrated that IRF5^{-/-}MRL/lpr mice survive longer, and display very mild glomerulonephritis and reduced levels of autoantibodies. We evaluated the activation of splenic DCs by TLR ligands and immune complexes (ICs). DCs from IRF5-deficient MRL/lpr mice produced reduced levels of inflammatory cytokines in response to TLR7 and TLR9 ligands and ICs purified from MRL/lpr mice sera. IFNα production in response to CpG was also decreased. IRF5 siRNA showed reduction of TNFα production from DCs induced by CpG. These data suggest that IRF5 promote TLR7- and TLR9-induced cell activation that leads to enhanced inflammation in MRL/lpr mice.

BS2-2

Analysis of the development of rheumatoid arthritis in mice model.

Tomohisa Nakamura, Taketoshi Kushida, Naofumi Okamoto
Department of orthopaedic surgery, Kansai Medical University, Osaka, Japan

Purpose: In this study, we examined whether bone marrow cells (BMCs) from SKG/Jcl (SKG) mice, which spontaneously develop arthritis, were able to cause autoimmune arthritis in normal mice.

Methods: BMC(3×10⁷/30µl) from SKG mice were transplanted into C57BL/6 (B6) mice[S→B]. We evaluated arthritis score, cell surface antigens, pathology of ankle joint, and cytokines in sera. **Results:** In [S→B] mice, BMCs, spleen cells, and lymphocytes were replaced donor-derived cells. The arthritis score was gradually increased 4 weeks after treatment. Furthermore, arthritis in the ankles was detected. TNF-α level in sera was significantly increased in comparison with normal levels. **Conclusion:** We suggested that BMCs in SKG mice might cause arthritis in normal mice.

BS2-3

Overexpression of RORγt inhibited collagen induced arthritis (CIA)

Zhaojin Yao¹, Masahiro Tahara¹, Yuya Kondo¹, Satoru Takahashi², Isao Matsumoto¹, Takayuki Sumida¹

¹Division of Clinical Immunology, Major of Advanced Biochemical Applications, Graduate School of Comprehensive Human Science, University of Tsukuba, Tsukuba, Japan, ²Department of Anatomy and Embryology, Biomolecular, and Integrated Medical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan

[Purpose] To clarify the effect of RORγt overexpression on CIA **[Methods]** 1) CIA was induced in C57BL/6 mice (WT) and RORγt transgenic (RORγt Tg) mice. The incidence and severity of arthritis was assessed. 2) 10 days after the first immunization, single-cell suspension from Lymph nodes was cultured. Cytokine production was analyzed by FACS and ELISA. 3) 56 days after the first immuniza-

tion, sera were collected, and titer of anti CII antibodies was measured by ELISA. [Results]1) The incidence and severity of arthritis was suppressed in ROR γ t Tg mice.2) IL-17 levels were significantly increased in ROR γ t Tg mice. 3) anti-CII antibodies are decreased in ROR γ t Tg mice. [Conclusion] Lower levels of antigen specific IgG production is one of factors for suppressing of CIA in ROR γ t Tg mice.

BS2-4

EBVInfected Humanized NOG Mouse Model For Experimental Erosive Arthritis.

Yoshikazu Kuwana¹, Masami Takei¹, Hirotake Inomata¹, Masaaki Shiozaki¹, Natsumi Ikumi¹, Takamasa Nozaki¹, Hidetaka Shiraiwa¹, Noboru Kitamura¹, Shigemasa Sawada¹, Hiroyuki Masuda¹

¹Department of Hematology and Rheumatology, Nihon University School of Medicine, Tokyo, Japan, ²Department of Microbiology, Yong Loo Lin School of medicine, National University of Singapore, Singapore, ³Department of Infectious Diseases, National Research Institute for Child Health and Development, Tokyo, Japan, ⁴Department of virology, Division of Medical Science, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan, ⁵Central Institute for Experimental Animals, Kawasaki, Japan

Whether EBV infection could result in erosive arthritis in humanized NOD/Shi-*scid*/IL-2R^{null} (NOG) mice was examined. Human CD34⁺ cells from cord blood (1x10⁴-1.2x10⁵ cells) were injected intravenously into 6–10-week-old, female, NOG mice. The NOG mice were inoculated intravenously through the tail vein with EBV (10⁰-10³TD₅₀) after transplantation. One to 12 months after being inoculated with EBV, their joints were examined pathologically. The joint tissues of the mice revealed pannus invading bone tissue, synovial membrane proliferation and CD4 T cells infiltrating the bone marrow (BM) space. Migration of multinuclear giant cells like osteoclasts, was evident in the pannus. The results of this study suggest that EBV-inoculated NOG mice develop erosive arthritis and BM edema that resemble RA.

BS2-5

Egr-3 promotes inhibitory cytokine production and induces regulatory activity

Shuji Sumitomo, Keishi Fujio, Tomohisa Okamura, Hirofumi Shoda, Mihoko Shibuya, Akiko Okamoto, Kazuhiko Yamamoto
Department of Allergy and Rheumatology, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan

Egr-3 is a transcription factor reported to inhibit T cell proliferation. According to the analysis we have done in mice, Egr-3 induced the production of an important inhibitory cytokine; IL-10 and TGF- β 1. Egr-3 inhibited antigen specific delayed type hypersensitivity (DTH). In addition, Egr-3 inhibited collagen-induced arthritis (CIA). Moreover, we identified T cell population expressing Egr-3 and TGF- β 1 in human tonsil. We announce the result of the analysis of this T cell population.

BS3-1

Splicing regulatory proteins bind to intron 5 in a mutant human DR3 gene.

Masaru Mizuhara¹, Akira Hashiramoto^{1,2,3}, Kohsuke Yoshida¹, Shunichi Shiozawa^{1,2,3}

¹Department of Biophysics, Kobe University Graduate School of Health sciences, Kobe, Japan., ²Department of Medicine, Kobe Uni-

versity Graduate School of Medicine, Kobe, Japan., ³The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan.

OBJECTIVE: We previously showed that the mutant DR3 (*mtDR3*) gene which predisposes Japanese to RA contains four SNPs and one 14-nucleotide deletion within exon 5 and intron 5 and generates a truncated DR3 gene product. The aim of this study is to identify the intron 5 pre-mRNA binding proteins in *mtDR3* gene.

METHODS: *Mt DR3* intron 5 pre-mRNA binding proteins were collected using magnetic beads, separated by SDS-PAGE and analysed by silver staining, mass spectrometry (nanoLC-MS/MS) and western blotting.

RESULTS: Mt DR3 pre-mRNA binding proteins were identified as SFPQ, hnRNP L and NONO, which are classified as splicing regulatory proteins.

CONCLUSION: We have identified SFPQ, hnRNP L and NONO, that specifically bound to the intron 5 *mt DR3* to generate a truncated DR3 gene product.

BS3-2

DcR3 inhibits cytokine-induced synovial cell proliferation by binding on TL1A.

Masayasu Takahashi¹, Yasushi Miura^{1,2}, Koji Fukuda¹, Shinya Hayashi¹, Koji Tateishi³, Masahiro Kurosaka¹

¹Department of Orthopaedic Surgery, Kobe Univ. Graduate School of Med, Kobe, Japan, ²Department of Rehabilitation Science, Kobe Univ. Graduate School of Health Sciences, Kobe, Japan, ³Department of Orthopaedic Surgery, Konan Kakogawa Hospital, Kakogawa, Japan

Objective: DcR3 protects the rheumatoid synovial fibroblasts (RA-FLS) from Fas-induced apoptosis. In the study, we analyzed the effects of DcR3 as a ligand on RA-FLS. **Material and Method:** RA-FLS were incubated with DcR3-Fc, TNF α , or IL-1 β , and anti-TL1A Ab. Proliferation rates, mRNA expression of DcR3-specific ligands, and MAPK activation were investigated. **Result:** DcR3-Fc inhibited the proliferation induced by TNF- α or IL-1 β . TL1A mRNA was predominantly expressed among the ligands. p38MAPK and ERK signalling were activated by DcR3-Fc and the activation was negated by anti-TL1A Ab. **Discussion:** Not only by inhibiting Fas-induced apoptosis as a decoy receptor, but also by inhibiting cytokine-induced proliferation directly via TL1A as a ligand, DcR3 plays an important role for proliferation.

BS3-3

Analysis for the expression of TL1A and DcR3 in rheumatoid synovial fibroblasts.

Koji Fukuda¹, Yasushi Miura^{1,2}, Masayasu Takahashi¹, Shinya Hayashi¹, Koji Tateishi³, Masahiro Kurosaka¹

¹Department of Orthopaedic Surgery, Kobe Univ. Graduate School of Med, Kobe, Japan, ²Department of Rehabilitation Sciences, Kobe Univ. Graduate School of Health Sciences, Kobe, Japan, ³Department of Orthopaedic Surgery, Konan Kakogawa Hospital, Hyogo, Japan

Objective: TL1A binds both death receptor 3 (DR3) and decoy receptor 3 (DcR3), however mostly induces inflammation by binding DR3 and contributes to the pathogenesis of autoimmune diseases. Meanwhile, we previously reported that DcR3 overexpressed in rheumatoid synovial fibroblast (RA -FLS) stimulated with TNF α inhibits Fas-induced apoptosis. In the present study, we analyzed the relative expression of TL1A, DcR3, and DR3 in RA-FLS stimulated

with TNF α .

Material and Methods: RA-FLS incubated with TNF α for 24h and the relative expression levels of mRNA of TL1A, DcR3 and DR3 in RA-FLS were quantified by real-time PCR.

Result: TL1A and DcR3 mRNA were increased by TNF α , while DR3 was not.

Discussion: TL1A and DcR3 are increased by inflammatory cytokines and may affect the pathogenesis of RA.

BS3-4

Endosomal antigen trafficking in cross-presentation causing lupus tissue injury

Mai Takimoto¹, Ken Tsumiyama¹, Shunichi Shiozawa^{1,2,3}

¹Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan, ²Department of Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, ³The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

Objective: We examined the manner of antigen cross-presentation in dendritic cell (DC) to generate the fully matured CD8⁺ T cells which cause autoimmune tissue injuries.

Methods: The bone marrow-derived DC was cultured with fluorescence-labeled ovalbumin (OVA). Endosomal marker EEA1, endoplasmic reticulum (ER) marker calnexin and Sec61, which is known as a translocon, were detected by using immunofluorescent staining. Localization of them was examined under confocal microscopy.

Results: OVA was co-localized with EEA1 and Sec61. However, OVA was never co-localized with calnexin.

Conclusion: Endosomal pathway, bypassing ER, is important in antigen cross-presentation. Further, the export of antigen from endosome to cytoplasm *via* Sec61 could be the first step in antigen cross-presentation.

BS4-1

Inhibition of mast cell activation leads to the suppression of arthritis.

Asako Chiba¹, Sachiko Miyake¹

¹National Institute of Neuroscience, National Centre of Neurology and Psychiatry, ²Neurogenomiks Laboratory, Universidad Del País Vasco (UPV/EHU), Parque Tecnológico de Bizkaia, ³IKERBASQUE, Basque Foundation for Science

We demonstrate that a trifluoromethyl analogue of celecoxib (TFM-C), with 205-fold lower COX-2-inhibitory activity exhibits a suppressive effect on autoimmune diseases in animal models. We show that TFM-C possesses a strong inhibitory effect on collagen-induced arthritis and antibody-induced arthritis. However, celecoxib has little effect in these models. TFM-C inhibits the activation of macrophages and mast cells. TFM-C also prevents the development of experimental autoimmune encephalomyelitis by inhibiting the production of IL-23 and inflammatory cytokines from dendritic cells as well as the subsequent production of IL-17 and IFN- γ in response to autoantigen. These results highlight the therapeutic potential of TFM-C for autoimmune diseases such as rheumatoid arthritis and multiple sclerosis.

BS4-2

Analysis of molecules for CD4⁺ T cell in the generation of GPI induced arthritis

Yuki Tanaka¹, Isao Matsumoto¹, Asuka Inoue^{1,2}, Yoko Tanaka¹, Naoto Umeda¹, Kayo Yamamoto¹, Takayuki Sumida¹

¹Division of Clinical Immunology, Doctoral Program in Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, ²JSPS Research Fellow

[Objective] To identify specific molecules specific for CD4⁺ T cells in GPI induced arthritis (GIA). [Methods] 1) The mRNA expression profile of splenic CD4⁺ T cells were examined by microarray in DBA/1 mice (arthritis susceptible) and B6 mice (arthritis resistant) after immunization of GPI (d7). 2) Fluctuated expression of HC gp-39 and ANX1 mRNA on splenocytes and splenic CD4⁺ T cells were analyzed in GIA. [Results] 1) We have identified highly expressed 14 genes, and focused on HC gp-39 and ANX1. 2) HC gp-39 and ANX1 mRNAs were clearly upregulated at the early phase of arthritis in splenocytes and CD4⁺ T cells. [Conclusion] These results suggest that HC gp-39 and ANX1 might be related to the generation of arthritis. We are elucidating which kind of T cell subset expresses these molecules.

BS4-3

Change of local cytokines and chemokines expression in BXSB treated with FTY720

Seiichi Ando¹, Hirofumi Amano¹, Eri Amano¹, Kentaro Minowa¹, Takashi Watanabe¹, Souichiro Nakano¹, Shinji Morimoto¹, Yoshiaki Tokano¹, Qingshun Lin², Rong Hou², Mareki Ohtsuji², Sachiko Hirose², Yoshinari Takasaki¹

¹Department of Rheumatology and Internal Medicine, Juntendo University School of Medicine, Tokyo, Japan, ²Department of Pathology, Juntendo University School of Medicine, Tokyo, Japan

We reported remedial effects of FTY720 such as the prolongation of survival period and the proteinuria in BXSB mice before. In this study, we examined the changes of local cytokines and chemokines expression after treatment by FTY720 on lupus nephritis of BXSB mice. Four-month-old BXSB male mice were given per os FTY720 1 mg/kg in distilled water three times a week for 2 months, then total RNA was isolated from kidney. Quantitative real-time RT-PCR analysis of CXCL13, MCP-1 and TNF- α mRNA were performed on these samples. In the result, all three type mRNA expression level was significantly reduced in FTY720-treated mice. The FTY720 treatment for the BXSB nephritis had an influence on local CXCL13, MCP-1 and TNF- α , and they might be involved in effect of treatment.

BS4-4

Elevation of *Bombina variegata* peptide 8 in mice with collagen-induced arthritis

Kentaro Noda, Eigo Takahashi, Taro Ukichi, Kazuhiro Furuya, Ken Yoshida, Isamu Kingetsu, Daitaro Kurosaka, Akio Yamada

Department of Rheumatology, The Jikei University School of Medicine, Tokyo, Japan

Background: Bombina variegata peptide 8 (Bv8) is a small protein secreted by frog skin. Recently it has been shown to contribute to tumor angiogenesis in mouse model. The purpose of this study was to investigate Bv8 in mice with type II collagen-induced arthritis (CIA). Methods: We induced CIA in male DBA/1J mice. RNA was examined for Bv8 mRNA expression by PCR. Joint tissue was immunohistochemically examined using anti-Bv8 antibody. Results: The level of Bv8 mRNA expression in the joint, was elevated in the CIA group. In addition, an increase in Bv8-positive cells was observed in the synovium and bone marrow in the CIA group. Conclu-

sion: Bv8 was elevated in the synovium and bone marrow of CIA mice, suggesting that Bv8 plays an important role in the pathogenesis of arthritis.

BS5-1

Thrombin cleaved osteopontin as biochemical marker for rheumatoid arthritis

Masahiro Hasegawa, Akihiro Sudo

Department of Orthopaedic Surgery, Mie University Graduate School of Medicine

Objective. We examined thrombin-cleaved osteopontin (OPN N-half) in synovial fluid (SF) from patients with rheumatoid arthritis (RA).

Methods. SF samples were obtained from 20 knees with RA and 111 knees with osteoarthritis (OA). OPN N-half was determined using Western blotting. Levels of OPN N-half and full-length OPN in SF were determined using an ELISA. Synovium were analyzed by immunohistochemistry.

Results. Immunoblotting showed the presence of OPN N-half in SF. ELISA results showed no difference between full-length OPN levels in RA and OA; however, OPN N-half levels in RA were 30-fold higher compared with OA ($p < 0.01$). Immunohistochemistry of the synovium showed stronger reactivity in RA than OA samples.

Conclusion. OPN N-half may be a useful biochemical marker of RA.

BS5-2

Differential effects of biological agents on in vitro IgM production

Toshihiro Tono, Satoko Tejima, Noriko Tono, Miho Kimura, Tatsuo Nagai, Shunsei Hirohata

Department of Collagen and infectious disease Kitasato University School of medicine

Biological agents provide beneficial clinical effects in RA patients. But, their immunomodulatory effects of biologics remain unclear. This study was therefore undertaken to explore the effects of various biologics on IgM production of peripheral blood mononuclear cells (PBMC). PBMC obtained from healthy adult volunteers were cultured in 1.25×10^6 /ml with staphylococcal enterotoxin B (100pg/ml) in the presence of infliximab, etanercept, tocilizmab or control IgG (1 or 10µg/ml) for 10 days. The concentrations of IgM in the culture supernatants were measured using ELISA. Tocilizmab suppressed the production of IgM of PBMC, whereas, infliximab and etanercept enhanced it. The result indicate that the mechanism actions of TNF antagonists and those of IL-6 receptor antagonist are totally different.

BS5-3

Analysis of the Effect of Medication to Malnutrition with Rheumatoid Arthritis

Wataru Fukuda¹, Atsushi Omoto¹, Toru Tanaka¹, Masataka Kohno², Yutaka Kawahito²

¹Division of Diabetes, Endocrinology and Rheumatology, Japanese Red Cross Kyoto Daiichi Hospital, Kyoto, Japan, ²Department of Inflammation and Immunology, Kyoto Prefectural University of Medicine, Kyoto, Japan

Objective: This is observational study to investigate the effect of medication, including TNF blockade (TNFB), to malnutrition in patients with RA. **Subjects and Methods:** Five nutritional indices:

BMI, arm muscle area (AMA), triceps skinfold thickness (TSF) and serum albumin were examined in 343 patients with RA. Results: After medication for twelve months, decrease of disease activity indicators, BMI, TSF and serum albumin and increase of AMA were observed on the whole, but any significant difference was not seen between patients treated with TNFB and with MTX, and between patients treated with GC and without GC. Conclusions: Although medication for twelve months seems to improve disease activity and malnutrition in RA, usage of TNFB or GC didn't make any difference in the improvement.

BS5-4

Possible roles of mesenchymal stem cells (MSCs) in bone edema

Akitomo Okada, Satoshi Yamasaki, Mami Tamai, Hideki Nakamura, Tomoki Origuchi, Atsushi Kawakami

1st Department of Internal Medicine, Nagasaki University Hospital, Nagasaki, Japan

Objectives: Bone edema is a pathological change in rheumatoid arthritis, and is known to be the replacement of adipose with inflammatory cells. We demonstrate the possible roles of MSCs in bone edema formation. **Methods:** Adipogenesis of MSCs was induced by induction medium in the presence or absence of cytokines. The cytokine productions were screened by an antibody array system and confirmed by ELISA. The cell migration assay was also performed. **Results:** TNFα, IL-6, etc. inhibit the adipogenesis of MSCs. IL-6 production and cell mobility was reduced after adipogenesis. **Conclusions:** Our data suggest that the inflammatory milieu promotes bone edema by blocking adipogenesis of MSCs in bone marrow. The enhanced IL-6 production and mobility of MSCs may affect the progression of bone edema.

BS5-5

Autoantibodies to killer immunoglobulin-like receptor activate NK cell activity

Hideaki Kawada¹, Yuko Takahashi², Shiori Haga¹, Yukihito Ishizaka¹, Akio Mimori²

¹Department of Intractable Diseases, Research Institute, National Center for Global Health and Medicine, Tokyo, Japan, ²Division of Rheumatic Diseases, National Center for Global Health and Medicine, Tokyo, Japan

We found serum autoantibodies to killer cell immunoglobulin-like receptor (KIR)-3DL1 (a subtype different from those reported by Matsui et al) in SLE patients, and the in vitro biological effect of the antibody on NK cells was determined. **Methods:** KIR-3DL1 was expressed in 721.221 NK cells and HLA-Bw4 in Jurkat (target) cells. **Results:** KIR-3DL1 expression suppressed NK activity, as measured using the LDH cytotoxicity detection kit. The baseline cytotoxicity index (mean 24.5%) was unchanged by IgG fraction from healthy donor sera, but was significantly elevated by IgG fractions obtained from 3 SLE patients positive for anti-KIR-3DL1 antibodies (56.4%, 57.6%, and 46.2%, $p < 0.05$). **Conclusions:** Autoantibodies to KIR-3DL1 in the sera of SLE patients are capable of activating NK cells.

BS6-1

Hormon replacement therapy (HRT) prevents menopausal women from occurring RA

Kiyomitsu Miyachi

We have investigated the efficacy of HRT for unclassified arthritis in these women, and have assessed the potential effect of HRT in preventing RA. one hundred fourteen patients diagnosed with early RA by fulfilling 1-3 items of the Japanese criteria were divided into four groups according to the presence or absence of RF and HRT. Two of 23 patients treated with HRT for 2 ~3 years and who were originally CRP (-) and RF(+), subsequently developed RA. Seve of 14 cases receiving no treatment developed RA. These findings suggest that HRT is effective in preventing RA in peri-/postmenopausal women.

BS6-2

The efficacy and safety of aggressive treatment in elderly patients with RA

Kazuhito Fukuoka, Hitoshi Koji, Tomoko Matsuda, Miho Karube, Ken Yoshihara, Yoshinori Komagata, Shinya Kaname, Yoshihiro Arimura, Akira Yamada
Kyorin University, School of Medicine, Department of Nephrology and Rheumatology

Early intervention and tight control must be important for prevention of joint deformity in the patients with early-onset rheumatoid arthritis (RA). However there are a considerable number of elderly patients, then the management of such as elderly RA is still unclear. To clarify the characteristics of these patients, we attempt to analyze the treatment agents including biologics, complication and prognosis. The total number of RA patients was 1024 cases, then elderly cases was shown in 39%. The amount of dosage of GC and MTX was lessor than non-elderly cases, but various anti-rheumatic drugs including biologics were used. Although high age is suggested the one of the risk of RA treatment, it might be possible to treat with immune-suppressant and biologics safely and effectively.

BS6-3

Characteristics of EORA: Clinical factors including musculoskeletal ultrasound

Eigo Kikuchi¹, Akitake Suzuki¹, Kazuaki Uekubo¹, Naoko Aoki¹, Taro Yoshioka², Yoshinobu Ishiyama², Ryuichi Yokohari¹, Takahiro Okai¹

¹Division of Rheumatology, Department of Internal medicine, Kawakita General Hospital, Tokyo, Japan, ²Division of Rheumatology, Department of Orthopedics, Kawakita General Hospital, Tokyo, Japan

Objective: We evaluated the characteristics of elderly onset rheumatoid arthritis (EORA) including musculoskeletal ultrasonography. **Method:** We analyzed 19 EORA and 16 RA for the clinical factors including ultrasonographic findings (total power Doppler scale scores (t-PDS: 0 - 9) of three locations of unilateral wrist and knee joints; each location was evaluated from grade 0 - 3). **Results:** The t-PDS of knee joints were significantly higher (2.9 ± 1.5 for EORA, 1.0 ± 1.4 for RA, $p < 0.05$) in EORA (aged 78.4 ± 5.0) than RA (aged 48.8 ± 11.6). ESR (72 ± 29 mm/hr, 41 ± 28 mm/hr) and MMP-3 (293 ± 493 ng/mL, 74 ± 60 ng/mL, $p < 0.05$) were significantly higher in EORA. **Conclusion:** This study revealed EORA patients tended to have synovitis of the knee joints compared to younger patients and showed high ESR and MMP-3.

BS6-4

The clinical features of elderly onset RA

Haruko Inoue, Atsuo Taniguchi, Inoue Eisuke, Mikiko Shinozaki, Wako Urano, Naomi Ichikawa, Yumi Koseki, Shigeki Momohara, Hisashi Yamanaka
Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Aim: To clarify the clinical characteristics of elderly onset rheumatoid arthritis (RA). **Method:** From the 5512 cases with RA participated in IORRA study at April 2009, 490 cases who had onset of RA after 65 years (EORA) were matched, on the basis of their disease duration, with 495 cases who had onset of RA before 65 years (YORA). Background, disease activity and treatments were compared. **Results:** Disease duration/%females of EORA were 6.3 years/75 and not different from YORA. DAS28/J-HAQ of EORA were significantly higher than YORA. The proportions of treatments with MTX/Biologics of EORA were significantly lower than YORA, and PSL were similar between groups. **Discussion:** Despite higher disease activity, EORA patients received MTX/biologics treatment less frequently than YORA patients.

BS6-5

Characteristics of late-onset rheumatoid arthritis in NinJa database 2009

Shigeru Yoshizawa^{1,3}, Yasutaka Kimoto^{1,3}, Shigeto Tohma^{2,3}

¹Fukuoka National Hospital, Fukuoka, Japan, ²Clinical Research Center, Ntiional hospital Organization Sagamiraha Ntional hospital, Sagamihara, Kanagawa, Japan, ³IR-net

The clinical futures of late-onset rheumatoid arthritis were examined in NinJa database 2009. The late-onset RA group, the onset was elder than 65 yrs (Group A), was compared with the other two groups; the onset was younger than 65yrs and age was elder than 65 yrs (Group B), and the age was younger than 65 yrs (Group C). Group A was consisted of 1108 patients, 326 male and 782 female. The percentages of the medication of corticosteroids were 54.0% in group A, 59.7% in Group B, and 47.7 % in group C, and those of MTX and biologics were 43.1% and 9.7%, 53.5% and 21.9%, and 60.5% and 21.9%, in each groups respectively. DAS28, the disease activity score, was 3.81, 3.74, and 3.38, and the ratio of hospitalization during one year was 20.8%, 21.9%, and 1.37% in each group, respectively.

BS7-1

Characteristics of P-glycoprotein expressed lymphocytes in highly active RA

Shizuyo Tsujimura¹, Kazuyoshi Saito¹, Yoshiya Tanaka¹

¹The First Department of Internal Medicine, University of Occupational & Environmental Health, School of Medicine, Kitakyushu, Japan, ²Department of Pathology and Cell Biology, University of Occupational & Environmental Health, School of Medicine, Kitakyushu, Japan

P-glycoprotein (P-gp) that pumps out intracellular drugs, on lymphocytes in highly active RA patients is involved in the drug-resistance. P-gp was predominantly expressed on CD69+ active peripheral lymphocytes and on lymphocytes that infiltrated in synovitis. CXCR4 that associated with extravascular migration and B cell survival, was highly expressed on B cells, and P-gp was expressed on CXCR4+ B cells both in peripheral blood and in synovitis. P-gp is reported to associate with migration from the bloodstream. P-gp

overexpression might cause drug resistance and migration to synovium. Measurement of P-gp expression on lymphocytes could be a potentially useful marker for assessing drug-resistance, for indicating possibility of joint destruction and for selecting biological agents for RA.

BS7-2

Synovial histopathology in rheumatoid arthritis treated with TNF inhibitors

Shunsei Hirohata¹, Tetsuya Tomita², Hideki Yoshikawa², Masahisa Kyogoku³

¹Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, ²Department of Orthopedic Surgery, Osaka University Medical School, ³Department of Pathology, Tohoku University School of Medicine

We examined the features of RA synovial tissues treated by TNF inhibitors. Synovial tissues were obtained from 12 patients treated with TNF inhibitors in addition to DMARDs for at least 5 months and from 12 patients treated with only DMARDs. There were no significant differences in serum CRP and treatment regimen except for TNF inhibitors between the 2 groups. The most prominent changes with TNF inhibitors were hyalinization and fibrosis in sublining layers with degeneration, vacuolization, detachment of synoviocytes and formation of multinucleated giant cells, probably related with the marked decrease in vasculature. There was no significant difference between infliximab and etanercept. The hyalinization in the sublining layers might be a characteristic feature of TNF inhibitors.

BS7-3

Role of n-3 polyunsaturated fatty acid on rheumatoid arthritis

Yasunori Tsubouchi¹, Masahide Hamaguchi², Atsushi Omoto⁴, Kunio Yanagida⁵, Kazuki Fujioka¹, Daisaku Tokunaga³, Hidetaka Ishino², Masataka Kohno², Yutaka Kawahito²

¹Division of Internal Medicine, Social Insurance Kyoto Hospital, ²Division of Inflammation and Immunology, Graduate School of Medical Science, Kyoto, ³Division of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, ⁴Division of Diabetes, Endocrinology and Rheumatology, Kyoto First Red Cross Hospital, ⁵Division of Internal Medicine, Nishijin Hospital

The evidence of the important role dietary intake of n-3 polyunsaturated fatty acid in inflammation was derived from epidemiological observations of the low incidence of inflammatory disorders, such as rheumatoid arthritis (RA), psoriasis, and ulcerative colitis in a population of Inuit compared with European people. We studied the role of eicosapentaenoic acid (EPA) on RA. Mean EPA/arachidonic acid (AA) ratio on RA was 0.33, significantly lower than that on diabetes mellitus (DM) (0.52). Low EPA/AA ratio which was suggested to be risk factor of cardiovascular event may be one of the background on onset of RA. The cell viabilities and proliferation of EPA treated RA synoviocytes were directly suppressed. So EPA may have antirheumatic effect.

BS7-4

The regulation of the post-translational modifications in rheumatoid arthritis

Satoko Aratani

Institute of Medical Science, Tokyo Medical University

Rheumatoid Arthritis (RA) is a chronic inflammatory joint disease and characterized by synovial hyperplasia. We previously cloned E3 ubiquitin ligase, Synoviolin, as a regulatory factor of cell proliferation and suggested that endoplasmic reticulum (ER) associated degradation system via Synoviolin has important roles for overgrowth of synoviocytes. Meanwhile, Peptidyl-Arginine Deiminase 4 (PADI4) is identified as the RA-susceptible gene. It is known that autoantibodies to citrullinated proteins are specific for RA and good markers for RA. However functions of citrullinated proteins are unclear. In this study, we hypothesize that the accumulation of citrullinated proteins in RA synoviocytes could associate for ER stress and explore the crosstalk of ubiquitination and citrullination.

BS8-1

Role of CD14+ cells in rheumatoid arthritis

Kenya Murakami^{1,2}, Akihisa Kamataki², Tadashi Shimamura¹, Takashi Sawai²

¹Institute of Orthopedic Surgery, Iwate Medical University School of Medicine, Morioka, Japan, ²Institute of Pathology, Iwate Medical University School of Medicine, Morioka, Japan

To elucidate the mechanism of long continuing inflammation of rheumatoid arthritis (RA), we examined the property of CD14+ cells which quantitatively characterize RA synovium by immunohistochemical and double immunofluorescence stainings. Both round and spindle shaped CD14+ cells were present in RA synovium. Area of CD14+ cells coexpressing CD68 or HLA-DR amounted to more than 50% of CD14+ positive area in RA synovium, but less than 20% in nonspecific granulation tissue. Some CD14+ cells and CD138+ plasma cells were showed cell to cell contact which was so called nursing phenomenon in RA synovium. These results suggest that RA synovium had different characteristics from nonspecific granulation tissue, and CD14+ cells may be play a central role in persisting inflammation of RA.

BS8-2

Acetyl-Proteomics for the Investigation of Pathological Molecules In RA

Mitsumi Arito¹, Kouhei Nagai¹, Yukiko Takakuwa², Seido Ooka², Manae S. Kurokawa¹, Kazuki Okamoto¹, Tomohiro Kato¹

¹Clinical proteomics and Molecular Medicine, St. Marianna University Graduate School of Medicine, ²Division of Rheumatology and Allergy, Department of Internal Medicine, St Marianna University School of Medicine

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. In PBMCs from RA, 29 acetylated protein spots were detected, some of which were predominantly acetylated in RA. One of the proteins predominantly acetylated in RA was identified to be α -enolase (ENO1). Next, we tried to investigate whether acetylation affect the function of the enzyme. As a result, we found that acetylation of ENO1 up-regulated the enzyme activity. These results indicate that the activation of ENO1 by acetylation may participate in the pathogenesis of RA.

BS8-3

Analysis of disease-specific modifications on a MPO, a major antigen of ANCA

Teisuke Uchida¹, Kouhei Nagai¹, Manae S. Kurokawa¹, Kazuki Okamoto¹, Yukiko Takakuwa^{1,2}, Seido Ooka^{1,2}, Mitsumi Arito¹, Tomohiro Kato¹

¹Clinical Proteomics and Molecular Medicine, St Marianna University Graduate School of Medicine, ²Division of Rheumatology and Allergy, Department of Internal Medicine, St. Marianna University of Medicine

[Introduction] Post-translational modifications (PTMs) of auto-antigenic proteins are proposed to be involved in the production of autoantibodies. In this study, we tried to detect the disease-specific PTMs on a myeloperoxidase (MPO), a major antigen of anti-neutrophil cytoplasmic antibodies (ANCA). [Methods] Neutrophils were collected from MPO-ANCA positive patients and healthy donors. Proteins were extracted from the neutrophils and separated by two-dimensional electrophoresis (2-DE). MPO-ANCA spots were detected by western blot using an anti-MPO antibody. [Result] On the 2-DE analysis *pI* values of MPO spots were different between the patient and the healthy groups. This indicated the presence of specific PTMs on MPO from MPO-ANCA active patient.

BS8-4

Muckle-Wells syndrome with a novel *NALP3* mutation and an activated inflammasome

Yuzaburo Inoue¹, Takayasu Arima¹, Yasushi Kawaguchi², Yoshinori Morita¹, Taiji Nakano¹, Minako Tomiita¹, Naoki Shimojo¹, Yoichi Kohno¹

¹Department of Pediatrics, Graduate School of Medicine, Chiba University, Chiba, Japan, ²Institute of Rheumatology, Tokyo Women's Medical University

A 12-year-old boy was hospitalized with recurrent episodes of fever.

We detected a novel missense mutation, *NALP3* R135H, whereas we did not find any mutations in *MVK*, *MEFV* nor *TNFRSF1A*. We did not find the *NALP3* R135H in 313 healthy individuals, indicating that R135H is not one of the SNPs. To check *NALP3* inflammasome activity, we measured the amount of active caspase-1 in monocytes by flowcytometry. The patient had two times more active caspase-1 in the monocytes than healthy individuals, indicating that his *NALP3* inflammasome activity was abnormally increased in the monocytes. Although the mutation did not locate in NACHT domain on exon 3 of *NALP3*, in which most of the mutations found in Cryopyrin-Associated Periodic Syndrome locate, we diagnosed him as Muckle-Wells syndrome.

BS8-5

Rare complication of rheumatoid arthritis and schizophrenia

Reo Yoshikawa¹, Satoshi Kamei¹, Sumie Moriyama¹, Yoshinori Masui¹, Junwa Kunimatsu¹, Kenji Takenouchi², Yuko Takahashi³, Hiroyuki Yamashita³, Kenji Takahashi², Hiroshi Nakamura², Akio Mimori³, Hiroshi Kaneko⁴

¹Department of Internal Medicine, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan, ²Department of Rheumatology, Nippon Medical School, Tokyo, Japan, ³Division of Rheumatic Diseases, Department of Internal Medicine, National Center for Global Health and Medicine, Tokyo, Japan, ⁴Department

of Rheumatology, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan

Schizophrenia is a disease with a high prevalence of one person in 100 people. It has been pointed out that the complication with schizophrenia and rheumatoid arthritis (RA) is a little, and there is wide evidence for a decreased risk of RA in patients with schizophrenia. We investigated the actual situation with two institutions. We found 3 RA patients in the database of 906 schizophrenia in the Department of Psychology at Kohnodai Hospital, the National Center for Global Health and Medicine, Chiba, Japan. On the other hand, we found only 2 patients complicated with schizophrenia in the database of 1018 RA patients in the Department of Rheumatology at the Nippon Medical School, Tokyo, Japan. We discussed about these example. The onset of the schizophrenia went ahead of the onset of RA.

Case Report

CR1-1

A case of amyopathic dermatomyositis with the positivity of anti-Ku

Takahiro Yoshikawa, Mitsuyo Matsumoto, Kunio Takada, Masahiro Nakashima, Takashi Nakanishi, Hideyuki Horikoshi, Tomoaki Higuchi, Kimihiro Suzuki

Department of Internal Medicine, Division of Rheumatology, National Defence Medical College, Tokorozawa, Japan

Case: A 65-y/o-female was admitted to our hospital because of fever, pericardial effusion. She was diagnosed as having amyopathic dermatomyositis (ADM) because of erythema on the extensor surfaces of extremities, interstitial pneumonia (IP), the positivity of anti-Ku. Corticosteroid, cyclosporine, cyclophosphamide were not effective, therefore, she died of respiratory failure caused by acute exacerbation of IP. [Discussion] ADM is characterized by the specific skin feature(s), poor muscle manifestations and refractory IP. Recently, anti-CADM-140 have been reported positive in some ADM cases. In this case, anti-CADM-140 was negative, but anti-Ku was positive. We report this case, discussing the bibliographic consideration on the relationship between ADM and autoantibodies.

CR1-2

Intractable chronic lupus pericarditis treated successfully with tocilizumab

Yasuyuki Kamata, Hitoaki Okazaki, Kazuko Matsumoto, Yoko Aoki, Takao Nagashima, Masahiro Iwamoto, Seiji Minota
Institute of Rheumatology and Clinical Immunology, Jichi Medical University, Tochigi, Japan

A 48-year-old woman developed SLE in 1995. In August 2005, she had massive pericardial effusion (PE) due to lupus pericarditis, which was compromising her circulation. A mPSL pulse, an intravenous cyclophosphamide pulse, and pericardiocentesis were all ineffective. Pericardium was cut surgically to make a fenestration for the drainage of fluid. The procedure was effective temporarily; however, massive PE recurred in 1 year. Because IL-6 level in PE was found markedly increased at 1,160 pg/ml, tocilizumab was administered intravenously at a dose of 8 mg/kg q4w. The effect was remarkable; there remained only a trivial amount of PE. Prednisolone was tapered successfully from 15 to 7 mg daily. We recommend to measure IL-6 levels in PE when confronted with an SLE patient with intractable PE.

CR1-3

Remission of CADM complicated with RPILD by early therapeutic intervention

Eriko Isomoto¹, Tomohiro Koga¹, Akitomo Okada¹, Shin-ya Kawashiri¹, Mami Tamai¹, Satoshi Yamasaki¹, Hideki Nakamura¹, Tomoki Origuchi¹, Masataka Kuwana², Atsushi Kawakami¹

¹Unit of Translational Medicine Department of Immunology and Rheumatology Nagasaki University Graduate School of Biomedical Sciences, ²Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine.

Case 1: 39-year-old female was diagnosed as clinical amyopathic dermatomyositis (CADM) based on Gottron's sign and Heliotrope rash without loss of muscle strength. Rapid progress interstitial lung disease (RPILD) was suspected by hypoxia and low diffusing capacity for carbon monoxide. We introduced steroid pulse therapy, and she improved well and kept remission status with oral prednisolone

and tacrolimus. Anti-MDA5 Ab and anti-CADM140kDa Ab were positive in the patient. Case 2: 63-year-old female with difficulty of breath was diagnosed as interstitial pneumonia by CT scan. Her cutaneous and muscle symptom were consistent with CADM. We also successfully treated the patient with corticosteroid and combination of immunosuppressants (tacrolimus and intravenous cyclophosphamide pulse therapy).

CR1-4

A case of systemic-onset JIA that EB virus reactivation was caused

Daisuke Hirano, Nobuko Tosaka, Shusaku Fukaya, Miyuki Nozaki, Yumi Iwasaku, Satoru Onoda, Tomonobu Iwade, Jo Nishino, Kenichi Kato, Shunji Yoshida

Division of Rheumatology and infectious disease Department of Internal Medicine, Fujita Health University School of Medicine, Aichi, Japan

[Case] A 29-year-old female with systemic juvenile idiopathic arthritis at X-15; a relapse with the pregnancy at X-5; treated by steroid hormone massive dose, methotrexate and tocilizumab, being refractory. Hospitalized for 38C fever with diarrhea on July 10, XXXX. July 13, cytopenia decreased and FDP-ferritin increased; hemophagocytic syndrome (HPS) was diagnosed; steroid pulse therapy started. July 15, atypical lymphocyte increased significantly; scrutiny confirmed EBV-DNA increase (44426 copy/ μ gDNA). Thus, HPS was likely to be caused by EB virus re-activation. [Consideration] Immunosuppression state by MTX and TCZ may have caused EBV re-activation. Causes of HPS with JIA should include EBV re-activation. This is a difficult case to distinguish original disease activity from other causes.

CR1-5

Successful treatment with rituximab for thrombocytopenia associated with SSc

Ayaka Honjo, Shuzo Yoshida, Nao Tatsukawa, Kentaro Isoda, Kenichiro Hata, Tohru Takeuchi, Shigeki Makino, Toshiaki Hanafusa

First Department of Internal Medicine, Osaka Medical College, Osaka, Japan.

A 63-year-old woman noticed Raynaud's phenomenon and skin sclerosis in her arms and legs. Physical examination showed distal skin thickness. Laboratory findings showed thrombocytopenia (PLT $2.9 \times 10^4/\mu$ l) and chest X-ray showed interstitial pneumonia. She was diagnosed with systemic sclerosis with interstitial pneumonia, and was treated with intravenous methylprednisolone 1000 mg/day for 3 days, followed by oral prednisolone (50 mg/day) with unfavorable response. Thrombocytopenia remained refractory to the additional treatment with tacrolimus, azathioprine, and intravenous pulse cyclophosphamide. She was treated with rituximab (375mg/m²/body \times 2), PLT counts returned to normal values ($20 \times 10^4/\mu$ l).

CR1-6

A case of IMAM with MEFV R202Q mutation

Fumiaki Nonaka¹, Katsumi Eguchi¹, Kiyoshi Migita², Hiroaki Ida³, Atsushi Kawakami⁴

¹Sasebo City General Hospital, ²Nagasaki Medical Center, ³Division of Respiratory, Neurology, and Rheumatology, Department of Medicine, Kurume University School of Medicine, ⁴Unit of Translational

We report a case of IMAM with MEFV gene mutation and marked CD64 expression on peripheral blood (PB) neutrophil. A 40 years old man had been considered as having dermatomyositis (DM) since 2002. Intermittent fever around 38°C has appeared from March, 2010. The swelling with local heat has become to be apparent beginning from femoral to knee joint of the left side from July. Elevation of CK, aldolase, CRP was found. MRI (T2STIR) demonstrated the remarkable thickening of fascia. Muscle biopsy showed a prominent infiltration of macrophages into the fascia, and he was diagnosed as IMAM. In addition, MEFV Exon2 R202Q mutation and strong CD64 expression of PB neutrophil were demonstrated. Our present case may indicate a new finding that IMAM coexists with FMF (Familial Mediterranean Fever).

CR2-1

Treatment of skin ulcers in polyarteritis nodosa (PN) with infliximab (IFX)

Mieko Yamagata, Isao Matsuura, Daisuke Kashiwakuma, Shunsuke Furuta, Itsuo Iwamoto, Shoji Yoshida
Department of Allergy and Clinical Immunology, Asahi General Hospital

We report a case of successful treatment of refractory skin ulcers in PN with IFX. A 34-year-old male patient had multiple skin and gastric ulcers in 1995 and was diagnosed as having PN in 2005. He was treated with prednisolone (PSL) 30mg/day and cyclosporin (CsA) 100mg/day. He responded well to the treatment and PSL was tapered to 5mg/day. His skin ulcers relapsed in December 2009 and was treated with PSL 15mg/day and CsA 50mg/day without improvement. He was transferred to our hospital in February 2010 and was treated with PSL 40mg/day, IVCY 500mg/month, and CsA 100mg/day. But ulcers were not improved. We used IFX 5mg/kg from May. His ulcers responded well to IFX with a thermographical improvement. His oral morphine 6600mg/day for pain relief gradually reduced to zero with healing ulcers.

CR2-2

Infliximab for pituitary Wegener's granulomatosis: a case report

Kazuki Yoshida¹, Hideto Oshikawa¹, Masako Utsunomiya¹, Tatsuo Kobayashi¹, Makiko Yamamoto¹, Mitumasa Kishimoto², Kazuo Matsui¹

¹Department of Rheumatology, Kameda Medical Center, Chiba, Japan, ²Section of Allergy and Rheumatology, St. Luke's Hospital, Tokyo, Japan

The patient is a 25-year-old female who was diagnosed with Wegener's granulomatosis at the age of 23. She had unilateral ovarian granuloma, gingivitis, facial skin ulcer, sinusitis, multiple lung nodules, and positive serum PR3-ANCA at the disease onset. She was treated with glucocorticosteroids and immunosuppressants for worsening lung nodules and pachymeningitis. She had a relapse of pachymeningitis two months prior to admission which was treated with an escalated dose of glucocorticosteroids. She then developed worsening headache, thirst, polydipsia, and polyuria. MRI showed pituitary mass. Central diabetes insipidus due to Wegener's granulomatosis was diagnosed. She was treated with infliximab (5mg/kg), glucocorticosteroids, and nasal vasopressin.

CR2-3

A case of Wegener's granulomatosis with pituitary involvement

Mai Morimoto, Masahiro Sekiguchi, Kiyoshi Matsui, Kazuyuki Fujita, Mika Okabe, Takuya Hino, Aki Nishioka, Ryota Okazaki, Naoto Azuma, Masayasu Kitano, Naoaki Hashimoto, Hajime Sano
Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan

A 65 years old woman presented with sinusitis and she was diagnosed as limited Wegener's granulomatosis 3 years ago. She was treated with prednisolone (PSL) and cyclophosphamide and symptoms have been improved. In 2010 she presented headache, abducens palsy, and polydipsia. Pituitary MRI revealed inhomogeneously enhanced mass with enlargement of pituitary gland and its stalk. Pituitary function test showed panhypopituitarism and hypertonic saline test was indicative of central diabetes insipidus (CDI). A biopsy of the mass showed the granuloma and necrotizing vasculitis, moreover the titer of PR3-ANCA increased again. We diagnosed pituitary involvement of Wegener's granulomatosis with CDI. Symptoms were promptly resolved with mPSL pulse therapy and CDI was controlled by intranasal desmopressin.

CR2-4

Efficacy of TMP/SMX in a case of Wegener granulomatosis with pulmonary emphysema

Kanae Tamura, Makoto Kondo, Masaya Mukai
Sapporo City General Hospital

A 78-year-old man with WG was referred to our hospital. At the time of his first consultation, we considered that his disease was getting worse because high levels of CRP and PR3-ANCA were revealed with his blood tests. Generally, patients with WG are treated with steroid and immunosuppressive agents. As the patient complicated with severe pulmonary emphysema, we regarded such therapies as intolerable concerning the risk of respiratory infections. We administered his treatment with TMP/SMX (trimethoprim-sulfamethoxazole) only. The levels of CRP and PR3-ANCA got lower. The level of CRP reached at normal level and chest CT showed nodular lesions decreased in size two months after treatment. This result suggests that treatment with TMP/SMX only is effective against patients with mild WG.

CR2-5

Reversible cerebral vasoconstriction syndrome in Takayasu arteritis

Shiho Iwagaitsu, Taio Naniwa, Kaneshige Sasaski, Maiko Watanabe, Shinji Maeda, Yoshihito Hayami
Division of Rheumatology, Nagoya City University Hospital, Aichi, Japan

Reversible cerebral vasoconstriction syndrome (RCVS) causes a reversible cerebral vasospasm. We report a case of RCVS that developed in the course of Takayasu arteritis. A 15-year-old girl presented with limb claudication for 6 months and abdominal angina for 3 months. Stenosed renal arteries and abdominal aorta were observed. Hypertension was absent. Corticosteroid therapy promptly normalized serum CRP level and reduced the wall thickness of the carotid artery. Two weeks after starting therapy, she developed headache and tonic seizures during defecation. Brain MRI angiography showed intense signals on FLAIR image dominated in the posterior brain and stenoses in the intracranial arteries. Two months lat-

er, these findings were resolved. On the basis of these findings, RCVS was confirmed.

CR2-6

2 cases of CSS with peripheral nerve involvement treated with IVIg

Remi Sasaki¹, Toshiyuki Aramaki¹, Munetoshi Nakashima¹, Atsushi Kawakami²

¹Rheumatology, Nagasaki Genbaku Hospital, Nagasaki, Japan, ²First Department of Internal Medicine, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan

Churg-strauss syndrome (CSS) is known to be treatable with corticosteroid except for peripheral nerve damage. We report 2 CSS patients treated with Intravenous immunoglobulin (IVIg) in early therapeutic phase to see its effect on peripheral nerve damage.

Case1: A 52-year female with bronchial asthma developed fever and numbness of both feet. She presented with eosinophilia and MPO-ANCA positive, which lead to the diagnosis of CSS, and was treated with PSL. Despite immunosuppressive therapy, mononeuritis multiplex was progressed and IVIg was administered 1 week later after PSL started.

Case2: A 52-year female with bronchial asthma developed polyarthritis and marked eosinophilia, but ANCA negative, and developed mononeuritis multiplex. She was treated with PSL and IVIg 3 weeks later.

CR3-1

Usefulness of elbow arthroplasty using inter-positional membrane with biologics

Ryuji Nagamine, Weijia Chen

Department of Orthopaedic Surgery, Sugioka Memorial Hospital

Purpose: Clinical results of arthroplasties using inter-positional membrane were not good. Today, RA activity can be controlled by means of biologics; therefore, the usefulness of inter-positional membrane was re-evaluated.

Case: Right elbow arthroplasty using inter-positional membrane was performed in 32 year-old female in 2003. biologics were administered since 2003. Preoperative ROM was 30 degrees.

Results: At 8 years after the arthroplasty, ROM is 110 degrees and clinical results is good. RA is now under control.

Discussion: In younger RA cases, even though elbow joints are destroyed, total replacement arthroplasty cannot be done due to the limited longevity. If RA activity is controlled with biologics, elbow arthroplasty using inter-positional membrane is thought to be useful.

CR3-2

A case: corrective fixation of luno-capitate joint erased snapping like motion

Makoto Hirao, Kenrin Shi, Tsuyoshi Murase, Hideki Yoshikawa, Jun Hashimoto

Department of Orthopaedics, Osaka University Graduate School of Medicine

Biologics increases the daily activity of RA patients, and many hand and foot surgeries are performed. Meanwhile, we experienced a case that makes us reaffirm the importance of the surgery under fine evaluation of small joint function. Fifty seven years old RA woman treated with tocilizumab had complaints that were motion pain around left wrist joint and snapping like motion in ring and small finger. There was small erosive change, however no bone de-

fect in radio-lunate joint, while abundant osteophyte was seen. Both ring and small finger joint were intact. However, dorsiflexion deformity in luno-capitates joint was severe, and carpal height decreased. In the operation, luno-capitate joint was corrected. After that, snapping like motion disappeared, and no motion pain around wrist is seen.

CR3-3

RA with remission after arthroscopic synovectomy & switching to Enbrel

Moriyuki Noguchi

Yonezawa City Hospital

Case 61 yo woman w/ stage III/class I RA. **History** Jun 2008, RA w/ swelling/pain in both knee joints & left wrist; worsened w/ SASP 1000 mg/d & PSL 5 mg/d at nearby GP. She was referred to us 10/Oct 2008. X-ray Larsen grade 4 w/ CRP 7.9, MMP-3 798 ng/ml, DAS28CRP 4.8. Switched to MTX 6 mg/w & knee TKA. Knee pain relieved but wrist swelling/pain worsened; MTX 8 mg/w & infliximab (Remicade) 3 mg/kg started. Swelling/pain relieved but relapsed. Further Remicade increase was not effective. After arthroscopic synovectomy (AS) of left wrist & switch to etanercept (ETN, Enbrel) 50 mg/w, swelling/pain relieved; clinical & functional remission is maintained for 1 year. **Conclusion** ETN & wrist AS was effective in single severe wrist arthritis that was treated w/ increased Remicade that lacked efficacy.

CR3-4

Two cases of RA with insufficient efficacy of ETN caused remission by syovectomy

Takeo Otsuki¹, Yasuo Morio², Hiroyuki Ishii²

¹San-in Rosai Hospital, ²Misasa Onsen Hospital

We experienced two cases of rheumatoid arthritis with insufficient efficacy of etanercept caused remission by synovectomy of the knee.[Case 1]50 years old woman diagnosed RA at 49 y.o..Though she was treated with MTX and IFX,DAS28 (CRP) showed moderate-high disease activity.Swelling of both knee persisted after switching IFX to ETN.Synovectomy was performed on both knee.At 5 months postop.DAS28 was 2.4.[Case 2]51 years old man diagnosed RA at 50 y.o..He was treated with MTX and TAC,disease activity was not well controlled.Even using ETN,swelling of left knee remained and DAS28 showed low-moderate disease activity.A month after synovectomy of knee,DAS28 became 2.0.Syovectomy was useful to control disease activity for RA patients with sustained synovitis of the knee by the use of biologics.

CR3-5

Total elbow replacement with Discovery Elbow System for RA. Short-term follow-up

Kosuke Okuda, Hiroshi Sunami, Tsukasa Matsubara

Department of Orthopedic Surgery, Matsubara Mayflower Hospital

PURPOSE: We use a linked-type elbow prosthesis, Discovery Elbow System (DES) for the destructive elbow joints of rheumatoid arthritis since June 2008. We assessed the short-term results eight DES in six patients with RA. **METHODS:** All patients were female. The mean age was 67.5 yrs. All were Stage 3. One was Class 2, and five were Class 3. The preop DAS28-CRP(4) was 4.28. The preop mHAQ was 1.23. **RESULTS:** The mean preop JOA score was 47.1 and at final follow-up was 83.8. The preop flexion was 116°,final was 132.5°. The preop extension was -31°, final was -26°. Radiolu-

cent line and loosening were not detected. We had one humeral condyle fracture, and one postoperative radial nerve paralysis. **CONCLUSION:** We had a good short-term results using DES for the RA destructive elbow joints

CR3-6

Insufficiency condylar fracture after total knee arthroplasty

Goh Hirata, Hisaaki Miyahara, Masanobu Ohishi, Yukio Esaki, Nobutaka Kaibara, Fuyuki Tominaga

Kyushu Medical Center, National Hospital Organization, Fukuoka, Japan

We experience three cases with supracondylar fracture of femur after total knee arthroplasty operation. The patients were from 61 to 72 years old. Duration of RA were from 22 to 24 years. Two of 3 patients took low dose steroid. All knees broken were valgus deformity before operations. Two fractures were treated with braces, the other was operated. We presume that risk factors for insufficient fracture in operated knee are elderly female, steroid intake and valgus deformity. It is important for better operation that RA patients received tight control treatment.

CR3-7

Revision of dislocated total knee arthroplasty : a case report

Yusuke Hara, Daisaku Tokunaga, Yuji Arai, Ryo Oda, Ryu Terauchi, Eigo Otakara, Toshikazu Kubo

Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine

A 65-years-old lady with RA was treated by bilateral TKA at the age of 44. 20 years after the surgery, she suddenly had severe pain at her right knee without any event. On the X-ray, the tibial component was found to be dislocated posterolaterally. Realignment of the soft tissue combined with reinsertion of polyethylene insert was performed. However, dislocation of the tibial component occurred four months after the surgery. Revision of all prosthesis using rotator hinge type components was performed subsequently. Dislocation of the components is not a common complication after TKA. In the present case, excessive moment of external rotation of the tibial component caused by malrotation of the femoral component and lateral dislocation of patella resulted in the dislocation of TKA.

CR4-1

Six cases in which bucillamine-associated lung injury was suspected

Yasunobu Takizawa, Keigo Setoguchi, Junko Maruyama, Misato Kawakami, Atsuko Murota

Department of Rheumatology, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

Medical records and radiographs were scrutinized for six patients with suspicion of bucillamine (Buc) induced lung injury. Three had preexisting lung disease. Lung injury, which occurred 4.0 (2.2 to 8.0) months after the introduction of Buc, improved spontaneously in three cases but required high-dose glucocorticoid for the others, among whom one died, one improved, and one required continuous oxygen. As for radiographic findings four had consolidation or ground glass opacity (GGO) predominantly in the central lung, a typical finding for the classical bucillamine lung, while two had GGO or consolidation diffusely in the peripheral lung, suggesting the acute exacerbation of preexisting lung disease. In conclu-

sion, Buc induced lung injury is diverse in its clinical and radiologic features.

CR4-2

Agranulocytosis secondary to salazosulfapyridine in rheumatoid arthritis

Kenta Momii, Jun-ichi Fukushi, Yasuharu Nakashima, Ken Okazaki, Taro Mawatari, Masanobu Ohishi, Yasutaka Tashiro, Yukihide Iwamoto

Department of Orthopaedic Surgery, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

[Purpose] We present the management of agranulocytosis secondary to salazosulfapyridine (SASP) with recombinant human granulocyte colony stimulating factor (G-CSF). [Case] A 72-year-old woman with a history of rheumatoid arthritis presented with general fatigue and fever four weeks after starting SASP. Oral ulceration, parianal abscess, and a marked decrease in white blood cell (WBC) counts (WBC 800/ul, neutro 0%) were observed. G-CSF was used as an adjunctive therapy with discontinuation of SASP, barrier nursing and a broad-spectrum antibiotic regimen. Total WBC and neutrophil counts returned to normal in ten days, and she made an uneventful recovery. [Discussion] Agranulocytosis secondary to SASP is rare, but rheumatologists should be aware of this severe adverse complication.

CR4-3

Case with RA contracted cholestatic hepatitis and severe icterus by using SASP

Takao Katsuragawa¹, Kiminori Hasegawa¹, Takumi Matsumoto¹, Hiroaki Tamura¹, Hidenori Nakai²

¹Department of Rheumatology, Kin-ikyo Chuo Hospital, Sapporo Japan, ²Department of Rheumatology, Kin-ikyo Sapporo Hospital, Sapporo Japan

We report severe drug-induced cholestatic hepatitis by SASP. Case: 80-year-old male. Past history: Diabetes. He felt pain on some joints in March 2010. We diagnosed it RA and start to use SASP in May 2010. After 2 months he came ER because of consciousness disorder. His laboratory data showed hypoglycemia and hepatic injury (glucose 25, AST582, ALT638, ALP2426, T-Bil6.5, D-Bil2.6). There were no rash and all kinds of hepatitis viruses and HHV-6, CMV were negative. We diagnosed it drug-induced hepatitis by clinical history and liver biopsy. Transaminase decreased slowly but icterus became worse, AST53, ALT94, ALP1751, γ GTP467, T-Bil25.0, D-Bil12.6 after 26days. As bilirubin elevated we used bilirubin absorption, but it was not continued because of wobble. We used ursodeoxycholic acid and he recovered.

CR4-4

Seven patients of malignant lymphoma and rheumatoid arthritis treated with MTX

Tomoo Murayama, Tomoki Yonaha, Tasuku Kikumura, Kiyomitsu Nagayama, Masato Oroku, Ken Kitamura, Tung-Huei Chang, Yoshiki Shiohira

Department of Medicine, Tomishiro central Hospital, Tomigusuku, Okinawa, Japan

We had 7 patients of malignant lymphoma with rheumatoid arthritis (RA) from April 2008 to October 2010. Age : 50 to 77 years old, Gender : 5 female 2 male. RA disease duration : 5 to 30 years. MTX use of the term from 5 years to 13.5 years, MTX usage of all

cases of 8mg/week respectively. Two patients had been treated with anti TNF α drug. Clinical outcome : Five patients were recovered by stopping treatment with MTX. One patient was died and one received chemotherapy. Histopathologically, 5 cases were Bcell-type and 2 cases were Tcell-type. Treatment with MTX brought dramatic remission in RA patients. We here discuss clinical relevance of the occurrence of malignant lymphoma in RA patients treated with MTX.

CR4-5

Methotrexate-induced lymphomatoid granulomatosis in rheumatoid arthritis

Hiroshi Oiwa, Kazuhiko Kumagai, Eiji Sugiyama

Department of Clinical Immunology and Rheumatology, Hiroshima University, Hiroshima, Japan

A 65-year-old woman was referred to us for multiple skin nodules, which had appeared with itching on extremities for 4 months. She had a 27-years-history of RA and had been taking 6 mg/wk of methotrexate (MTX) for 17 years. CT of the chest showed multiple lung nodules. A biopsy of the skin nodule showed massive infiltration of large EBER-positive lymphoid cells in the peri-vascular area, surrounded by moderate infiltration of small CD3-positive lymphoid cells in the dermis and the subcutaneous tissue. She was diagnosed as lymphomatoid granulomatosis (LyG) and eventually had a tonic-clonic seizure with cerebrospinal fluid pleocytosis. She recovered within 4 weeks after discontinuation of MTX. This is the first case with MTX-induced LyG with a seizure, associated with spontaneous resolution.

CR4-6

Two Cases of Methotrexate-associated Hodgkin's lymphoma in patients with RA

Karin Shimada, Tomoya Miyamura, Akiko Idemoto, Yoshiro Hourai, Motoko Ishida, Soichiro Takahama, Rumi Minami, Masahiro Yamamoto, Eiichi Suematsu

Department of Internal Medicine and Rheumatology, Clinical Research Center, National Hospital Organization, Kyushu Medical Center, Fukuoka, Japan

Case 1, A 62-year-old woman treated with MTX for since May 1995 showed increased level of CRP and abdominal lymphadenopathy in May 2008. Histological examination of the lymph node revealed Hodgkin's lymphoma. She received chemotherapy, and achieved clinical remission. A case 2, a 67-year-old woman had been treated with MTX for RA since August 2008. She presented with fever and showed increase level of CRP in June 2010, computed tomography showed enlarged paraaortic lymph nodes and histological examination revealed Hodgkin's lymphoma. After the interspersion of MTX therapy, the enlarged lymph nodes were decreased, so she was followed without therapy. We need to be aware of Hodgkin's lymphoma as well as Non-Hodgkin's lymphoma in RA patients treated with MTX.

CR4-7

Cases of rheumatoid arthritis with severe side effects of methotrexate (MTX)

Keiichi Yoshimoto

Department of Internal Medicine, Kurobe City Hospital, Toyama, Japan

We present here four cases of rheumatoid arthritis (RA) with severe side effects of MTX. Three cases were diagnosed as MTX associated acute interstitial pneumonia (IP) and each cases were complicated hypoxia. They, however, were responded well with methyl prednisolone pulse therapy. Their pattern of IP markers varied from each cases and it were difficult to distinguish from pneumocystis *jiroveci* pneumonia. Another one patient was admitted to our hospital due to pancytopenia and treated with antibiotic, folic acid, G-CSF and blood transfusion. Conclusion: When we treat RA, we have to pay attention to direct drug side effect. Especially, MTX can cause severe side effect such as IP and pancytopenia. These are sometimes fatal, so the early diagnosis and therapy are basic but very important.

Poster

P1-001

Synovial cell proliferation and reparative regeneration in knee osteoarthritis

Shuichi Karasaki

Research Laboratory of Nippon Well-Being Foundation, Aizu Chuo Hospital, Aizuwakamatsu, Japan

Knee joint aspirations of synovial fluids were obtained from OA outpatients for consecutive <18 years. The fluids contained fine pieces of synovial villi (SV), which were densely packed with growing embryonic-like mesenchymal cells, in order to restore the missing parts of degenerated cartilage surface. In vitro properties of SV cells were examined within syringes (suspension) and flasks (adherence). Hyaluronan was produced during the mitosis period of growth cycle of SV cells and provided an environment conducive to the growth and migration of mesenchymal cells in suspension culture. Released SV cells took on the characteristic of growing macrophages. SV mesenchymal cells continued to proliferate in adherent culture and further made cell-type conversion into osteocytes and adipocytes.

P1-002

Total knee arthroplasty combined with osteotomy treatment for osteoarthritis

Nobutaka Kaibara, Hisaaki Miyahara, Yukio Esaki, Goh Hirata, Fuyuki Tominaga

Department of Orthopedic Surgery, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan

In the presence of extra-articular deformity, malalignment and imbalance may result in total knee arthroplasty. We report our experience with corrective femoral osteotomy and total knee arthroplasty associated with extra-articular femoral deformity. A case is a man who was treated supracondylar fracture of the femur conservatively when he was eighteen years old. Forty years later, he complained gonalgia at the affected site. At the initial visit, we observed a varus knee malalignment and osteoarthritis of the knee. Then, we performed corrective femoral osteotomy and total knee arthroplasty at the same time. The site of osteotomy was fixed with locking plate that allowed early partial weight bearing. Six months later, there are no correction loss and radiolucent line around implants.

P1-003

Clinical results for revision total hip arthroplasty with cementless cup

Takaaki Shishido, Toshinori Masaoka, Yoichi Katori, Toshiyuki Tateiwa, Kengo Yamamoto

Department of Orthopedic Surgery, Tokyo Medical University

The purpose of this study is to review the outcome revision hip arthroplasty using cementless acetabular cup. 43 revisions using cementless acetabular cup were performed in 42 patients. The mean follow up period was 54 months. These cases were divided into two groups as follows: group A; revisions without bone graft (22 joints), group B; revisions with bone graft (21 joints). Postoperative X-ray showed there was no significant deference of the cup setting position in each group. The migration of the socket has not been observed in all cases at the latest follow-up. The mean JOA hip score improved in each groups. We are confident that results of acetabular

reconstruction using cementless acetabular cup are satisfactory. If there is large bone defect, bone graft should be considered.

P1-004

The difference of serum MMP-3 during operative procedure in highly activated RA

Naohiro Asada

Tsuruga Municipal Hospital

We have evaluated change of serum MMP-3 level between pre and post operative procedures including the synovectomy in patients with highly activated RA. Five patients were female, and one was male. The average of age was 71 years old. Total joint replacement was performed in 5 cases, arthroscopic synovectomy was performed in 4 cases, in all 6 patients. They had not been treated with Bio-therapy before the surgery. The significant difference between before and after surgery was estimated by Wilcoxon signed-ranks test. In 7 of 9 cases, serum MMP-3 level significantly decreased in post-operation, compared with pre-operation ($p < 0.05$). Especially, total joint replacement was effective in all 5 cases. The surgical procedure including the synovectomy was still effective option before Bio-therapy.

P1-005

Analysis of RF and anti-CCP antibody at our hospital and medical checkup center

Eishi Uechi, Yuri Ohara, Atsushi Nomura, Hisanori Shimizu, Yasuhiro Suyama, Mitsumasa Kishimoto, Ken-ichi Yamaguchi, Yukio Matsui, Masato Okada

St. Luke's International Hospital, Tokyo, Japan

Rheumatoid factor (RF) and anti-CCP antibody test in the new rheumatoid arthritis (RA) classification criteria is more important than before. It is thought that many people take these tests, its interpretation is important. We extracted patients who had RF and anti-CCP antibody test from St Luke's hospital and medical checkup center's medical record between 2003 and 2010 and analyzed these data. 65535 patients are measured RF, 1.9% have high value, 5.4% and 1.6% respectively at our hospital and checkup center. There were 112 patients who were pointed out high RF by checkup and visited us. 3 people of those were diagnosed as RA. We consider whether the RF measurement of the checkup helps early diagnosis of RA. We increase the number of the cases more and examine the confounding factors.

P1-006

ACPA as a disease activity marker of RA

Koji Nomura¹, Yasuaki Aoki¹, Hidetoshi Kagawa²

¹Dept. of Orthopedic Surgery, Himeji Red Cross Hospital, ²Dept. of Internal Medicine, Himeji Red Cross Hospital

(Introduction) Anti-cyclic citrullinated peptide antibodies (ACPA) have recently emerged as sensitive and specific markers of RA and are important in ACR/EULAR new criteria. However it has been unknown whether ACPA is also important in RA disease activity. We have experienced a RA patient case whose ACPA value was decreased in respond to good course of treatment and finally became negative. (Case) 77-year-old Japanese woman presented with sudden onset of severe and progressive multiple joint pains one year ago. At the first medical examination, her ACPA showed 69.3, RF negative, CRP 19.98, and MMP-3 1867. After the DMARDs treatment and bilateral TKA, her ACPA became negative (2.6) and

DAS-CRP was 2.7. (Conclusion) ACPA seems to be a useful marker in judging a disease activity of RA.

P1-007

Analysis of plasma pentraxin 3 in rheumatoid arthritis

Shunichi Miyauchi¹, Kunihiko Umekita¹, Yumi Kaneko¹, Shota Sakaguchi², Yayoi Hashiba¹, Motohiro Matsuda¹, Kazuyoshi Kubo², Shiro Ueno¹, Norio Kusumoto¹, Ichiro Takajo¹, Yasuhiro Nagatomo¹, Toshihiko Hidaka², Akihiko Okayama¹

¹Department of Internal Medicine, Rheumatology, Infectious Disease, and Laboratory Medicine, University of Miyazaki, Miyazaki, Japan, ²Institute of Rheumatology, Zenjinkai Shimin-no-Mori Hospital, Miyazaki, Japan

The plasma concentration of pentraxin 3 (PTX3) was measured and compared with the diseases activity markers (CRP, ESR, and DAS-28) in patients with rheumatoid arthritis (RA). Its change after the treatment with biologics and leukocytapheresis (LCAP) was also assessed in the present study. Plasma PTX3 in patients with RA was significantly higher than that in normal controls, however, it did not correlated to the other diseases activity markers. Although the diseases activity markers showed marked decrease after the treatments with biologics and LCAP, PTX3 did not. Therefore, the mechanism of high PTX3 may be different from that of the increased levels of other diseases activity markers in RA.

P1-008

Significance of Serum pepsinogen I / II ratio in Patients with Rheumatoid Arthritis

Akinori Matsumori, Fumitaka Ogushi

National Hospital Organization Kochi National Hospital, Kochi, Japan

Objective: To investigate relationship between clinical features in patients with rheumatoid arthritis (RA) and serum levels of pepsinogen (PG).

Methods: Serum PG levels were measured in 104 patients (male 22, female 82) without renal failure and administration of proton pump inhibitor. And then we analyzed clinical features including smoking history and *Helicobacter pylori* (HP) gastric infection in 19 RA patients (male 9, female 10) with both low PG I titer (≤ 70) and low PG I / II ratio (≤ 3).

Results: Eight of the 19 patients (male 7, female 1) were smoker, and 13 patients of them had HP infection. Anti-HP therapy induced increase of PG I / II ratio.

Conclusion: These results suggest that lower serum PG I / II ratio in RA patients is associated with smoking history and HP infection.

P1-009

The Examination of the availability of Indirect Fluorescent ANCA Measurement.

Hiromi Nakaishi¹, Kentaro Susaki², Tomohiro Kameda², Yohei Takeuchi², Shusaku Nakashima², Hiromi Kizu², Miharu Izumikawa², Hiroaki Dobashi²

¹Department of Clinical Laboratory, Faculty of Medicine, Kagawa University, ²Division of Endocrinology and Metabolism, Hematology, Rheumatology, and Respiratory Medicine, Department of Internal Medicine, Faculty of Medicine, Kagawa University

[Purpose] ANCA plays an important role in ANCA-associated vasculitis (AAV). Recently, it is common to measure MPO/PR3-ANCA by ELISA for the diagnosis and the evaluation of the disease

activity. In this study, we tried to evaluate the availability of IF-ANCA in MPO/PR3-ANCA negative vasculitis at disease onset or through the treatment. We also identify the specific antigen of MPO/PR3-ANCA negative and IF-ANCA positive vasculitis. [Method] We used MPO-ANCA test, fluoro ANCA test and ANCA panel kit for measurement. [Results] IF-ANCA was positive about 60-70% in MPO/PR3-ANCA negative vasculitis. BPI positive cases was tend to be with chronic respiratory infection. [Discussion] Only the measurement of MPO/PR3-ANCA is inadequate for the diagnosis and the treatment marker of AAV.

P1-010

PTX3 in vasculitis syndromes

Shunichi Fujita, Takashi Nakazawa, Keisuke Nishimura, Natsuko Miura, Toshihiko Yokota

Department of Endocrinology and Rheumatology, Kurashiki Central Hospital, Kurashiki, Japan

〈Objectives〉Pentaxin 3 (PTX3) is made in response to primary proinflammatory signals, and it was reported that PTX3 levels were elevated in active phase of acute coronary syndromes and small vessel vasculitis. We evaluated PTX3 feasibility to provide an activity tool in vasculitis syndromes. 〈Methods〉PTX3 levels were measured in 8 vasculitis syndromes at active phase. We examined time-dependent changes of PTX3. 〈Results〉PTX3 levels were elevated in 4 cases with patients in active Takayasu's arteritis. PTX3 level was abnormally high in acute renal failure. PTX3 levels did not always correlate well with disease activity of vasculitis syndromes. 〈Conclusions〉PTX3 levels were not always elevated at the active phase, but it is necessary to be going to pile up further cases in the future.

P1-011

Quantitative evaluation of corticosteroid myopathy with a bio-impedance method

Mari Ushikubo¹, Hirotoshi Mtsumoto¹, Kazuhide Gomi¹, Taku Yabuki¹, Ikuko Tanaka², Kumiko Akiya¹, Hirotoshi Tanaka³, Hisaji Ohshima¹

¹National hospital organization Tokyo medical center, Tokyo, Japan,

²Department of Laboratory Medicine, Fujita Health University School of Medicine, Toyoake, Japan, ³Division of Clinical Immunology, ACRC, Institute of Medical Science, University of Tokyo, Tokyo, Japan

Background) Corticosteroid myopathy (CS-My) is one of the well known adverse effects of CS. Quantitative analysis of CS-My, however, has not been established. Purpose) To clarify varilities of a bio-impedance method (BIA) for CS-My. Method) Six patients who started taking > 30mg/day of prednisolone. A body composition analyzer (InBody) was used as BIA to measure the muscle weight (BIAMw). Results) 1; MMT and Kagen scores showed significant reduction after CS therapy. 2; BIAMw also showed a significant reduction ($p < 0.05$) from 22 ± 3 to 18 ± 3 . 3; Changes in the BIAMw and in MMT or Kagen score correlated significantly ($p < 0.05$). 4; BIAMw showed a low value after 1y while the body weigh recovered. Conclusion) It was suggested that the BIA could be used for quantitative evaluation of CS-My.

P1-012

Examination about the effects of glucocorticoid for renal function.

Hiroki Mitsunaka, Junichi Danjo, Kenji Akiyama

Glucocorticoid (GC) is widely used for treatment of various incurable diseases. We evaluated the association between GC and renal dysfunction in 107 collagen disease patients. We investigated the markers of renal function (microalbuminuria, cystatin C) and lipid metabolism (LDL/HDL rate) in patients with or without GC treatment. We excluded the patients who had type 2 DM, SLE, vasculitis, and glomerulonephritis. Cystatin C was significantly elevated in patients treated by GC compared with untreated group. As for the group treated GC more than 40 months, cystatin C was significantly increased compared with untreated group. We found microalbuminuria were positively correlated with cystatin C. Moreover we found positive correlation between cystatin C and L/H rate.

P1-013

The clinical characteristics of RS3PE syndrome

Tomoki Origuchi^{1,2}, Kazuhiko Arima², Tomohiro Koga², Shin-ya Kawashiri², Mami Tamai², Hideki Nakamura², Satoshi Yamasaki², Atsushi Kawakami², Toshiyuki Aramaki³, Nozomi Iwanaga⁴, Masako Furuyama⁵, Toshiaki Tsukada⁶, Yojiro Kawabe⁷, Taiichiro Miyashita⁸, Masanobu Mine⁹, Katsumi Eguchi¹⁰

¹Department of Rehabilitation Sciences, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan, ²Department of Immunology and Rheumatology, Graduate School of Biomedical Sciences, Nagasaki University, ³Nagasaki Atomic Bomb Hospital, ⁴Sasebo Chuo Hospital, ⁵Nagasaki Kita Hospital, ⁶Isahaya General Hospital, ⁷Ureshino Medical Center, ⁸Nagasaki Medical Hospital, ⁹Suga Orthopedic Hospital, ¹⁰Sasebo General Hospital

Objective. To clarify the clinical characteristics of RS3PE syndrome. **Method.** The total of 31 cases, who were diagnosed as having RS3PE syndrome, were subjected to be analyzed the clinical characteristics. **Results.** Average age was 77.3 ± 7.8 years old. 18 patients had a fever with arthralgia. Pitting edema was seen in the hands of 19 patients and the feet of 27 patients. The levels of MMP-3 were extremely high in patients with RS3PE syndrome. All patients had a good response to prednisolone. But malignancies were complicated in 13 patients (41.9%) with RS3PE syndrome. **Discussion.** We suggested that RS3PE patients had extremely high levels of MMP-3 and VEGF, and were frequently complicated with malignancies.

P1-014

Anti-ds-DNA antibodies (DNA Ab) determined by two kits and activity of SLE

Daisuke Kashiwakuma¹, Shunsuke Furuta¹, Isao Matsuura¹, Kei Ikeda², Hiroshi Nakajima², Shoji Yoshida¹, Itsuo Iwamoto¹

¹Research Center for Allergy and Clinical Immunology, Asahi General Hospital, Chiba, Japan, ²Department of Allergy and Clinical Immunology, Chiba University Hospital, Chiba, Japan

DNA Ab are correlated with activity of SLE, but their detection differs in assay kits. Methods: DNA Ab were determined in 150 samples from SLE patients and 177 samples from non-SLE patients, using MESACUP DNA-II test ds (MBL) and UniCAP ELIA dsDNA (Phadia). Results: Positive and negative agreement rate between two assays in SLE patients were 70.5% and 71.6%, respectively. Sensitivity and specificity for SLE were 50.6% and 87.0%, respectively, for MESACUP and 41.3% and 91.0%, respectively, for ELIA. There were discrepancies in DNA Ab in 37 samples between

two assays. But there were no significant differences in the levels of C3, leukopenia or other autoantibodies prevalence. Conclusion: There are few SLE patients that show discrepancies in DNA Ab determined by the different detection kits.

P1-015

CD64 expression on neutrophils in healthy persons--The third report--

Yoshiaki Kuga¹, Jinju Nishino², Keita Nishimura³, Sakae Tanaka⁴, Toshihiro Matsui⁵, Shigeto Tohma⁵, Akiko Komiya⁵

¹Center for Rheumatic diseases, Wakaba Hospital, ²Nishino Clinic, Orthopaedics and Rheumatology, ³Teikyo University School of Medicine, Department of Orthopaedic Surgery, ⁴Department of Orthopaedic Surgery Faculty of Medicine The University of Tokyo, ⁵Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagamihara Hospital, National Hospital Organization

CD64 expression on neutrophils is a useful marker to detect infection. But the effect of general health conditions on CD64 was not investigated. We examined age, sex, body mass index, blood pressure, serum lipid level, transaminases, complete blood count, blood sugar, and the expression level of CD64 per neutrophil on 170 healthy persons. CD64 expression on neutrophils was as follows: median 926molecules/cell, interquartile 690-1236, the minimum 416 the maximum 2560. In seven persons CD64 were higher than cutoff level of 2000. There was positive correlation between BMI and CD64. But the number of person with obese was only one among seven false positive persons. Our result suggests that these conditions do not affect CD64 expression on neutrophils in healthy persons.

P1-016

Lansoprazole increase the cyclosporine concentration in CVD patients

Takuya Kotani, Kentaro Isoda, Koji Nagai, Daisuke Wakura, Kenichiro Hata, Shuzo Yoshida, Tohru Takeuchi, Shigeki Makino, Toshiaki Hanafusa

Department of Internal Medicine (I), Osaka Medical College, Takatsuki, Osaka, Japan

We investigated the influence of a lansoprazole (LPZ), on the blood CSA level in patients with collagen disease. Among collagen disease patients treated with CSA in our department after January 2008, the subjects were 19 serial patients who had not received any agent that influences CYP metabolism other than LPZ. The CSA C0 (trough) levels were measured and compared between LPZ-treated (n=8) and non-LPZ-treated (n=11) groups. The mean CSA C0 levels were 214.5 ± 23.6 and 137.7 ± 18.3 ng/ml in the LPZ-treated and non-LPZ-treated groups, respectively, showing a significant difference ($P=0.02$). The mean CSA C0 level/dose/body weight ratios were significantly higher in the LPZ-treated group ($P=0.02$). Combination therapy with LPZ may increase the blood level of CSA. This must be considered.

P1-017

The factors which give influence to the salivation in collagen diseases

Etsuko Maeshima^{1,2}, Kanako Furukawa², Shinichiro Maeshima³, Yasutaka Yamauchi⁴

¹Department of Health and Sport Management, Osaka University of Health and Sport Sciences, ²Third Department of Internal Medicine,

The diagnosis of the oral xerosis is important for the health maintenance of a whole body and the oral cavity in the autoimmune disease. We examined the influence of disease or medicine to salivation by using new filter paper. Fifty-three collagen disease patients were recruited. Steroid use and dose did not give influence to quantity of saliva. The quantity of salivation decreased significantly in the case of SjS or in the patients complicated with SjS ($p < 0.01$). However, in SLE, SSc and MCTD, there was the case that the decrease of the quantity of saliva was accepted even if SjS did not accompany. New filter paper was useful for the diagnosis of the oral xerosis, but it seemed that more detailed examination was necessary for a cause search.

P1-018

Allopurinol therapy in CKD patients with hyperuricemia

Izaya Nakaya

Department of Nephrology, Iwate Prefectural Central Hospital

Objective: We performed one year prospective study in 107 patients with CKD to examine the effect of allopurinol on a combined outcome of death, renal failure, cardiovascular event or increase of serum creatinine by more than 20%. **Results:** Both at base line and one year, mean urate levels in allopurinol group ($n = 59$) were lower than those in control group ($n = 48$) (6.9 ± 1.4 vs. 7.6 ± 1.6 and 7.0 ± 1.4 vs. 7.8 ± 1.6 mg/dL, respectively). Twenty four patients reached the outcome in allopurinol group and 14 in control group. Multivariable analysis showed no association of allopurinol with the outcome (HR 1.64, CI 0.54-5.05, $p = 0.39$) and no gout attack was observed in both groups. **Conclusion:** This study demonstrates allopurinol had no definite effect on CKD patients with hyperuricemia.

P1-019

Treatment discontinuation in patients with gout

Naomi Ichikawa, Atsuo Taniguchi, Wako Urano, Haruko Inoue, Mikiko Shinozaki, Yumi Koseki, Hisashi Yamanaka
Institute of Rheumatology, Tokyo Women's Medical University

Poor compliance is a problem in the management of gout. However, no study has been performed on treatment discontinuation in gout patients. 267 male patients with gout were included in the study. 30% of patients stopped treatment during the first month. The clinical characteristics at the 1st medical examination were compared between patients who stopped treatment before 12th month and patients who continued treatment for 12 months. Multivariate analysis showed that factors associated with treatment discontinuation were higher serum urate levels, and history of urolithiasis. The number of gouty attacks, the presence of tophi and metabolic syndrome were not influenced the treatment continuation. This study suggests that the adherence is enhanced by prevention of early drop-out.

P1-020

The patients who needs to enter the hospital with pseudogout

Satoshi Kashiwagi, Yoshikiyo Ohasawa, Syuichi Nakagawa, Hitoshi Nakata, Haruki Imura

Amagasaki medical coop hospital, Hyogo, Japan

Pseudogout is one of the important disease which we diagnose what kind of arthritis in daily examination. In this time, we research about pseudogout in our hospital. The patients who came to internal medicine, orthopedics, rheumatology were 63.290 from April 2009 to March 2010. The patient who were diagnosed as pseudogout were 30 patients, and who needed to enter the hospital were 10 people (male 1, female 9, the average of year 74 years). They were diagnosed by joint injection and appeared the calcium pyrophosphate dihydrate. The reasons to enter the hospital were that they had hard pain and it was difficult to treat with only NSAID, and it was hard to live in their house by themselves. If patients had pain in lower joints, it is important to treat in bed at first.

P1-021

Survey of crystal-induced arthritis in patients with rheumatic arthritis

Naofumi Chinen¹, Ikuko Masuda², Takahiro Nunokawa¹, Katsuaki Shiroto¹, Yoshiki Nagai¹, Satoshi Watanuki¹, Mutsuhito Ui¹, Kota Shimada¹, Shoji Sugii¹, Shinichi Inada¹, Naoto Yokogawa¹

¹Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center, Tokyo, Japan, ²Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

[Introduction] Crystal disease can coexist in patients with rheumatoid arthritis (RA). **[Purpose]** We investigate the types and incidence of crystals in the synovial fluid of RA patients. **[Methods]** With informed consent, synovial fluid was taken from RA patients and examined blindly by a crystal expert at Tokyo Women's Medical University using polarizing microscope and alizarin red staining. **[Results]** Three of 16 RA patients complicated with Calcium pyrophosphate dehydrate (CPPD) disease. Case 1: acute monoarthritis, Case 2: refractory polyarthritis, Case 3: acute poly-arthritis. **[Conclusion]** CPPD disease can coexist with RA. Joint aspiration and crystal examination of the synovial fluid can establish the diagnosis.

P1-022

Crowned dens syndrome and Calcific tendinitis of the longus colli

Keita Fujikawa¹, Toshiaki Tsukada¹, Atsushi Kawakami²

¹Department of Rheumatology, Isahaya Health Insurance General hospital, ²Department of Immunology and Rheumatology, Graduate School of Biomedical Sciences, Nagasaki University

Calcium phosphate crystal deposition disease are caused by the deposition of CDDP crystals and BCP crystals in joints and periarthritic tissues. We report three cases of Crowned dens syndrome (CDS) and two cases of Calcific tendinitis of the longus colli. All patients had acute neck pain. The patients of CDS had calcification surrounding odontoid process in cervical CT examination. Two patients had radiographic calcification in deltoid ligament of wrist joints and in cartilage of knee joints. The patients of Calcific tendinitis had swallowing pain, calcification in preodontoid and inflammation in the prevertebral space. All patients improved with NSAIDs. Differences between these diseases were observed in clinical symptom and the region of calcification.

P1-023

Therapy experience of three cases of lung cancer with rheumatoid arthritis.

Kohei Miyake, Keiko Morishita, Katsuhiko Murakami, Katsutoshi Sunami

Chugoku central hospital, Mutual Aid Association of Public School Teachers, Fukuyama, Japan

Previous studies report that the risk of lung cancer is increased in Rheumatoid arthritis (RA) patient than general population. But little is reported about therapy of RA with lung cancer. Three RA patients with lung cancer at 2010 diagnosis in our hospital were examined. Chemotherapy, Operation, and Radiation were performed individually. In chemotherapy patient, leucopenia was observed without deny influence of MTX although stopped before therapy. In operation, MTX and TAC were stopped before surgery, and recovery was satisfactory, but RA was relapsed. In radiation, MTX was used safely. DMARDs like Methotrexate (MTX) may influence cancer therapy. We report therapy three case of lung cancer with RA. Further investigation is required for therapy of RA with lung cancer.

P1-024

Anti-TNF Therapy for Rheumatoid Arthritis in Ten Patients with Tuberculosis

Tomoshige Matsumoto

Department of Clinical Research and Development, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases

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).

We successfully treated RA in ten patients with tuberculosis reactivated by infliximab therapy. 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.

P1-025

Effect of tacrolimus on interstitial lung disease with rheumatoid arthritis

Kensuke Oryoji, Naoko Ueki, Fumihiko Konishi, Kazuo Kamada, Shinichi Mizuki, Eisuke Yokota

Matsuyama Red Cross Hospital, Matsuyama, Japan

Tacrolimus is an antirheumatic drug. Meanwhile, there are some reports that tacrolimus is also effective on interstitial lung disease (ILD) with collagen diseases. We report the effect of tacrolimus on rheumatoid arthritis (RA) associated ILD, by comparing retrospectively 18 patients treated with tacrolimus to patients without tacrolimus. We analyze whether tacrolimus is effective on RA-ILD, by investigating their age, sex, disease duration, staging, titer of rheumatoid factor (RF) and anti-CCP antibody, exacerbation of ILD, lung vital capacity, lung diffusing capacity, the pattern of ILD, KL-6, SP-D, disease activity, the use of other DMARDs or biologics, RF immune complex, antinuclear antibody, etc.

P1-026

Organic pneumonia associated with RA during TNF inhibitor treatment

Junya Nagasawa, Kazuhiro Kurasawa, Ryutaro Yamazaki, Satoko Arai, Takayoshi Owada, Reika Maezawa, Takeshi Fukuda

Pulmonary Medicine and Clinical Immunology, Dokkyo Medical University, Tochigi, Japan

We report 3 cases of RA patients who developed organic pneumonia (OP) during treatment with TNF inhibitors. Case1: 46 year old female. The patient had received adalimumab (ADA) for 1 month and developed OP with fever. ADA and MTX was stopped and OP was improved. Restart of ADA did not cause OP. Case2: 53 year old male. He was treated with ADA for 6 month developed OP with fever. Glucocorticoid (GC) improved OP and ADA was restarted without recurrence of OP. Case3: 53 year old female. She had been treated with etanercept (ETN) for 2 years and developed OP. GC improved OP and ETN was switched ADA that improved arthritis without development of OP. These 3 cases suggest TNF plays little roles in the development of OP in RA.

P1-027

Pulmonary nocardiosis in a patient with RA receiving infliximab

Seiji Yoshizawa¹, Ayako Takagi¹, Satomi Hisamoto¹, Shun-ichiro Ota¹, Tatsuoki Mashima², Kenji Tanaka¹

¹Division of rheumatology, Hamanomachi Hospital, Fukuoka, Japan, ²Division of orthopedics

A 66-year-old woman, who was diagnosed rheumatoid arthritis (RA) in 2003, had been treated with etanercept since January 2008. In August 2008, the scleritis developed in her left eye. She was treated with corticosteroid but the scleritis deteriorated frequently with the reduction of corticosteroid. Etanercept was changed to infliximab (INF) for the purpose of the treatment of the scleritis. After third infusion of INF, a chest radiograph showed nodules in both lung fields. Subsequently, Nocardia was detected in her sputum. We started treatment with sulfamethoxazole and trimethoprim. As a result, nodular lesions thereafter became scarred. Since anti-TNF- α therapy increases the risk of the opportunistic infection, Nocardia infection should be noted when the lung involvement appears.

P1-028

A case of RA with influenza, pneumocystis and cryptococcal pneumonia

Ayako Takagi¹, Yasushi Inoue¹, Masahiro Ayano¹, Kosuke Sumida¹, Kentaro To¹, Yojiro Arinobu^{1,2}, Hiroaki Niiri¹, Hiroshi Tsukamoto¹, Natsumi Nagao¹, Sho Ueda², Satomi Hisamoto¹, Takahiko Horiuchi¹, Koichi Akashi^{1,2}

¹Department of Clinical Immunology, Rheumatology, and Infectious Diseases, Kyushu University Hospital, Fukuoka, Japan, ²Center for Cellular and Molecular Medicine, Kyushu University Hospital, Fukuoka, Japan

A 61-year-old woman, treated for RA with a combination of PSL (10 mg/day), MTX (8 mg/week) and TAC (3 mg/day), was transferred to us for dyspnea and high fever. On arrival, she had severe hypoxia and her chest X-ray revealed diffuse ground-glass opacities. After influenza and pneumocystis pneumonia were diagnosed, she transiently recovered by administration of antiviral agents, trimethoprim-sulfamethoxazole and high-dose PSL, but there was a recurrence of high fever in two weeks. Antifungal drugs were given as cryptococcal pneumonia was diagnosed by intratra-

cheal aspiration. She gradually got better and left our hospital in three months. We should be aware biologic-naïve nonelderly patient with no previous pulmonary complications would concurrently have many serious infections.

P1-029

A case with life-threatening organizing pneumonia associated with RA

Kosei Tsuchida, Hiromasa Nakano, Yukiko Takakuwa, Seido Ooka, Tomohiko Shibata, Hitoshi Ogawa, Kohei Azuma, Kumiko Tonooka, Hiroko Nagafuchi, Takahiro Okazaki, Hidehiro Yamada, Shoichi Ozaki

Division of Rheumatology and Allergy, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan

We report a 59-year-old female case of organizing pneumonia (OP) associated with RA. She was diagnosed with RA in 1997. She was admitted because of severe dyspnea in October 2010. No infectious agent was identified. The diagnosis of acutely developed OP was made based on the clinical course and radiologic findings. Respiratory failure worsened even after administration of high-dose glucocorticoid, and mechanical ventilation was required. Arterial oxygenation improved after the initiation of ventilatory support. On the 8th hospital day, she was weaned from ventilatory assistance. On the 36th hospital day, she was discharged without oxygen supplementation. The prognosis of OP is generally good in patients with RA. However, life-threatening OP has been reported rarely.

P1-030

A case of rheumatoid arthritis complicated by *Streptococcus milleri* lung abscess.

Makiko Maekawa¹, Kentaro To¹, Soshi Takahashi¹, Ayako Takaki¹, Hiroshi Tsukamoto¹, Hiroaki Niino¹, Yojiro Arinobu², Yasushi Inoue¹, Kosuke Sumida¹, Masahiro Ayano¹, Sho Ueda¹, Satomi Hisamoto¹, Takahiko Horiuchi¹, Koichi Akashi¹

¹Department of clinical Immunology, Rheumatology, and Infectious Disease, Kyushu University Hospital, ²Center for Cellular and Molecular Medicine, Kyushu University Hospital

A 62-year-old woman, treated with methotrexate, salazosulfapyridine, and prednisolone for rheumatoid arthritis, had an increase of neutrophil count and level of serum CRP in September 2010. Chest X-ray revealed a mass lesion in the right mid-lung field. Bacterial culture of sputum and bronchial secretion resulted in an isolation of mainly oral resident bacteria. CT-guided percutaneous lung biopsy showed necrotic tissue with inflammatory granulation, and *Streptococcus constellatus*, one of the *Streptococcus milleri* group (SMG) was isolated from the necrotic tissue. She was diagnosed as lung abscess with SMG, which was rapidly improved after administration of SBT/ABPC. Percutaneous lung biopsy was useful to isolate resident bacteria as pathogen, such as SMG in patients with lung abscess.

P1-031

Two cases of nocardia lung abscess in collagen disease patients

Toshioki Sawaki, Takuji Nakamura, Haruka Iwao, Akio Nakajima, Miyuki Miki, Tomoyuki Sakai, Yoshimasa Fujita, Yasufumi Masaki, Toshihiro Fukushima, Hisanori Umehara

Kanazawa Medical University Hematology and Immunology, Uchinadamachi Ishikawa, Japan

We report two cases of lung abscess caused by *nocardia sp.* in collagen disease patients. Case1: 70-year-old man, who was treated with systemic prednisolone and cyclosporin A for Dermatomyositis and Interstitial pneumonia. Follow-up chest plain CT revealed a right-lung nodule. Bronchoscopy performed, but any findings were not detected. As a result of pneumoresection with thoracoscope, he diagnosed nocardiosis. Any dissemination wasn't found with several examinations. Case2: 76-year-old man, who was regularly treated with systemic prednisolone for poor controlled microscopic polyangiitis. It found in chest X-ray film to have a right lung nodule. Nocardiosis was diagnosed by sputum culture. Later he improved with trimethoprim-sulfamethoxazole according to in vitro susceptibility tests.

P1-032

An outbreak of *P. jirovecii* infection among outpatients with RA

Shunsuke Mori

Clinical Research Center for Rheumatic Disease and Department of Rheumatology, NHO Kumamoto Saishunsou National Hospital, Kumamoto, Japan

Since March 2005, we have advised RA outpatients to undergo PCR tests for *P. jirovecii* on induced sputum. During the first 2 years, only 1 case of *P. jirovecii* pneumonia (PCP) was observed and no asymptomatic carriers were found. Between November 2006 and October 2008, we found 9 asymptomatic carriers, and among these, 3 developed PCP within 1 month. During this period, we encountered additional 5 cases of PCP in outpatients who had not yet undergone PCR tests. Through the eradication of *P. jirovecii* from asymptomatic carriers and PCP patients, the outbreak was resolved. Epidemiological data suggest person-to-person transmission of *P. jirovecii* in our outpatient facility as the predominant route of acquisition. Asymptomatic carriers can serve as an infectious reservoir for *P. jirovecii*.

P1-033

A case of mixed connective tissue disease with cryptogenic organizing pneumonia

Nao Tatsukawa, Koji Nagai, Ayaka Honjo, Takuro Ozaki, Daisuke Wakura, Shuzo Yoshida, Kenichiro Hata, Tohru Takeuchi, Shigeki Makino, Toshiaki Hanafusa

First Department of Internal Medicine, Osaka Medical College

A 62-year-old woman was diagnosed with MCTD because of Raynaud phenomenon, scleroderma, positive anti-RNP antibody, and leukocytopenia in 2007, and had been followed without medication. In January 2010, she was admitted to our hospital for fever, cough, sputum, elevated CRP and hypoxia. Her chest CT revealed multiple consolidation. She was treated with several antibiotics, resulting in an unfavourable response. She was treated with prednisolone 40 mg/day for COP. Her clinical and laboratory findings were improved. COP was associated with collagen vascular disease, but rarely with MCTD. We review this case with reference to previous literature.

P1-034

A case of interstitial pneumonia associated with amyopathic dermatomyositis

Katsura Hohtatsu¹, Kentaro Doe¹, Michiaki Kageyama¹, Makio Kusaoi¹, Kaoru Sugimoto¹, Shouseki Lee¹, Hirofumi Amano¹, Ken Yamaji¹, Yoshinari Takasaki¹

¹Department of Rheumatology and Internal Medicine, Juntendo University school of Medicine, Tokyo, Japan, ²Department of Geriatric General Medicine, Juntendo Tokyo Koto Geriatric Medical Center, Juntendo University School of Medicine

A 36-year-old woman who admitted our hospital because of dyspnea and dry cough showed Gottron sign without any myositis symptoms. Chest computer tomography showed Interstitial shadows in both lower lung fields. We diagnosed interstitial pneumonia (IP) associated with amyopathic dermatomyositis (ADM). Her respiratory failure was not improved despite administration of oral high dose prednisolone and tacrolimus hydrate. So we treated her with methylprednisolone pulse therapy, cyclophosphamide pulse therapy and polymyxin B-immobilized fiber column direct hemoperfusion (PMX-DHP). Her respiratory function and symptoms were recovered and finally she was discharged. Although it is known that IP has an acute course and poor diagnosis in ADM, the present case responded well to these treatments.

P1-035

Clinical significance of KL-6 and SP-D in collagen diseases.

Satoko Arai, Kazuhiro Kurasawa, Junya Nagasawa, Ryutaro Yamazaki, Takayoshi Owada, Takayoshi Owada, Takeshi Fukuda
Department of Pulmonary Medicine and Clinical Immunology

Objective: To evaluate clinical significance of serum KL-6 and SP-D inpatients with active interstitial pneumonia (IP) associated with polymyositis/dermatomyositis (PM/DM) and systemic sclerosis (SSc). **Methods:** Serum KL-6 and SP-D were measured longitudinally. **Result:** Inactive IP of PM/DM, serum KL-6 and SP-D levels were normal in 38% and 53.8% of the patients on admission, respectively. Two weeks later, serum KL-6 and SP-D levels were increased in 68% and 39% of them, respectively. Patients with large increase in KL-6 levels or with high SP-D levels (>200) revealed poor prognosis. **Conclusion:** Serum KL-6 and SP-D levels in PM/DM were not markers of active IP at first visit. However, increase of these markers in 2-4 week predicts poor prognosis.

P1-036

The investigation of CTD-PAH in our facility

Shusaku Nakashima, Tomohiro Kameda, Miharū Izumikawa, Hiromi Kizu, Yohei Takeuchi, Kentaro Susaki, Hiroaki Dobashi
Department of Internal Medicine, Division of Endocrinology and Metabolism, Hematology, Rheumatology and Respiratory Medicine, Faculty of Medicine, Kagawa University, Kagawa, Japan

(Objective) CTD such as MCTD and SSc often complicates with PAH. CTD-PAH indicates poor prognosis. CTD-PAH is categorized in one of the PAH in *Dana Point* classification and we treat under idiopathic PAH guidelines. The efficacy of immunosuppressive therapy (IT) of the CTD-PAH is not established though some reports describe that early intervention is effective. (Methods) We underwent UCG and RHC for CTD-PAH, and evaluate the efficacy of IT and pulmonary vasodilator. (Results) Some cases estimated systolic pulmonary artery pressure ranged 35-45 mmHg by UCG were diagnosed as PAH by RHC. Methylprednisolone pulse therapy would be

useful as IT. (Conclusion) The therapy of CTD-PAH has not been established, and it is necessary to investigate the usage of IT and pulmonary vasodilator for each CTD-PAH.

P1-037

Long term efficacy and safety of Abatacept in 28 patients with RA

Takafumi Hagiwara, Takako Miura, Kosuke Okuda, Takeshi Nakamura, Hiroshi Sunami, Keiko Funahashi, Tsukasa Matsubara
Matsubara mayflower Hospital, Rheumatology, Kato, Japan

Background: Since Sep in 2010, abatacept (ABT) has been widely prescribed in Japan. However, the long term efficacy and safety of ABT in Japanese patients has not been presented yet.

Objectives: To assess the long term efficacy and safety of ABT.

Methods: Clinical efficacy, safety profiles and persistence rate were assessed for 28 patients over a 3 year period.

Results: Of 28 patients, the persistence rate was 82.1% at year 3. 34.6% achieved remission defined by DAS28-CRP < 2.3 at year 2.

Conclusions: ABT was well tolerated with sustained efficacy. In our experience, persistence rate of ABT at year 3 was higher than those of other Biological agents. We will also present the data of 15 patients experienced wash out period (3 months) of ABT.

P1-038

The Abatacept treatment for rheumatoid arthritis in our hospital.

Jiro Yamana, Keisuke Kobayashi, Rie Sasaki, Motoaki Kin, Mitsuhiro Iwahashi, Seizo Yamana
Higashi-Hiroshima Memorial Hospital

We reviewed the efficacy and tolerability of abatacept in 7 cases of RA, participated in clinical trial for active RA despite methotrexate treatment in our hospital. DAS28CRP in 6 of 7 patients were high (> 4.1) and one was moderate (2.7~4.1) at base line. Average DAS28CRP of all patients at base line, 48, 96, and 144 weeks was 5.5, 3.3, 2.8, and 2.6, respectively. DAS28CRP in 3 of 7 patients were moderate, 2 were low (2.3~2.7), and 2 were remission (< 2.3) at 144 weeks. We experienced one case who could continue the treatment despite the recurrence infectious events, such as external anal fistula and perimandibular inflammation. No patients discontinued this treatment through all the periods. Abatacept might be slowly acting, but reliable and tolerable treatment for active RA patients.

P1-039

Experience of treatment by abatacept for rheumatoid arthritis

Katsuaki Kanbe, Atsushi Nakamura, Junji Chiba, Koichiro Hayata, Yasuo Inoue, Kaori Hobo
Department of Orthopaedic Surgery, Tokyo Women's Medical University, Medical Center East

Abatacept is possible to use for rheumatoid arthritis in 2010 in Japan. However it is unknown the efficacy and safety after using abatacept in early phase. We experienced 31 cases, 4 male, 27 female, average age of 59.3 years old, average disease duration of 15.2 years. CRP 0.9 mg/dl, MMP-3 125.9 ng/ml, DAS28 3.95 before using abatacept changed to CRP 0.9 1mg/dl, MMP-3 135.3 ng/ml, DAS28 3.14 at 4 weeks. There are three cases of hypertension and one case of laryngitis. Bone erosion was improved in one case

after two years. Thus CRP was not significantly decreased in 4 weeks however DAS28 was improved by abatacept.

P1-040

Results of a long-term, open-label, randomized clinical trial of Abatacept

Dai Tanaka¹, Ryoko Uesato¹, Kenji Kowatari¹, Taisuke Nitobe¹, Yukitomo Urata²

¹Department of Orthopaedic surgery, Seihoku Chuo Hospital, Aomori, Japan, ²Department of Rheumatology, Seihoku Chuo Hospital, Aomori, Japan

Abatacept is a selective T-cell co-stimulation modulator for the treatment of rheumatoid arthritis (RA). We report the results of clinical trial of Abatacept. **Materials and methods** We studied 13 patients with RA. The patients included 3 males and 10 females with a mean age of 61.8 years (37-72 years). We performed a second phase examination in 12 patients and a third phase examination in 13 patients. Follow-up period was about 3 years after a third phase examination start. **Result** At a third phase examination, the average Disease Activity Score (DAS) 28 scores at study entry, and 3 years were 5.89 and 3.45, respectively. 3 patients were achieved DAS28 remission (<2.6). The average CRP level was improved to 1.3 from 3.2. Repair of focal bone erosions was observed in a patient.

P1-041

SNP algorithms for prediction of efficacy and adverse events of abatacept (ABT)

Tsukasa Matsubara¹, Satoru Koyano², Keiko Funahashi³, Takafumi Hagiwara¹, Takako Miura¹, Kosuke Okuda¹, Mitsuyoshi Iwahashi³, Tomomi Tsuru⁴, Shoichi Uchimura⁵, Shigeru Honjo⁶

¹Matsubara Mayflower Hospital, ²Research Institute of Joint Diseases, ³Higashi-hiroshima Memorial Hospital, ⁴PS Clinic, ⁵Kanzaki Municipal General Hospital, ⁶Honjo Rheumatism Clinic

Purpose: We established SNP algorithms for prediction of responder (R) or non-responder (NR), and adverse events in ABT-treated patients. **Patients and Methods:** 50 RA patients treated with ABT were included in this study. Efficacy was assessed by DAS28(CRP) at 48 weeks after the initial treatment. We scored the relationship between each SNP and efficacy, and estimated total score of 10 SNPs. **Results:** Approximately 92-95% of R or NR group in ABT-responsiveness could be determined by one algorithm. Similarly, 90-95% of adverse events plus or minus in ABT-treated group could be determined by other algorithm. **Conclusion:** The SNP algorithm could be useful for prediction of efficacy and adverse events before treatment with ABT.

P1-042

Abatacept triggers reactivation of HBV-DNA replication in rheumatoid arthritis

Yukitomo Urata¹, Ryoko Uesato², Dai Tanaka², Kenji Kowatari², Taisuke Nitobe², Yoshihide Nakamura³

¹Department of Rheumatology Seihoku Chuo Hospital, Gogyogawara, Japan, ²Department of Orthopaedic Surgery, Seihoku Chuo Hospital, Gogyogawara, Japan, ³Department of Orthopaedic Surgery, Hirosaki University Graduate School of Medicine, Hirosaki, Japan

The first case was a 68-year-old man. HBsAg was negative at the time of infusion of abatacept, but after the 15th Abatacept infusion, he developed appendicitis and underwent appendectomy. Al-

though liver function was normal; HBsAg, positive; HBsAb negative; HBeAb positive; HBV-DNA. HBV reactivation was strongly suspected. HBV-DNA levels decreased to 2.1 log copies/ml after entecavir (0.5 mg/day) was administered. The second case was a 60-year-old woman. HBsAg was negative, HBsAb and HBeAb were positive at the time of infusion of abatacept. HBV-DNA had been negative during monitoring every 3 months; however, after the 26th abatacept infusion, HBV-DNA and HBsAg were positive. After 18 days of entecavir (0.5 mg/day), HBV-DNA became negative.

P1-043

The efficacy of abatacept in a patient with malignant rheumatoid arthritis.

Wataru Fujii, Hidetaka Ishino, Masataka Kohno, Aihiro Yamamoto, Takahiro Seno, Kaoru Nakamura, Ken Murakami, Hidetake Nagahara, Takashi Kida, Amane Nakabayashi, Yutaka Kawahito
Inflammation and Immunology, Kyoto Prefectural University of Medicine, Kyoto, Japan

We report a case of malignant rheumatoid arthritis (MRA) who well respond to abatacept after failed to respond to three anti-TNF- α and anti-IL6 therapies. A 38-year-old woman was diagnosed as RA on April 2006. Despite of treatment with methotrexate (MTX) and infliximab, she complicated vasculitis syndrome with hypocomplementemia, increase of RAPA and cutaneous vasculitis. Three TNF or IL6 blockades with immunoabsorption plasmapheresis, weekly 12mg of MTX and daily 100mg of azathioprine were insufficient to taper the dose of oral prednisolone less than 20mg daily. Administration of abatacept instead of adalimumab improved her joints pain and skin eruption, and normalized complement activity by 4 weeks after the induction of it. Abatacept may be effective for vasculitis syndrome with RA.

P1-044

The validity of abatacept for treatment of RA-Dermatomyositis overlap syndrome

Koichiro Yoda

Rheumatology, Osaka City University Graduate School of Medicine, Osaka, Japan

The case 38yo RA patient, She showed muscle weakness, Gottron's sign, CK 979IU/l and anti Jo-1 antibody positive and was diagnosed accompany DM with interstitial pneumonia at 30yo. Sauve-Kapandji procedure was performed at 33yo. Treated with 10mg/day PSL, 240mg/day CsA and bucillamine but the efficacy was modest. ETN was added in July, 2009. In January, 2010, She was diagnosed with early gastric cancer, which was cured with ESR and withdrawal of ETN. THA and TKA were performed in June. We added abatacept because of severe manifestations of joint, ESR1h 33mm and RF 820 IU/ml. The improvement was found even 2 weeks after administering without any advance event and reactivation of DM and IP. Abatacept is one of the effective and safe agents for treatment of refractory overlap syndrome.

P1-045

A case of SLE with urticarial vasculitis and orbital panniculitis

Hiroshi Abiko¹, Yuta Oyama¹, Mizue Goto¹, Tsuneo Konta²

¹Department of Internal medicine, Nihonkai General Hospital, Sakata, Japan, ²The First Department of Internal medicine, Yamagata University School of Medicine, Yamagata, Japan

A 47-year-old woman was developed urticarial vasculitis (UV) and successfully treated with PSL in April 2000. In 2004, she was diagnosed as having SLE by the presence of UV, pleuritis, nephritis (WHO II) and anti-DNA antibody. She became little better with single IV-CYC and PSL+MZR+DDS. In May 2009, she had been treated with PSL (5mg/day)+MZR+DDS and was referred to our hospital because of deteriorating UV and comorbid arthritis. Her symptoms was not ameliorated by PSL (20mg/day)+TAC. In October 2009, her auricular region swelled up and orbital panniculitis developed which lesions were steroid dependent. She was retreated with monthly administered IV-CYC from December 2009 to May 2010, and the treatment caused complete remission of disease in her. She is now well maintained with PSL+AZA.

P1-046

A case of SLE with hemorrhagic diathesis by low factor XIII and thrombocytopenia

Kazuyuki Fujita, Masayasu Kitano, Mai Morimoto, Takuya Hino, Chieri Kanda, Mika Okabe, Ryota Okazaki, Aki Nishioka, Sachi Tsunemi, Masahiro Sekiguchi, Naoto Azuma, Naoaki Hashimoto, Kiyoshi Matsui, Hajime Sano
Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan

We experienced a case of 61-year-old female with the notable decrease of platelets and hemorrhagic diathesis. She was diagnosed as SLE due to malar rash, photosensitivity, non-erosive multi arthritis, thrombocytopenia, high titer of ANA and positive anti-Sm antibody. There were no abnormalities found in prothrombin time or activated partial thromboplastin time, however, low activity of coagulation factor XIII was detected. Despite administration of F.XIII concentrated product, she was not improved; that indicated to be a presence of some inhibitor of F.XIII attributed by immunoabnormality of SLE. The medication with 50mg/day of prednisolone was effective. Paying an attention to the possibility of decrement of F.XIII is essential to treat SLE patients with hemorrhagic diathesis.

P1-047

A case of RPLS developing after the treatment of lupus nephritis

Shuzo Teruya, Hitoshi Miyasato, Tomoatsu Sakuda
Okinawa Prefectural Chubu Hospital

A 42 year old Japanese woman with systemic lupus erythematosus (SLE) came hospital complaining fever, systemic edema and arthralgia. She developed nephrotic syndrome at the time of admission. We performed renal biopsy and the diagnosis was lupus nephritis (WHO Type IV-S(A)+V). We treated her with methylprednisolone and cyclophosphamide. Six days after second cyclophosphamide pulse (and fifth methylprednisolone pulse), the patient developed sudden visual loss, but her blood pressure was as usual. CT scan and MRI showed occipital lobe of cerebrum impairment. Her symptom gradually improved within 96 hours. She was diagnosed as reversible posterior leukoencephalopathy syndrome (RPLS). We report this rare case of SLE developing RPLS without hypertension with a review of the literature.

P1-048

HPS secondary to SLE successfully treated with tacrolimus

Tsuyoshi Odai¹, Naoto Yokogawa², Mutsuhito Ui², Naofumi Chinen², Yoshiki Nagai², Katsuaki Shiroto², Takahiro Nunokawa², Shoji Sugii², Shinichi Inada²
¹Showa University Hospital, Tokyo, Japan, ²Tokyo Metropolitan Tama Medical Center

A 31-year-old woman with systemic lupus erythematosus (SLE) presented with fever and joint pain for 4 weeks. Hemophagocytic syndrome (HPS) was diagnosed from pancytopenia, elevated serum LDH, hyperferritinemia and prominent hemophagocytosis in bone marrow biopsy. She dramatically improved after a course of steroid pulse therapy followed by oral steroids and tacrolimus. She is in remission with prednisolone 10mg/day and tacrolimus 5mg/day for a year. Early diagnosis and prompt initiation of tacrolimus can significantly improve the clinical outcome.

P1-049

A case of SLE complicated with pure red cell aplasia and retinal vein occlusion

Satoshi Oota
The Department of Internal Medicine, Toyama City Hospital, Toyama, Japan

A 46-year-old man, suffered from SLE and treated with 10 mg of prednisolone(PSL) presented with progressive anemia. Hb 6.6 g/dl, reticulocyte 0.9x10⁴/mL, coombs test and haptoglobin was normal. Serum erythropoietin (EPO) 10000mIU/ml, anti-EPO antibody(Ab)(-), anti-parvovirus B19 Ab(IgM)(-). Anti-β2GPI 3.6U/ml, anticardiolipin Ab(IgG) 17u/ml. Bone marrow asoirate showed erythroid hypoplasia. He was treated with cyclosporin A(CyA) 200mg/day. Then he revealed lt. visual disturbance and was diagnosed as retinal vein occlusion. His visual acuity gradually improved after anticoagulation therapy. 2 week after commencement of CyA he showed fever and dosage of PSL was increased to 40mg/day, then anemia and fever improved. I report rare case of SLE complicated with pure red cell aplasia and APS.

P1-050

A case of fasciitis in a patient with SLE.

Yuichi Maeda¹, Eriko Kudo-Tanaka¹, Hideki Tsuboi⁴, Soichiro Tsuji¹, Shosuke Akita¹, Yoshinori Harada², Masato Matsushita¹, Shiro Ohshima³, Yoshinori Katada², Yukihiko Saeki³

¹Division of Rheumatology, NHO Osaka-Minami Medical Center, Osaka, Japan, ²Division of Allergology, NHO Osaka-Minami Medical Center, Osaka, Japan, ³Department of Clinical Research, NHO Osaka-Minami Medical Center, Osaka, Japan, ⁴Division of Orthopedic surgery, NHO Osaka-Minami Medical Center, Osaka, Japan

A 32-year-old woman was suffered from polyarthralgia and myalgia in the thighs since June. SLE was diagnosed because she had arthralgia, hematological disorders, positive for anti-nuclear antibody, positive for anti-DNA antibody and anti-Sm antibody. The level of serum CK was increased to 1887 (IU/l). MRI showed abnormal high intensity on the T2-weighted images in muscle fascia. Electromyogram showed group voltage just after penetrating the fascia and en bloc biopsy revealed fasciitis evidenced by inflammatory infiltrates around the fascial small blood vessels.

We considered her case as fasciitis associated with SLE. We started

treatment with 60mg/day of prednisolone, resulting in improvement of clinical condition and laboratory findings.

P1-051

Successful treatment with plasma exchange and rituximab for refractory TTP

Yoko Dote¹, Yasuhiro Akai^{1,2}, Yukinari Yamaguchi¹, Kimihiko Nakanani¹

¹First Department of Internal Medicine, Nara Medical University, Nara, Japan, ²Center for Postgraduate Training, Nara Medical University

A 62-year-old woman developed dizziness and slurred speech followed by confusion and thrombocytopenia. She was diagnosed as thrombotic thrombocytopenic purpura (TTP). Plasma exchange (PE) and steroid were started urgently and mental status and thrombocytopenia resolved, however, confusion and thrombocytopenia recurred soon after cessation of PE. As anti-ADAMTS13 autoantibody titer on the seventh hospital day was found to be high, rituximab was started with marked improvement of clinical and laboratory findings. Notably anti-ADAMTS13 autoantibody titer was dramatically reduced after several doses of rituximab. TTP typically responds well to PE. Rituximab should be considered as therapeutic option when refractory TTP is related to high titer of anti-ADAMTS13 autoantibody.

P1-052

A case of SLE with APS that remission was obtained by renal transplantation.

Noriko Hayami, Yoshifumi Ubara, Tatsuya Suwabe, Keiichi Sumida, Rikako Hiramatsu, Eiko Hasegawa, Masayuki Yamanouchi, Naoki Sawa, Kenmei Takaichi
Toranomon Hospital

The case was a 36-year-old man. He had a diagnosis of systemic lupus erythematosus (SLE) in 1986. He was introduced hemodialysis because of lupus nephritis in October, 2008. As a renal function worsened, platelet count decreased and visual field defect developed. Brain CT scan revealed multiple cerebral infarctions. Lupus anticoagulant and anti-CL- β 2-GP I complex antibody were elevated, so he was diagnosed with antiphospholipid syndrome (APS). He underwent living renal transplantation in March, 2010. Not only renal function but also SLE and APS were improved after renal transplantation. Therefore, it was speculated that improvement of uremia may have contributed to the progression of SLE and APS as well as the effect of an immunosuppressive drug (MMF) of renal transplantation.

P1-053

Influence of proton pump inhibitors on the blood level of tacrolimus

Kentaro Isoda, Takuya Kotani, Tohru Takeuchi, Shigeki Makino, Toshiaki Hanafusa

First Department of Internal Medicine, Osaka Medical College

PPIs are primarily metabolized CYP3A4 and CYP2C19, and influence the blood level of tacrolimus (TAC), which is also metabolized by CYP3A4. We investigated the influence of lansoprazole (LPZ), on the blood TAC level. Among the patients treated with TAC after January 2008, the subjects were 25 patients without any agent that influences CYP metabolism other than LPZ. The CSA C0 (trough) levels was measured and compared between LPZ-treated

(n=11) and non-LPZ-treated (n=14) groups. There were no differences in the patient background or dose of TAC between the two groups. The mean TAC C0 levels were 7.9 ± 1.4 and 3.2 ± 0.6 ng/ml, and the mean TAC C/D were 4.2 ± 1.0 and 1.6 ± 0.3 ng/ml in the LPZ-treated and non-LPZ-treated groups, showing a significant difference ($P=0.0025$, $P=0.0097$).

P1-054

Sitagliptin therapy for steroid-induced DM associated with autoimmune diseases

Ayako Sohma¹, Yoko Wada¹, Daisuke Kobayashi¹, Shuichi Murakami¹, Takeshi Kuroda², Masaaki Nakano³, Ichiei Narita¹

¹Division of Clinical Nephrology and Rheumatology Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, ²Health administration center of Niigata University, Niigata, Japan, ³Department of Medical Technology, School of Health Sciences, Faculty of Medicine, Niigata University, Niigata, Japan

Purpose; To examine the effect of DPP-IV inhibitor, sitagliptin, for steroid-induced diabetes (DM) associated with autoimmune disorders. Methods; Five patients with autoimmune disorders who were admitted to our hospital and administered sitagliptin for steroid-induced DM between January to December 2010 were enrolled. Results; Their HOMA-IR was elevated and urine C-peptide was increased in 4 patients before sitagliptin administration. Postprandial hyperglycemia was improved without any fasting hypoglycemic event in all patients after the initiation of sitagliptin. No significant adverse event was observed during the follow-up period. Conclusion; Sitagliptin was feasible, and effective for postprandial hyperglycemia in patients with steroid-induced DM associated with autoimmune disorders.

P1-055

Long-time efficacy of rituximab therapy for autoimmune hematological disorder

Yohei Takeuchi, Tomohiro Kameda, Kentaro Susaki, Miharuru Izumikawa, Hiromi Kidu, Syusaku Nakajima, Hiroaki Dobashi
Department of medicine, Kagawa University, Kagawa, Japan

【Background】Recently, some reports published series of the useful treatment of rituximab for autoimmune hematological disorders. We report the long-time efficacy of rituximab treatment in autoimmune hematological disorders complicated with connective tissue disease. 【Result】Ten patients (nine patients with SLE, one with Dermatomyositis) were treated with rituximab. Nine patients were responded after initial induction of rituximab. One case failed to rituximab therapy. Additionally, one patient who achieved remission relapsed. 【Conclusion】Although there have been a few reports that are refractory and recurrent cases against rituximab treatment, rituximab can be a useful agent for treatment of autoimmune hematological disorder complicated with connective tissue diseases.

P1-056

Identification of dual dimer forming interfaces in Fc γ R2II transmembrane (TM)

Zen-ichiro Honda

Department of Allergy and Rheumatology, Faculty of Medicine, University of Tokyo, Tokyo, Japan

How clustered antigen receptors undergo ITAM tyrosine phosphorylation is not fully understood. This issue was addressed in Fc γ R2IIA, using Cys scanning and disulfide bond formation on B

cells. I show that an extended G/A/S right motif found in TM provides dual dimer forming interfaces, the former of which associates constitutively, and the latter in a ligand-dependent manner, resulting in the formation of a receptor tetramer. The position of the SLE-associated IIB polymorphism (Ile232Thr) is next to the central Ala in the motif, which is critical for dimer formation as well as signal transduction and distribution to lipid rafts. Therefore, IIA clustering is not an amorphous process, but a structured one required for functional oligomer formation.

P1-057

Three cases resulting in etanercept (ETN) -free status

Sayori Suzuki¹, Mariko Oota¹, Syougo Eguma², Tomohiko Yoshida¹
¹Setagaya Rheumatology Center Yoshida Naika Clinic, ²Setagaya Rheumatology Center IORY

Introduction We report 3 biologic-free pts that were on ENBREL (ETN). **Case 1** 38-yo woman RA from Dec/07 was on MTX. ETN started Jan/09; anti-CCP antibody 207 U/ml, RF 3.0 U/ml, CRP 0.55 mg/dl, ESR 12 mm/h, MMP-3 72.5 ng/ml, DAS 3.2. ETN 50 mg/w was added to MTX 14 mg/w+PSL 2mg/d. Drug-free since Oct/09 w/out relapse. **Case 2** 55-yo woman RA from Mar/08 was on MTX 14 mg/w. ETN 50 mg/w started Aug/09; RF 28 U/ml, CRP 0.06 mg/dl, ESR 14 mm/h, MMP-3 130 ng/ml, DAS 5.8. Jun/10 discontinued ETN, now on MTX 10 mg/w+MZ only. **Case 3** 73-yo man RA from 1999 was on GST, SASP, PSL etc. at former hospital. Switched to MTX 15 mg/w, PSL 10 mg/d, ETN 50 mg/w in 2004; RF 177 U/ml, CRP 0.44 mg/dl, ESR 41 mm/h, MMP-3 633 ng/ml, DAS 5.68. Dec/07 discontinued ETN, now on MTX 10 mg/w only.

P1-058

Three cases of RA successfully discontinued etanercept (ETN)

Masahiro Kondo, Mariko Sato, Mayuko Moriyama, Yoshiko Sumita, Yohko Murakawa
 Department of Rheumatology, Shimane University, Faculty of Medicine

Whether biologics can be discontinued or not is a matter of interest. We report three cases of RA who could be discontinued ETN. **Case 1** 68 y.o. man. His disease duration was twenty years (stage IV class II). ETN was prescribed for a year, and discontinued. **Case 2** 80y.o. woman. Her disease duration was twenty-two years (stage IV class II). ETN was prescribed for four years, and discontinued. **Case 3** 70y.o. woman. Her disease duration was two years (stage I class I). ETN was prescribed for four years, and discontinued. **Discussion** Although ETN is good compliance and high safety, it is thought to be difficult to discontinue. We experienced three cases successfully discontinued ETN. Two cases of them were advanced stage. ETN may be discontinued even though in advanced, long disease duration cases.

P1-059

Assessment of etanercept withdrawal in rheumatoid arthritis patients

Masato Kamiya, Satoshi Soen, Mitsuo Ueno, Kenji Yamazaki, Souya Kanata
 Department of Orthopaedic Surgery and Rheumatology, Nara Hospital, Kinki University School of Medicine

[Background]Therapy aiming toward biological-free remission maintenance has become a frequently topic. [Objectives]The present study aimed to investigate changes in disease activity, with emphasis

on remission maintenance after etanercept(ETN) withdrawal in RA patients. [Methods]Patients who maintained remission for 6 months or longer after ETN withdrawal (Group A), and patients who failed to maintain remission and were returned to ETN therapy (Group B), were compared. [Results]The mean duration of RA before receiving ETN therapy was significantly shorter in Group A than B.DAS28-ESR levels were significantly lower at the end of ETN therapy in Group A than B. [Conclusions] In order to maintain drug-free remission, it is considered necessary to achieve remission by earlier diagnosis of RA.

P1-060

The outcome of etanercept therapy without methotrexate for rheumatoid arthritis

Asako Oguma, Soshi Takahashi, Hiroshi Miyagawa, Junji Otsuka, Takuya Sawabe

Department Rheumatology, Hiroshima red cross hospital and atomic-bomb survivors hospital

We have administered etanercept (ETN) for 73 cases of RA. Among them, 31 cases are without MTX, because of lung diseases, adverse effects, renal diseases, pregnancy wishes and others. Fifteen cases were effectively treated with continuous ETN (C Group), and ETN was discontinued in 16 cases (D Group). Compared to D Group, C Group showed younger average age, lower Steinbrocker's stage and class, less tender and swollen joints, and longer disease duration. In D Group, ETN was discontinued because of ineffectiveness, pulmonary diseases, infections, malignancies and others. In C Group, some cases experienced reduced dosage of ETN, PSL or DMARDs. ETN can be effective without MTX, especially for patients of younger age, less tender and swollen joints.

P1-061

Comparison of ETN twice a week and once a week injection on patients with RA

Tamao Nakashita, Akira Inoue, Natsuki Fujio, Shinji Motojima
 Rheumatology and Allergy, Kameda Medical Center, Chiba, Japan

Etanercept is basically injected twice a week, but it has been injected once a week practically. We compared the clinical data of RA patients injected by either method up to 24 weeks. Once a week method (ETN-1) was applied to 36 patients and twice a week (ETN-2) to 24 patients, respectively. The selection was dependent on attending doctors. In both groups DAS28-ESR and MMP-3 improved significantly in the same fashion. Termination of administration was done in 4 in ETN-1 group and in 3 in ETN-2 group, respectively. ETN-1 was tended to be applied to elderly, and the dose of PSL at the introduction of ETN tended to be high in ETN-2 group. Because these two groups improved in the same fashion, some bias by attending doctors in the treatment selection seems reasonable.

P1-062

Disease activity (DA) and QOL changes of patients under ETN 50 mg/w treatment

Mariko Oota¹, Sayori Suzuki¹, Syougo Eguma², Tomohiko Yoshida¹
¹Setagaya Rheumatology Center Yoshida Naika Clinic, ²Setagaya Rheumatology Center IORY

Introduction Conventional dosage of ENBREL (etanercept: ETN) for RA is 25 mg ´ 2/w. We compared DA and QOL in RA pts before & after switching to ETN 50 mg/w. **Methods** Our 10 pts with high DA receiving ETN 25 mg ´ 2/w switched to ETN 50 mg/w

treatment. They were evaluated for DA based on DAS and HAQ every 4 wks and answered our unique questionnaire using VAS etc. before & after treatment switch: ETN procedural trouble; injection pain; degree of stress for numerous injections; household & occupational change; others. **Conclusion** Although ETN 50 mg/w resulted in no DA change, pts' questionnaire revealed alleviating injection-related pain and stress that lead to daily QOL improvement. This regimen also caused no new side effects thus ETN 50 mg preparation can be an effective therapeutic option.

P1-063

Reminding effects on patients (pts) on etanercept (ETN) self-injection (SI)

Mayumi Kaneko, Shigeru Honjo
Honjo Rheumatism Clinic

Purpose Temporal effects & changes after reminding instruction (R-INST) were studied on the understanding of RA pts on ETN SI, regarding procedure, hygiene, & treating infection. **SUB & Methods** Pts took practical & specific question tests at 1/2 year or more after starting SI w/out R-INST. We compared test scores of before & after R-INST to study the effects, also comparing w/ recent SI starters. **Results** Test scores: pts w/out R-INST 86.7 ± 9.7 , recent SI starters 93.0 ± 5.5 . After R-INST, scores significantly improved to 97.0 ± 4.4 ($p < 0.001$) & 98.6 ± 3.4 ($P < 0.05$), respectively. **Conclusion** Home SI is effective to maintain QOL of RA pts but procedure in own way or lack of understanding of treatment risks tend to arise as time pass. Periodical R-INSTs are also important to enforce benefits of biologics.

P1-064

Efforts on switching to etanercept (ETN) self-injection and patient satisfaction

Naoko Tomita
Satoru orthopedics clinic, Towada, Japan

Background Important tasks of nurses on inducing ETN, self-injectable agent, include instruction of self-injection (SI) to pts. We report our efforts on switching to SI regimen. **Subjects** 16 pts who started ETN in 2007, switched to SI regimen & continuing as of Oct 2010 **Results** Mar 2010 instructions were improved; 2 pts switching to SI before then needed 6 instruction sessions on average. Improvement plan focuses on timely changing content from SI initiation to completion of switching. After improvement, all pts switched to SI in shortly as in 2 mths w/ only 4 sessions. Simultaneous satisfaction survey is also utilized to follow up pts. **Discussion** W/ timely efforts, early switch to SI is possible. Such switch may directly relate to improvement in pts satisfaction, leading to good compliance.

P1-065

Etanercept (ETN) treatment in tie-up with home-visit nursing station (HVNS)

Yuichi Takahashi
Yu Family Clinic

Currently, our clinic is working w/ HVNS to achieve low disease activity (DA) in RA pts bedridden or in whom ETN self-injection instruction as outpatient is difficult through self-injection instruction or visiting nurse (VN)-injection at home. Of 82 ETN treated pts, 7 w/ difficulty of outpatient instruction or injection were studied. VN instructed pts or their family on home self-injection. DA decreased in all pts; 2 discontinued ETN due to eczema. No

ADRs (eg. infection) were noted. Biologics are used to achieve clinical remission. It may be also given to pts w/ severely impaired function to reduce DA or improve general status. ETN use in tie-up w/ HVNS may be a promising treatment option in RA pts bedridden or w/ difficulty of clinic visit due to severely impaired function.

P1-066

A refractory case of adult-onset Still's disease in pregnancy.

Tetsuya Tabeya, Hidetaka Yajima, Mikiko Obara, Chisako Suzuki, Motohisa Yamamoto, Yasuyoshi Naishiro, Toshiaki Sugaya, Hiroki Takahashi, Yasuhisa Shinomura
First Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan

The onset of adult-onset Still's disease (AOSD) during pregnancy is rare. We report a case of a 28-year-old pregnant woman diagnosed as AOSD. She presented with high fever, myalgia, and lymph node swelling at 21 weeks' gestation. She was referred to our department and diagnosis of AOSD was made on the basis of hyperferritinemia (8582 ng/ml) and leukocytosis. No response to high-dose glucocorticoids were observed and development of hemophagocytic syndrome was suspected due to thrombocytopenia. So she had undergone treatment with steroid pulse therapy and plasmapheresis. Although cyclosporine A (CsA) was orally administered, her fever continued. We administered dexamethasone palmitate and CsA intravenously following second steroid pulse therapy, which dramatically ameliorated her condition.

P1-067

Two cases of multiple-drug-resistant AOSD treated successfully with tocilizumab

Akinori Yamamoto, Kojiro Sato, Yoshihiro Yoshida, Yu Asanuma, Yuji Akiyama, Toshihide Mimura
Department of Rheumatology and Applied Immunology, Saitama Medical University, Saitama, Japan

We report two cases of adult-onset Still's disease (AOSD) treated successfully with tocilizumab (TOC). (1) A 36-year-old woman, who was diagnosed 8 years before and had been treated with various DMARDs plus etanercept (ETA) or adalimumab (ADA), presented with a high spiky fever and elevated liver enzymes. After excluding infection, she was treated with TOC. (2) A 26-year-old man with new-onset AOSD, which was resistant to multiple immunosuppressants including infliximab (INF) and ETA, was treated with TOC 7 months after the diagnosis. In both cases, serum IL-18 was extremely high, and TOC improved clinical symptoms and liver function promptly. High level of serum ferritin also became normalized. We propose that TOC may be a first-line biologic against multiple-drug-resistant AOSD.

P1-068

Long-term tocilizumab therapy for patients with adult-onset Still's disease

Masafumi Kobayashi, Hiroyuki Yamashita, Yuko Takahashi, Yasuo Nagafuchi, Haruka Tsuchiya, Kenji Itoh, Hiroshi Kaneko, Akio Mimori
Division of Rheumatic Diseases, National Center for Global Health and Medicine

Five patients with intractable adult-onset Still's disease and receiving tocilizumab (TCZ) therapy underwent long-term observation. The 3 females and 2 males (20–60 years old) had been resistant

to previous combination therapy including 60-120 mg prednisolone (PSL) equivalent/day and suffered repeated relapse over 1–10 years. Two patients had macrophage activation syndrome. Following TCZ-induced remission, none of the patients had a disease flare during 17.5 ± 13.0 (4 to 31) months of observation, and the PSL dose was therefore reduced to 3–10 mg/day. All patients are currently receiving TCZ every 3–6 weeks.

P1-069

Successful treatment with tocilizumab for intractable adult Still's disease

Ryuta Endo, Takehiko Ogawa, Takehisa Ogura, Yuichi Izumi, Ayako Hirata, Norihide Hayashi, Hideki Ito
Division of Rheumatology, Toho University Ohashi Medical Center, Tokyo, Japan

A 55-year-old woman presented spiking fever, rash, arthritis and elevated CRP and ferritin in 1998. She was initially treated with 80mg/day prednisolone following intravenous methylprednisolone (1000mg per pulse), resulting in significant but transient improvement. As the disease persisted, she was treated with steroids and infliximab, with short period response despite attempt to increasing dose, gold and MTX, with poor response. Finally, TCZ (8mg/kg) was administered. Subsequently, her symptoms markedly improved, and this therapy sustained a stable condition. This report suggest that TCZ might be useful in multirefractory adult Still's disease.

P1-070

A case of adult-onset Still's disease mimicking tuberculous pleuritis

Isao Murakami, Yoshinobu Matsuura, Miwa Nishida, Saori Hatachi, Masato Yagita
Kitano Hospital, Tazuke Kofukai Medical Research Institute, Osaka, Japan

A 64-year-old woman with adult-onset Still's disease (AOSD) and old tuberculosis presented low-grade fever, arthralgia, and pleural effusion during the treatment with 5mg/day prednisolone. The increases of both lymphocyte and adenosine deaminase in the pleural effusion strongly suggested tuberculous pleuritis, and anti-tuberculosis drugs were administered. However, she developed high-grade fever and disseminated rash a week later. Laboratory data revealed pancytopenia, highly elevated liver enzymes and the remarkable increase in serum ferritin. Hemophagocytic syndrome and disseminated intravascular coagulation were also noticed. Accordingly, she was diagnosed as the relapsed AOSD. She was successfully treated with steroid pulse, oral cyclosporine and tocilizumab.

P1-071

A case of adult-onset Still's disease occurred on pregnant woman and her baby.

Junya Ajiro, Katsumitsu Arai
Niigata Prefectural Central Hospital

We treated 36 weeks pregnant women with fever with three types of antibiotics, but she did not improve, and gave birth by Caesarean section. Although treating with other two types of antibiotics after birth, She didn't get better.

We diagnosed her Adult onset-Still's disease and started treatment with 40mg.

Then her condition has improved, but her newborn baby had a high

fever and rash.

Baby's Blood tests showed leukocytosis and high serum ferritin. the symptoms of baby was looks like Adult onset-Still's disease. We treated with steroid, baby got well.

We suspected these symptoms caused by something from the mother. We report this case with some bibliographic consideration

P1-072

The remission and maintenance treatment statuses caused by combined therapy

Kazunori Uehara, Masaki Akamine, Takashi Oura
Hemodialysis Unit, Oura's Lupus Clinic, Nahacity Okinawa Japan

Recently, anti-interleukin-6 (IL-6) receptor monoclonal antibody named 'Tocilizumab' became a powerful treatment and called our attention. The patient was 46 year-old male with clinical course of acute onset of Still's disease and flare consecutively for 10 years. The destruction and deformity of joints were observed. During his visit, he was complicated with cataract as a side effect of steroids. Therefore, low dose of steroids were used. During remission period, steroid was tapered to complete cease. At that time, acute exacerbation and flare were detected. We restarted the procedure of low-dose steroid treatment with 3 sessions of leukoapheresis against acute exacerbation. The patient's flare remitted. At present, he is going on the treatment with Tocilizumab.

P1-073

A case of adult Still's disease with pulmonary and hematological complications

Kenji Fujii^{1,2}, Yasuhiro Osugi²

¹Department of Laboratory and Transfusion Medicine, University of Occupational and Environmental Health, Fukuoka Japan, ²Kaita Hospital, Fukuoka Japan

A 65-year-old Japanese woman was admitted with fever, arthralgia and eruption. Adult-onset Still's disease (AOSD) was diagnosed, pancytopenia associated with extreme hyperferritinemia and hemophagocytosis in bone marrow biopsy were showed. Concurrently interstitial pneumonia with mediastinal emphysema was occurred, the patient was treated with methylprednisolone pulse therapy of 1000 mg/day for 3 days and followed by 80 mg of prednisolone (PSL) administration. Remission was induced. Then the dose of PSL was gradually reduced to 20mg, pneumothorax was recurrently occurred. Patient was managed with chest drainage, pneumothorax was improved. This AOSD case was a rare presentation which interstitial pneumonia with pneumothorax and hemophagocytic syndrome.

P1-074

A case of adult onset Still disease with multiple complications

Mayumi Kusumoto, Masato Mori, Yoshitaka Imura
Department of Rheumatology, Osaka Red Cross Hospital, Osaka, Japan

We report a case of 68-year-old woman. She consulted us for fever and arthralgia. We first suspected pseudogout, but naproxen and moderate-dose prednisolone (PSL) were not effective. Neutrophilia, splenomegaly and high serum ferritin suggested adult onset Still disease (AOSD). High-dose PSL after methylprednisolone (mPSL) pulse was not effective, so methotrexate was combined. Next week, acute exacerbation of interstitial pneumonia (IP) was revealed. We administered mPSL pulse and combined cyclosporin (CsA). Pancytopenia was exacerbated later, and we administered etoposide as

macrophage activation syndrome. Cerebral infarction was emerged next day, but thereafter, she was improved with CsA and PSL. This case was severe AOSD with rare complications such as IP and cerebrovascular disorder.

P1-075

Prednisolone and tacrolimus refractory Still's disease treated with tocilizumab

Hideki Kasahara, Masahide Shinohara

Department of Rheumatology, Sapporo Medical Center NTT East Corp., Hokkaido, Japan.

We report a 77-year-old man with multi-refractory flare of adult-onset Still's disease treated with tocilizumab (TCZ). On Dec, 2008, he was treated with 60mg of prednisolone (PSL) and 2mg of tacrolimus (TAC) and one course of pulse methylprednisolone (mPSL), his disease activity could be controlled, but he was suffered from thrombocytopenia and skin ulcers due to cytomegalovirus and herpes zoster virus infection. Skin ulcers were successfully treated with anti-viral therapy. When PSL was reduced to 6mg, he had a relapse and had treated again with 40mg of PSL and 3mg of TAC and two courses of mPSL pulse, on Jan, 2010. Gradually, PSL was reduced to 11mg, his disease flare-up had occurred on July. We administered 30 mg of PSL and TCZ once a month, which dramatically improved his symptoms.

P1-076

A case of AOSD patient administrated ADA 40mg biweekly

Atsushi Kohno¹, Yasue Shimogaki², Yoshikiyo Toyoda³

¹Department of Rheumatology, Osaka Kaisei Hospital, Osaka, Japan, ²Osaka Kaisei hospital Immunity plaza, Osaka, Japan, ³Department of Orthopedic Surgery, Osaka Kaisei Hospital, Osaka, Japan

We report here that the effectiveness and safety of administration of ADA (40mg/2w) on the AOSD (adult Still's disease) patient. [Case] A 33 years old male suffering from AOSD since 2009, had fever, rheumatoid papules and arthralgia (both knee joints) again on July, 2010 in spite of continuing the treatment by PSL+MTX. The effect was insufficient even after increasing the dosage of PSL (20mg/day) and MTX (8mg/w). Then ADA (40mg/2w) was added from October 1, 2010. On 14 days after administering ADA, almost clinical symptoms were improved and also laboratory data such as the titers of CRP, ESR were markedly declined. This case might suggest that the effectiveness of ADA (40mg/2w) on AOSD patients.

P1-077

Elevated serum levels of CX3CL1 in adult-onset Still's disease

Tsuyoshi Kasama, Kumiko Otsuka, Michihito Sato, Ryo Takahashi, Kuninobu Wakabayashi, Tsuyoshi Odai, Nobuyuki Yajima, Yusuke Miwa

Division of Rheumatology, Department of Medicine, Showa University School of Medicine

OBJECTIVE: To investigate the prevalence of patients with adult-onset Still's disease (AOSD), serum levels of chemokines were measured. **METHODS:** Serum samples were obtained from patients with AOSD (n=17) and healthy controls. Chemokines, including CXCL8, CXCL10, CCL2 and CX3CL1 were determined by ELISA. **RESULTS:** Significantly higher serum levels of all chemokines were observed in patients with active AOSD. The elevated CX3CL1 levels seen in AOSD patients correlated positively with clinical activity, as well as with ferritin levels. Levels of serum CX3CL1 and

ferritin were all significantly higher in AOSD patients with hemophagocytic syndrome (HPS) than in those without HPS. **CONCLUSION:** The high levels of serum CX3CL1 and ferritin encountered in AOSD may reflect the presence of HPS.

P1-078

HLA-DRB1*04 and anti-CCP Abs in early development of DMARD-resistant RA

Shunsuke Mori

Clinical Research Center for Rheumatic Disease and Department of Rheumatology, NHO Kumamoto Saishunsou National Hospital, Kumamoto, Japan

In this study, we evaluated HLA-DRB1 alleles and anti-CCP Abs for their value in predicting patient responses to treatment with DMARDs in early RA. The subjects were 124 Japanese patients who had received their first treatment with DMARDs within 1 year of disease onset. Approximately 40% of patients developed DMARD resistance during the 2-year follow-up period. Multivariate logistic regression analysis showed the strong association of DMARD resistance with the presence of shared epitope (SE)-positive *04 alleles and anti-CCP Abs. After stratification, the highest rate of DMARD resistance was observed in patients having both SE-positive *04 alleles and anti-CCP Abs. The presence of both markers is the strongest predictor for development of DMARD-resistant RA early in the disease course.

P1-079

The effect of conventional DMARDs on the joint destruction in early-onset RA

Jun-ichi Fukushima¹, Tomomi Tsuru², Yasuharu Nakashima¹, Ken Okazaki¹, Taro Mawatari¹, Masanobu Ohishi¹, Yasutaka Tashiro¹, Yukihide Iwamoto¹

¹Department of Orthopaedic Surgery, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, ²PS Clinic, Fukuoka, Japan

The effect of DMARDs on the joint destruction in early-onset RA was evaluated. The subjects were sixty-four Japanese patients, who (a) were evaluated within the first year after the onset of symptoms; and (b) began DMARDs treatment and underwent at least 1 year of follow-up without changing the DMARDs regimen. The patients were treated with methotrexate (MTX; n = 23), sulfasalazine (SASP; n = 15), bucillamine (BUC; n = 14), auranofin (AUR; n = 6), and prednisone (PSL; n = 6). Radiographs of the hands were evaluated using the modified Sharp score methods. Increasing rates of Sharp score per year (delta-Sharp) were 1.51, 1.49, 0.56, 2.67, and 2.72 when patients were treated with MTX, SASP, BUC, AUR, and PSL, respectively. Delta-Sharp was positively correlated with DAS28 after treatment.

P1-080

Treatment for the early RA with salazosulfapyridine

Yasuhiro Tani, Noriyuki Miyazaki

Japan Agricultural Yamaguchi Kouseiren, Nagato General Hospital, Yamaguchi, Japan

[Purpose] We evaluate the treatment for the early rheumatoid arthritis (RA) with salazosulfapyridine. [Treatment] We use the salazosulfapyridine for the RA patients, of the low and moderate activity RA. We don't use steroid. The treatment responses after 6 months were estimated by EULAR criteria. [Method] There are 22 ca-

ses. Average DAS28 are 3.54. [RESULT] 11 cases achieved good response, but, 11 cases Moderate and No response. 11 cases were received therapy by MTX, add on or change. [Conclusion] It may be possible that we treat the low activity RA with SASP. However, we should add on, or change to the MTX, if it achieved moderate and no response for the therapy by SASP.

P1-081

BU/SASP combination therapy might be a candidate for MTX contraindicated RA

Satoshi Ando¹, Kae Tsuruoka¹, Ayumi Uchino¹, Toshiyuki Ota², Yoshinobu Koyama¹

¹Center for Rheumatology, Iizuka Hospital, Fukuoka, Japan, ²Department of Laboratory and Transfusion Medicine, University of Occupational and Environmental Health, Fukuoka, Japan

Background: In RA treatment, the importance of early remission induction therapy with MTX as an anchor drug has become a common knowledge. Although it is contraindicated in some patients with viral hepatitis and organ damage, the evidence for the alternative treatment is not enough.

Method: RA patients (n=243) who had moderate to high disease activity at baseline were studied for 12 months. Therapy persistence rate and remission rate were assessed and compared between MTX, BU/SASP and SASP group retrospectively.

Results: After 12 months, therapy persistence rate was 53% in MTX, 41% in BU/SASP and 54% in SASP group. Also, remission rate was 25.7%, 29.1% and 23.3%.

Conclusion: In RA patients who can't be treated with MTX, BU/SASP combination therapy might be an alternative treatment.

P1-082

Combination of bucillamine+salazosulfapyridine vs each drug alone in early RA

Yasuo Suzuki¹, Shunsei Hirohata², Shohei Nagaoka³, Shigeto Tohma⁴

¹Department of Rheumatology, Tokai University Medical School affiliated Hospital, ²Department of Rheumatology, Kitasato University School of Medicine, ³Department of Rheumatology, Yokohama Minami Kyou Sai Hospital, ⁴Department of Rheumatology, Sagami-hara National Hospital, National Hospital Organization, ⁵BASIC Study Group

Eighty two 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 1-year multicenter open label study. The primary end point was the proportion of patients in low disease activity (LDA). The percentages of LDA and DAS28-defined remission at month 6 in Group B, S, and C were 43.4%, 30.0% and 56.4%, respectively, and 39.1%, 25.0%, and 34.7%, 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.

P1-083

A Multi-Center Study of the Usefulness of DMARDs (Bc) Therapy for Early RA

Izumi Yasuda¹, Akira Sagawa², Atsushi Fujisaku³, Katsunori Ohnishi⁴, Masaya Mukai⁵, Masato Shimizu⁶, Kenji Ichikawa⁷, Hirofumi Ohsaki⁸, Yoshiharu Amasaki⁹

¹Yamanotodori Yagi Hospital, ²Sagawa Akira Rheumatology Clinic, ³Tomakomai City Hospital, ⁴Ohnishi Clinic Internal Medicine & Rheumatology, ⁵Sapporo City General Hospital, ⁶Hokkaido Medical Center for Rheumatic Diseases, ⁷Hokkaido Medical Center, ⁸Ohsaki Clinic, ⁹KKR Sapporo Medical Center Tonan Hospital

As a first-choice of DMARDs, Bucillamine (Bc) was administered 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). A total of eighty eight 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. Fifty-two percent of patients continued Bc at 48 months, while in some patients Bc was continued in combination with MTX. Mean DAS28 values were 4.2 at the baseline, and 2.3 after 48 months of treatment. These results indicate the usefulness of Bc therapy for early RA.

P1-084

Combination pulse therapy using MTX and mizoribine in RA - latest cases

Takehiro Murai

Department of Orthopedic Surgery, Niigata Cancer Center Hospital, Niigata, Japan

(Introduction) We reported results of cases from 2003 to 2007. This time, latest new cases were examined. **(Patients and methods)** From 2008 to 2010, 12 of RA cases. Four cases had rejected treatment using biologic agents. Mean age 60, mean value of CRP was 1.86 mg/dl, and disease activity using DAS28-CRP (3) was low: 0, moderate: 11, high 1. MTX and mizoribine were used 6 or 8mg and 300mg in a week., respectively. **(Results)** The judgment using EULAR response criteria were good: 2, moderate: 3, no: 7 at 6 months, and good: 3. Moderate: 3 at 12 months. In 5 cases, this therapy could be continued over 2 years, and of 3 cases kept low disease activity. **(Conclusion)** This therapy was slow-acting and has limitation of indication, but in several cases long term efficacy can be expected.

P1-085

Efficacy of Combination Pulse Therapy with Methotrexate and Mizoribine in RA

Tomoko Matsuda, Yoshihiro Arimura, Hitoshi Koji, Kazuhito Fukuoka, Miho Karube, Ken Yoshihara, Yoshinori Komagata, Akira Yamada

First Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan

OBJECTIVE: To assess an efficacy of Combination Pulse Therapy with Methotrexate (MTX) and Mizoribine (MZB) in patients with Rheumatoid Arthritis (RA). **METHOD:** 13 Patients, who were poorly controlled by MTX (monotherapy or combined with another DMARDs or Biologics) were tried Combination Pulse Therapy with MTX (4~10mg/week) and MZB (100~400mg/week). Efficacy and safety were evaluated at 3, 6, 9, and 12 months. **RESULT:** This combination therapy improved CRP, MMP3, and DAS28. Reduction rate: 1) CRP 81.3%/ 44.4% (at 3 months/6 months). 2) MMP3: 81.8%/ 100% (at 3 months/6 months) 3) DAS28-CRP: 39.0% patients showed moderate response at 3 months. 4) Adverse effect occurred dermatitis in a patient. **CONCLUSION:** It is suggested that Combi-

nation pulse therapy of MTX and MZB is safe and effective in RA patients.

P1-086

Analysis of efficacy of MZR pulse therapy

Hideki Shimazu, Kayo Asato, Toshihiko Shiga, Yukihito Nakano, Shoichi Hino, Tomohiro Yano, Kazuya Kishimoto, Yuji Nozaki, Shinya Ikoma, Shigeo Irimajiri, Koji Kinoshita, Masanori Funauchi
Department of Nephrology and Rheumatology, Kinki University School of Medicine, Osaka-Sayama, Osaka, Japan

We analyzed the efficacy of Mizoribine (MZR) in patients with rheumatoid arthritis (RA) who were uncontrollable with MTX, etc. Ten patients who received MZR from Apr. '09 to Oct. '10 were examined. Of these, 3 had MZR alone and 8 had combination therapy. The concomitant drugs were MTX in 5; biologics etc. in 3. Four patients received MZR 300 mg/week in 1-2 divided doses; 1 had 150 x 1/2days; 2 had MZR at the same time as MTX. Five out of 10 showed good response. At 24 weeks, the tender joint counts, swollen joint counts CRP and DAS-CRP were improved with the mean value of 7.8, 5.4, 2.1, 4.29 to 2.5, 0.3, 0.7, 2.66 respectively. No serious adverse events were seen during the observational period. MZR appears to be effective and safe for multidrug-resistant RA patients.

P1-087

Mizoribine as a single dose between meals for patients with rheumatoid arthritis

Junsei Iseki¹, Akira Kouchi¹, Shin Nakajima¹, Naotsugu Nakamura¹, Yasuyoshi Konaga¹, Reiko Seki¹, Yuko Hotta¹, Chisato Kawabata¹, Jinju Nishino², Keita Nishimura¹, Takashi Matsushita¹

¹Teikyo University School of Medicine, Tokyo, Japan, ²Nishino Clinic Orthopedics and Rheumatology, Tokyo, Japan

Patients with RA who had been taking mizoribine (MZR) in triple or double doses of 50 mg, or in single doses of 100 or 150 after breakfast, for over 3 months without any clinical response were switched to a single dose between meals without a change in the total daily dose. The efficacy, safety and changes in serum MZR levels were then analyzed in the 6 months following the switch. Of the 23 enrolled patients, 17 met all eligibility criteria and received MZR between meals for the full 6 months. CRP, VAS-general health and DAS-CRP were significantly improved, and the serum levels (C max) were significantly elevated, in comparison to those at the time of switching. No severe adverse events related to this dose schedule occurred. Between-meal administration of MZR as a single dose is useful.

P1-088

Whether mizoribine therapy could be an effective treatment in Sjögren's syndrome

Ayumi Uchino¹, Satoshi Ando¹, Toshiyuki Ota², Yoshinobu Koyama¹

¹Center for Rheumatology, Iizuka Hospital, Fukuoka, Japan, ²Department of Laboratory and Transfusion Medicine, University of Occupational and Environmental Health, Fukuoka, Japan

Sjögren's syndrome (SS) is known as one of the rheumatic inflammatory disorders. The sicca symptoms as well as extraglandular manifestations often severely impair the patients' QOL. Although the efficacy of immunosuppressive therapy in SjS has been suggested, there is still no common consensus because of few clinical studies to date. In this study, we tried to investigate immunosuppressive

therapy including mizoribine (MZB) in patients of SS. Lip biopsy, gland function tests and blood tests were assessed after 6-month-administration of GC followed by 6-month-administration of MZB. Although extraglandular symptoms and some immunological markers were improved after the treatment, there was no significant difference in inflammation of salivary glands.

P1-089

Combined therapy with MTX and LEF in patients with rheumatoid arthritis

Ko Katayama

Katayama Orthopedic Rheumatology Clinic

Objective: Evaluating leflunomide (LEF) and methotrexate (MTX) combination. **Method:** DAS24-ESR and adverse events were evaluated on 34 (Male 16, Female 18) RA cases, mean age of 52 years old, RA duration of 8.6 years, observation for 14.6 month. LEF was added to 24 MTX cases, and MTX was added to 10 LEF cases, because of ineffective at monotherapy. Chest CT was checked in all cases at the start of LEF treatment. **Results:** DAS28-ESR at baseline was 4.78. Eleven cases achieved DAS remission at the last observation. Treatment terminated in 9 cases by adverse events. No interstitial pneumonia observed. **Conclusion:** Benefit of combination therapy seems high, as which is efficacious and the risk of new lung complication would be small after confirming no preexisting lung disease by CT.

P1-090

Analysis of 125 cases diagnosed with polymyalgia rheumatica

Makoto Kondo, Masaya Muakai

Sapporo city general hospital, Sapporo, Tokyo

Polymyalgia rheumatica (PMR) is rheumatic disease more prevalent in the elderly and characterized by severe myalgia. It is not life-threatening disease unless giant cell arteritis is co morbid. But its severe myalgia impairs patient's quality of life significantly. This disease lead to typical clinical manifestation, so a trained doctor can diagnoses it easily. This disorder well responds to steroid. And the illness is frequently curable, so physicians can stop all therapy finally. For these reasons, it is a important disease in the practical clinic. This retrospective study analyzed about treatments and prognosis from medical records of 125 patients who were diagnosed or had been diagnosed as PMR at Sapporo City general hospital from 2005.

P1-091

The Crowned Dens Syndrome confused with polymyalgia rheumatica: two case reports

Yoshihisa Nasu¹, Koji Takasugi², Misuzu Yamashita², Masamitsu Natsumeda², Kayo Ezawa², Kazuhiko Ezawa², Keiichiro Nishida³

¹Department of Orthopaedic Surgery, Kurashiki Kousai Hospital,

²Department of Internal Medicine, Kurashiki Kousai Hospital, ³Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences

The case 1 is 88 years old male. His symptoms were acute and severe pain with his neck, upper extremities, back and thighs. From these symptoms, acute phase proteins level (CRP 21.0mg/dl) and fever (37.4°C), we diagnosed him as polymyalgia rheumatica. Oral predonisolone (10mg/day) was started and tapered slowly. While systemic symptoms were remitted in a few days, severe neck pain remained. The neck CT images showed calcification around the odontoid process. These findings defined the diagnosis of Crowned

Dens Syndrome (CDS). The Case 2 showed similar clinical features to the case 1. But the first evoked diagnosis was CDS in this case. NSAID showed marked efficacy for her. CDS should be considered in the differential diagnosis of PMR like symptoms with neck pain.

P1-092

Synovial osteochondromatosis of knee joint. 2 cases report

Ichiro Itonaga, Masanori Kawano, Tatsuya Iwasaki, Hiroshi Tsumura

Department of Orthopaedic Surgery, Faculty of Medicine, Oita University

We report 2 cases of synovial osteochondromatosis of knee joint. Case 1 was 62 year-old female. Case 2 was 24 year-old male. They felt pain on their left knee joint at first. Both cases had joint effusion in left knee, and case 1 had soft tissue mass in popliteus. X-ray photographs showed left knee osteoarthritis in both cases, and many ossified clusters. Those small clusters showed low intensity in both T1 and T2 MRI. Case 1 had popliteal cyst and small clusters were also found in the cyst. Arthroscopy showed many white color beads floating in the joint, and that those beads were squeezed between femur and tibia. Tumor resection and synovectomy were performed in both. Pathological diagnosis was osteochondromatosis. Both cases felt relief of pain after operation.

P1-093

RA in Outpatient Department for Musculoskeletal Tumors

Akira Kido¹, Yasunori Kobata¹, Takashi Fujimoto², Takamasa Shimizu¹, Ryota Hara¹, Kenichi Nakano¹, Yasuhito Tanaka¹

¹Department of Orthopedic Surgery, Nara Medical University School of Medicine, ²Department of General Medicine, Nara Medical University School of Medicine

We have experienced 4 cases of RA in our OPD for musculoskeletal tumors. Former two cases had a solitary and destructive tumor-like lesion without positive RA tests at the first examination. Latter two were cases in an advanced stage of cancers, which we found difficulty for proceeding chemotherapy. Case1: 51 y.o. man with solitary tumor-like lesion in his left metatarsophalangeal joint. The tumor was resected and histologically confirmed. Case 2: 59 y.o. woman with a soft tissue tumor at the achilles tendon, which was invasive to the calcaneus. Case 3: 70 y.o. woman with breast cancer and RA. PET showed high signal intensity in the both lesions. Case 4: 69 y.o. woman with recurrent uterus cancer and RA. Because for cancer treatment, we could not choose immunosuppressive therapies for RA.

P1-094

RA which is difficult to differentiate from bone and soft tissue tumor: 3 cases

Yoshitada Sakai^{1,2,3}, Akira Hashimoto², Teppei Hashimoto², Nao Shibamura^{1,2}, Ryosuke Kuroda¹, Shunichi Shiozawa², Masahiro Kurosaka¹

¹Department of Orthopaedic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan, ²The Center of Rheumatic Diseases, Kobe University Hospital, Kobe, Japan, ³Faculty of Health Care Sciences, Himeji Dokkyo University, Himeji, Japan

We present the 3 patients with RA to whom biopsy were performed for differential diagnosis from malignant tumor.

Cases: All female. The complained joint was a foot metacarpophalangeal joint, a shoulder, and a calcaneal region. MR imaging

showed tumor-like tissues with bone invasion. The blood examinations showed increase one case of CRP, RF positive in 2 cases, antiCCP antibody positive in all cases. Needle biopsy was performed in all cases, and these results were appearance of inflammatory cells and no malignancy. Open biopsy was performed in 2 cases, and these results were RA with no malignancy.

Discussion: Synovial lesions with RA sometimes multiply in tumor-like, invade into the bone. Therefore, the differential diagnosis from malignant bone and soft tissue tumor may be required.

P1-095

A case of Poncet's disease (tuberculous rheumatism)

Taichi Minami¹, Akiko Suda¹, Haruko Ideguchi², Kenji Ohmura^{1,2}, Shohei Nagaoka¹, Yoshiaki Ishigatsubo³

¹Department of Rheumatology, Yokohamaminamikyosai Hospital, Yokohama, Japan, ²Center for Rheumatic Disease, Yokohama City University Medical Center, Yokohama, Japan, ³Department of Internal Medicine and Clinical Immunology, Yokohama Japan, ⁴Department of Respiratory, Yokohama Minamikyosai Hospital

Case: A 70-year-old male patient **Present illness:** In December 2008, refractory erythema and polyarthritis developed. In September 2010, he was referred to our hospital. RF and ACPA were negative, and chest X-ray findings was normal. Skin biopsy revealed panniculitis with caseating granulomas (erythema induratum), required differentiation from tuberculosis. QFT yielded a strong positive result, and a small nodule was observed on chest CT. He began to receive an anti-tuberculosis regimen. Then his arthritis was improved, and diagnosed with Poncet's disease. **Discussion:** Although Poncet's disease is a rare condition characterized by reactive arthritis associated with acute tuberculosis, we should include this condition in the differential diagnosis in patients with seronegative arthritis.

P1-096

Destructive arthritis of the wrist caused by Mycobacterium intracellulare

Akiko Sasaki¹, Haruki Nakano¹, Suran Yang¹, Yuya Takakubo¹, Hiroshi Orui², Toshihiko Ogino¹, Michiaki Takagi¹

¹Department of Orthopaedic Surgery, Yamagata University School of Medicine, Yamagata, Japan, ²NHO Yamagata National Hospital, Yamagata, Japan

A 79-year-old male patient presented with a monoarthritis of the wrist. Radiograph findings of his wrist were multiple erosions and radio-carpal joint narrowing. C-reactive protein and matrix metalloproteinase-3 were high, however, anti-CCP antibody and rheumatoid factor were negative. A tuberculin reaction was negative. The patient underwent open synovectomy for diagnosis, and culture was taken of the synovial tissue. Mycobacterium tuberculosis PCR was negative from the fresh synovial tissue. Two weeks later, Mycobacterium intracellulare was identified from the synovial tissue culture. The diagnosis of destructive arthritis of the wrist was septic arthritis caused by Mycobacterium intracellulare.

P1-097

A case of autoimmune hepatitis complicated with palindromic rheumatism

Michiko Komatsu¹, Hiroo Hashimoto¹, Kazuhiko Moriwaki¹, Kiichi Komoto¹, Fumio Otsuka²

A 74-year-old woman was referred for examination of acute fever with abrupt pain in bilateral joints with swelling of multiple joints. The patient was complicated with autoimmune hepatitis (AIH) that was treated with PSL (initially 25mg decreasing to 5mg). Laboratory data revealed the presence of acute seronegative arthritis: AST 38 IU/l, ALT 45 IU/l, CRP 10.0 mg/dl, ANA (-), RF (-) and anti-CCP antibody (-). The findings on joints X-ray and hands Gd-MRI were compatible to non-specific arthritis. Administration of PSL (20mg) with NSAIDs alleviated high fever; however, her arthralgia was migrated and disappeared 10-days after. She was diagnosed as palindromic rheumatism complicated with AIH. Palindromic rheumatism should be considered in patients with arthritis with elderly onset.

P1-098

A case of spondylarthritis associated with retroperitoneal fibrosis.

Hiroto Nakano¹, Makiko Yamamoto², Hideto Oshikawa², Kazuki Yoshida², Masako Utsunomiya², Tatsuo Kobayashi², Mitsumasa Kishimoto³, Kazuo Matsui²

¹General Internal Medicine, Kameda General Hospital, Kamogawa, Japan, ²Rheumatology, Kameda General Hospital, Kamogawa, Japan, ³Section of Allergy and Rheumatology

A 35-year old woman was given a diagnosis of iridocyclitis on 2007. Local therapy was effective. In 2009, bilateral back pain and shortness of breath developed. When she visited a local hospital, post renal failure was diagnosed and bilateral ureteral stenting was performed. We initiated administration of 30 mg/day prednisolone because there were no specific findings to explain the retroperitoneal thickening. We gradually reduced the prednisolone and successfully removed the ureteral catheter within 1 month.

In May 2010, her uveitis worsened and sacroiliitis developed. Spondylarthritis was diagnosed and sulfasalazine and infliximab were administered.

There are few reports regarding spondylarthritis associated with retroperitoneal fibrosis. We report this case with a review of the literature.

P1-099

A case of SAPHO syndrome complicated with tibial osteitis

Aki Nishioka, Naoaki Hashimoto, Kazuyuki Fujita, Takuya Hino, Mai Morimoto, Ryota Okazaki, Masahiro Sekiguchi, Naoto Azuma, Masayasu Kitano, Kiyoshi Matsui, Hajime Sano
Division of Rheumatology Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan

A 23-years-old woman who had pain of left lower limb in 2003. She was suspected to have pustulotic arthro-osteitis, and was treated tonsillectomy. She admitted to our hospital due to progressive pain of both lower limbs in July 2008. MRI revealed tibial osteitis and peri-tibial myositis. She was diagnosed as having SAPHO syndrome, and treated with PSL. However, osteitis became recrudescence on tapering of the dosage of PSL and it was resistant to treatment of MTX, MZR and TAC. Because of refractory osteitis, she was given etanercept. Her clinical symptoms, laboratory data and MRI findings improved markedly. She continued to receive etanercept, and PSL has been gradually tapered. We report a case of suc-

cessful treatment for refractory SAPHO syndrome with osteitis by etanercept.

P1-100

SAPHO syndrome during infliximab therapy; A case report

Yukari Bando, Teruhisa Azuma, Yukio Tsugihashi, Ryuichi Sada, Hiroyasu Ishimaru, Kazuhiro Hatta
Tenri Hospital

We describe a 57-year-old woman with SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome. She had a rheumatoid arthritis and was successfully treated with infliximab (IFX) and methotrexate. However, after 5 courses of IFX administration, she developed a palmoplantar pustulosis with severe anterior chest pain. She was diagnosed as having a SAPHO syndrome by positive findings of skin biopsy and Tc-99m-HMDP scintigraphy. After failure of switching IFX to tocilizumab, she has been successfully treated with cyclosporine. This case indicates that TNF blockers are not only effective but also triggering factors for psoriasis and SAPHO syndrome.

P1-101

A female patient complicated psoriatic arthritis with Behcet's disease

Keiji Okamoto, Hitoshi Goto, Shinsuke Yamada, Koichiro Yoda, Maki Nishimura, Yasuo Imanishi, Masaaki Inaba
Department of Metabolism, Endocrinology and Molecular Medicine, Faculty of Internal Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan

A 40-year-old female began to develop joint symptoms in 1997. She had abdominal pain, genital ulcer, folliculitis, oral aphtha, and so she was diagnosed with Behcet's disease in 2003. She was treated with mesalamine and bucillamine. She was diagnosed with psoriatic arthritis in May 2007. Because she had ankylosis of sacroiliac joints, symphysis pubica and cervical spine, treatment with methotrexate was started. Skin manifestation improved, but spondylarthritis symptoms did not improve. Treatment with infliximab was started in August 2010, joint symptoms improved markedly. She might have severe ankylosis despite female, because she was complicated with psoriasis arthropathica and Behcet's disease. Treatment with TNF- α inhibitors was expected to improve functional prognosis.

P1-102

Therapeutic efficacies of tocilizumab in RA patients by DAS28 and by compact MRI

Takeshi Suzuki, Masanobu Horikoshi, Makoto Sugihara, Hiroshi Ogishima, Hiroto Tsuboi, Taichi Hayashi, Isao Matsumoto, Takayuki Sumida

Division of Clinical Immunology, Doctoral Program in Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan

[Objective]To compare the therapeutic efficacies of tocilizumab (TCZ) in RA patients by DAS28 and compact MRI at 0w and 24w. [Methods] The evaluation of DAS28 and cMRI was compared in 5 patients treated by TCZ. cMRI images were evaluated by cMRI score (cMRI) [Results]All patients had good or moderate response by DAS28 and DAS28 was decreased significantly at 24w (DAS28-ESR 5.32 \pm 0.95 \rightarrow 2.70 \pm 1.26 p<0.05). cMRI was decreased in 1 patient (cMRI 83 \rightarrow 76.25). However cMRI in other patients were not decreased (cMRI 76.25 \pm 28.18 \rightarrow 72.85 \pm 24.27). [Conclusion] The re-

sult of cMRI showed that synovitis and bone edema still remained at 24w in patients who had achieved good or moderate response even by DAS28. We conclude that cMRI evaluation is useful for the estimation of local inflammation in RA treated by TCZ.

P1-103

MRI studies of affected joints in patients with polymyalgia rheumatica (PMR)

Norihiro Nagamura, Junji Mashino

Department of General Medicine, Shimane Prefectural Central Hospital, Izumo, Japan

PMR, commonly occurs to the elderly people is a rheumatic disease characterized by aching and morning stiffness in shoulder, neck, and pelvic girdles. It is also associated with arthralgia in some joints. We examined the affected joints of seven patients diagnosed as PMR by MRI. Arthralgia in PMR is observed in shoulder, elbow and knee, relatively large joints compared with rheumatoid arthritis (RA). Capsular fluid retention, synovitis, bursitis, tenosynovitis are observed in MRI studies in PMR, like in RA. Besides such findings, inflammatory changes in soft tissue around the joint capsules were also observed. That findings seem to be one of the reasons why musculoskeletal pain occurs in PMR. It is difficult to differentiate elderly onset RA from PMR, this MRI findings are helpful to diagnose PMR.

P1-104

A case of RA in which anti-TNF therapy showed CR and improvement of MRI findings

Makoto Onishi, Yasuaki Okuda, Sho Mokuda, Naoya Sawada, Masashi Takebayashi, Kenichiro Matoba, Akihiro Yamada, Kazuo Johyama, Kiyoshi Takasugi

Center for Rheumatic Disease, Dohgo Spa Hospital

Case: 42 y/o woman. History: June 2006, patient complained about pains in right shoulder & right fingers. Checkup results by X-ray showed no arthritic destruction. MRI showed synovitis, no bone marrow edema observed. Course of treatment: Treatment began with bucillamine, with no results. March 2007, MTX therapy began, of little avail. MRI showed bone marrow edema in right 3rd finger, infliximab therapy began. From 3rd adm., 200mg infliximab used, from 4th adm., dosing interval set to 7 weeks. Therapy successful, MRI showed ease in lesion. As rashes developed, intravenous 100mg hydrocortizone injection combined. As RA worsened, therapy switched to Etanercept. Remission achieved. MRI scan 1 yr later showed bone marrow edema disappeared. October 2010 Etanercept adm. reduced to 10mg/w.

P1-105

MRI Findings in One Case of Rheumatoid Arthritis with Biologic-Free Remission

Yasuhiro Kubota^{1,2}, Nobuo Matsui², Kae Kikuchi^{2,3}

¹Kubota Orthopedic and Rheumatology Clinic, Toyota, Japan, ²Nagoya City Rehabilitation Center, Nagoya, Japan, ³Nagoya City University, Dept. of Orthopedic Surgery

The patient is a 58-year-old female rheumatoid arthritis (RA). She began taking infliximab (IFX) 2.5 years after onset and went into clinical remission. She discontinued IFX after a year, but remains in clinical remission even after a year since discontinuation. Synovitis observed in MRI before IFX was diminished one year into IFX and one year after discontinuation. MRI is useful for the evaluation

of RA treatments. However, there are no reports on MRI of biologic-free remission, and it is unclear whether MRI can be an indicator for ceasing biologics. In the present case, clinical remission and synovitis reduction were observed not only when IFX was discontinued, but even one year after discontinuation. This suggests MRI's potential as an indicator for ceasing and resuming biologics.

P1-106

Near-infrared camera could visualize joint synovial vascular flow

Jun Fukae, Yuko Aoki, Akemi Kitano, Akihiro Narita, Mihoko Henmi, Fumihiko Sakamoto, Masato Isobe, Masato Shimizu, Megumi Matsuhashi, Takeya Ito, Akio Mitsuzaki, Kazuhide Tanimura

Hokkaido Medical Center for Rheumatic diseases

Background and Objective: The therapeutic goal for rheumatoid arthritis (RA) has moved to complete remission. Accuracy and objectivity have been demanded in RA assessment. Photo-dynamic eye (PDE) system could visualize vascular flow by fluorescent image with indocyanine green. The PDE is a clinical application for ophthalmology and oncology. We used PDE to detect finger joint synovial vascular flow. Methods: A patient with active RA was examined after obtained informed consent. Indocyanine green (0.25mg/kg) was injected intravenously. Results: Abnormal vascular images were detected in same areas of power Doppler images. Discussion: The PDE has advantages of low cost and less invasive. PDE could obtain abnormal images from multiple joints simultaneously. PDE might be a useful tool for RA.

P1-107

Usefulness of 'Hip to Calcaneus View' in evaluation of lower limb alignment

Kenrin Shi, Makoto Hirao, Tetsuya Tomita, Hideki Yoshikawa, Jun Hashimoto

Department of Orthopaedic Surgery, Osaka University Graduate School of Medicine

Lower limb alignment was evaluated by 'Hip to Calcaneus View (HC View)' in patients either with knee OA (10 patients, 17 limbs) or RA (31 patients, 55 limbs) with mean age of 70.4 and 60.4, respectively. We measured femoro-tibial angle (FTA) and passing point of weight-bearing line (PPWBL) at knee as well as at ankle. Also, tibio-calcaneal angle (TCA) was measured in standing subtalar view, and correlations of measured values were examined. HC View and conventional whole limb view demonstrated strong correlation as for FTA and PPWBL at knee in both diseases. In OA, increased FTA exhibited correlation with medialization of PPWBL at ankle as well as increased TCA, but not in RA. HC View, reflecting the true weight-bearing line, is a useful method in evaluation of lower limb alignment.

P1-108

Diagnostic value of ¹⁸F-FDG PET /CT with unexplained signs of inflammation

Toshiaki Tsukada¹, Keita Fujikawa¹, Hideki Nakamura², Satoshi Yamasaki², Atsushi Kawakami²

¹Isahaya General Hospital, department arthritis and connective tissue disease, ²First department of Internal Medicine, Graduate School of Biochemical Science, Nagasaki University School of Medicine

【background】¹⁸F-FDG PET /CT is very useful tests for malignancies. But its utility for inflammatory diseases is not clarified. **【purpose】**In the field of connective tissue diseases, to clarify the utility of ¹⁸F-FDG PET /CT in single center. **【materials and methods】**¹⁸F-FDG PET /CT was done in 11 patients with unexpected inflammatory signs. **【results】** significant accumulation of ¹⁸F-FDG was observed in 10 cases, In 6 cases, ¹⁸F-FDG PET /CT was very useful for final diagnosis **【conclusion】**¹⁸F-FDG PET /CT is very useful tests to make diagnosis of inflammatory diseases and connective tissue diseases, especially, vasculitis and lymphadenopathy.

P1-109

FDG-PET/CT findings of polymyalgia compared with those of rheumatoid arthritis

Daisuke Wakura¹, Takuya Kotani¹, Takaaki Ishida¹, Takuro Ozaki¹, Nao Tatsukawa¹, Kentaro Isoda¹, Koji Nagai¹, Shuzo Yoshida¹, Kenichiro Hata¹, Tohru Takeuchi¹, Shigeki Makino¹, Toshiaki Hanafusa¹

¹First Department of Internal Medicine, Osaka Medical College,

²Department of Radiology, Hokusetsu General Hospital

【Objective】To compare ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET) findings between three polymyalgia rheumatica (PMR) patients and two rheumatoid arthritis (RA) patients. **【Results】**PMR patients have increased FDG uptake within joint capsules, rotator cuff and the biceps long-head tendon in the shoulder, and interspinous ligaments and zygapophysial joints in the spine. In the pelvis and its circumference, they have increased FDG uptake within joint capsules and muscle attachments such. RA patients have increased FDG uptake within shoulder joint capsules. PET findings of PMR patients were increased FDG uptakes within entheses of tendons and ligaments in comparison to RA. **【Conclusion】**PET is a useful tool for differential diagnosis between PMR and RA.

P1-110

The assessment of anti-TNF agents by ¹⁸FDG-PET in a patient with AS

Hiroyuki Shiozawa, Yukio Yonemoto, Koichi Okamura, Tsutomu Kobayashi, Tetsuya Kaneko, Tsuyoshi Ichinose, Kenji Takagishi
Department of Orthopaedic Surgery, Gunma University Graduate School of Medicine

Recently we treated AS by biologics. We have reported PET is effective for assessment of therapeutic effect of biologics in RA patients. A 24 years old man had low back pain from March 2008. The pain got worse and he had arthritis of the arms and legs. He had medical examinations and was diagnosed as AS. He was treated by diclofenac sodium, salazosulfapyridine and MTX, but these were not effective. We started to administer infliximab from August 2009. BASDAI was 8.5, HLA-B27 was positive, CRP, ESR and MMP-3 were high. MRI revealed arthritis of both sacroiliac joints. PET revealed uptake at both sacroiliac joints and left knee joint. After treatment, PET findings were improved. We use BASDAI to assess disease activity of AS, but it is subjective assessment. We hope we evaluate inflammation objectively by PET.

P1-111

The assessment of therapeutic effect in patients with RA using FDG-PET/CT

Koichi Okamura¹, Yukio Yonemoto¹, Kimihiko Takeuchi^{1,2}, Tsuyoshi Ichinose¹, Tsutomu Kobayashi¹, Kenji Takagishi¹

¹Department of Orthopaedic Surgery, Gunma University Graduate School of Medicine, Maebashi, Japan, ²Department of Orthopaedic Surgery, Isesaki Fukushima Hospital, Isesaki, Gunma, Japan

FDG-PET could image synovial inflammation in RA patients. In this study, we evaluated if there was a correlation between the difference of FDG uptake and improvement of clinical findings. 28 RA patients (5 men, 23 women; average age: 58.8) who underwent anti-TNF α 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. The average of DAS28 and sum of SUVmax before the treatments were 5.27 and 25.1, and after treatment; 3.71 and 19.0. Δ SUV were significantly correlated with Δ DAS28 ($r=0.600$), Δ DAS28-CRP ($r=0.625$), Δ RF ($r=0.613$), Δ ESR ($r=0.493$) and Δ CRP ($r=0.394$). FDG-PET might play an important role in the evaluation of treatment for RA.

P1-112

The assessment of disease activity in patients with RA using FDG-PET/CT

Koichi Okamura¹, Yukio Yonemoto¹, Kimihiko Takeuchi^{1,2}, Tsutomu Kobayashi¹, Kenji Takagishi¹

¹Department of Orthopaedic Surgery, Gunma University Graduate School of Medicine, Maebashi, Japan, ²Department of Orthopaedic Surgery, Isesaki Fukushima Hospital, Isesaki, Gunma, Japan

FDG-PET can image synovial inflammation in patients with rheumatoid arthritis (RA). In this study, we evaluated if the FDG uptake of the affected joints represented by SUV correlated with the clinical assessment of patients with RA. 40 patients (6 men, 34 women; average age: 55.6 years) were assessed. For the semiquantitative analysis, functional images of the standardized uptake value (SUV) were produced and the maximal SUV (SUVmax) was used as a representative value for the assessment of ¹⁸F-FDG uptake. The sum of SUVmax among measured joints (total SUVmax) per patient significantly correlated with DAS28 ($r=0.594$), DAS28-CRP ($r=0.544$), ESR ($r=0.582$), RF ($r=0.401$) and CRP ($r=0.376$). FDG-uptake represented by SUVs in the inflamed RA joints may reflect disease activity.

P1-113

High serum IgG4 in patients with allergic granulomatous angitis

Tomohiro Koga¹, Yoshiro Horai³, Toshiyuki Aramaki², Satoshi Yamasaki¹, Hideki Nakamura¹, Tomoki Origuchi¹, Munetoshi Nakashima², Eiichi Suematsu³, Katsumi Eguchi⁴, Atsushi Kawakami¹

¹Unit of Translational Medicine Department of Immunology and Rheumatology Nagasaki University Graduate School of Biomedical Sciences, ²The Japanese Red Cross Nagasaki Genbaku Hospital, ³NHO Kyushu Medical Center, ⁴Sasebo City General Hospital

Allergic granulomatous angitis (AGA) is the disease characterized by eosinophilia, serum MPO-ANCA, peripheral neuropathy, renal dysfunction and pulmonary involvement. Meanwhile, IgG4 related disease is also characterized as high serum IgG4 and varying organ damage. Good response to prednisolone and complication

with allergic conditions are similar in both diseases. It is also known that IgG4 shows the inhibitory effect against Th2-mediated allergy. Thus, we examined serum IgG4 in patients with AGA in order to examine the above diseases condition. Serologic feature (ANCA, count of eosinophil, inflammatory cytokines and so on) and clinical characteristics (severity of organ damage, recurrence and neurological sign) are compared between serum IgG4-high group and serum IgG4-normal group.

P1-114

The possible pathogenesis of IgG4 in a patient with MPA

Motoko Ishida, Tomoya Miyamura, Karin Shimada, Yoshiro Horai, Soichiro Takahama, Rumi Minami, Masahiro Yamamoto, Eiichi Suematsu

Department of Internal Medicine and Rheumatology, Clinical Research Center, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan

A 66-year-old female was admitted to our hospital in August, 2010 because of fever and paresthesia of lower legs. She showed mononeuritis multiplex and interstitial pneumonia. The laboratory data indicated elevated levels of CRP (9.44mg/dl), MPO-ANCA (48EU) and serum IgG4 (321IU/ml). The biopsy specimen of sural nerve showed an infiltration of IgG4 positive plasma cells. Serum IgE was 1055IU/ml, although she has had neither allergic symptoms nor eosinophilia. She was diagnosed with MPA. PSL (50mg/day) was started, levels of CRP and MPO-ANCA normalized immediately. Although several studies have reported that IgG4 suppress the allergic response induced by IgE, IgG4 may be associated with angitis by switching the Fc portion. Our case showed the possible role of IgG4 in pathogenesis of angitis.

P1-115

A case of MPO-ANCA related vasculitis with serum IgG4 elevation

Mikiko Yoshikawa¹, Koji Harada¹, Yasuhiro Akai²

¹Department of Nephrology, Rakuwakai-Otowa Hospital, ²Center for Postgraduate Training, Nara Medical University

74 year-old man was admitted for progressive numbness, weakness and leg edema 6 months after prostatectomy. He had no family history of rheumatic or collagen vascular diseases. Laboratory data showed elevation of MPO-ANCA and IgG with hypocomplementemia. Further exam also showed an elevation of serum IgG4 (435 mg/dl) and proteinuria. Nerve biopsy demonstrated small-vessel necrotizing vasculitis. Renal biopsy revealed crescentic glomerulonephritis without interstitial nephritis. IgG4-positive plasma cells were not detected. As the role of IgG4 in MPO-ANCA positive vasculitis has remained to be elucidated, we present this case with some discussion and literature review.

P1-116

The examination of MPO-ANCA positive cases in our hospital

Junichi Danjo¹, Kohei Kohashi², Hiroki Mitsunaka¹, Kenji Akiyama¹

¹Kagawa Prefectural Central Hospital, Tamatsu, Japan, ²Inoue Hospital, Suita, Japan

MPO-ANCA associated vasculitis causes various clinical symptoms by the systemic vasculitis. It is difficult to treat the disease in the onset of fatal complications such as infectious diseases, pulmonary alveolar hemorrhage, and renal failures. We examined clinical symptoms, histopathology, treatment, outcomes, causes of death, and

addresses of 82 MPO-ANCA positive patients treated in our hospital. Renal biopsy was carried out in 42 patients, about 60% cases showed crescentic glomerulonephritis. In some areas of Kagawa there are many patients of this disease per the population. Because a large number of the patients died caused by respiratory infection, the prognosis of the disease is determined by regulation of infectious disease and of primary disease activity.

P1-117

A case of micropolyangitis with oculomotor and abducent nerve paralysis

Shino Ishizuka, Kenji Kubota, Kayu Nakayama

Nephrology, Saiseikai Kawaguchi General Hospital

We reported the case of a 75 year male who was diagnosed with micropolyangitis in 2007. A treatment started with PSL (50mg/day), but proteinuria, hematuria, renal dysfunction revealed when his PSL was 20mg/day. His MPOANCA titer was 209EU. A renal pathological examination revealed antineutrophil cytoplasmic antibody (ANCA) vasculitis. Intravenous pulse methylprednisolone therapy and intermittent cyclophosphamide pulse therapy were performed twice. His renal symptoms recovered by this treatment. In 2009, severe headache, fever, oculomotor and abducent nerve paralysis were occurred suddenly. His spinal fluid and MRI were almost normal. A result of pathology rejected temporal arteritis. Intravenous pulse methylprednisolone therapy were performed twice, which disappeared his paralysis.

P1-118

A case of ANCA-associated-vasculitis (AAV) developed after cataract surgery

Michita Suzuki, Kyoko Takano, Eiji Nagasawa, Masao Katayama

National Hospital Organization Nagoya Medical Center

A 76-year-old female, who had a cataract-intraocular lens surgery in her right eye in April 2007, suffered the redness and pain in the right eye in January 2008. She was diagnosed as necrotizing scleritis in July. Multiple nodules were found in bilateral lungs in February 2009 followed by subcutaneous sterile abscesses on her extremities in April. Ophthalmectomy was performed for the pain and sterile discharge in the eye, but they continued. She was admitted in October and diagnosed as AAV based on clinical features and MPO-ANCA positivity. Oral PSL40mg/day improved her symptoms and nodules in the lungs dramatically. Surgically induced necrotizing sclerokeratitis (SINS) is a rare autoimmune disorder developed after any eye surgeries. We had a rare case that SINS was initial symptom of AAV.

P1-119

Plasma exchange therapy for microscopic polyangitis with pulmonary hemorrhage

Atsuma Nishiwaki, Hiroshi Sato, Isamu Yokoe, Shinji Tsuruta, Hitomi Haraoka

Itabashi Chuo Medical Center, Tokyo, Japan

A 72-year-old woman presented dry cough and blood-stained sputum in July. Myeloperoxidase-anti-neutrophil cytoplasmic antibody (MPO-ANCA) was 1370EU and she was diagnosed microscopic polyangiitis (MPA) with pulmonary hemorrhage (PH) and rapidly progressive glomerulonephritis (RPGN). She was initiated steroid pulse therapy and following five times of plasma exchange therapy (PE). A 48-year-old woman was diagnosis with bilateral

pneumonia in July 2010. Despite antibiotic therapy, the progressive hypoxemia. She presented PH and RPGN. Because of titer of MPO-ANCA (498EU), she was diagnosed with MPA. She was initiated steroid pulse therapy and following six times of PE. Combination with PE and steroid therapy is recommended in the most severe case. PH and RPGN improved in two cases.

P1-120

A case of Microscopic PolyAngitis complication SIADH

Fumiharu Konishi, Noriko Ikegaya, Masaki Saito, Toshihiko Fukuoka, Yoshinori Komagata, Shinya Kaname, Yoshihiro Arimura, Akira Yamada

First Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan

A 62-year-old man had cough from November in 2009 and was diagnosed as pulmonary fibrosis. A month later he was hospitalized due to consciousness disturbance associated with hyponatremia (Na 101 mEq/L), which was treated with water restriction and demeclocyclin. In March 2010, he was admitted to our hospital because of continuing peripheral neuropathy. Blood tests were Na 128 mEq/L, CRP 4.8 mg/dl, MPO-ANCA 396 EU, ADH 2.6 pg/ml, osmolality 267mOsm/l, and urine tests showed proteinuria/hematuria and Na 102mEq/l, suggesting the presence of SIADH. Renal Biopsy revealed crescentic glomerulonephritis, providing a clinical diagnosis of microscopic polyangitis(MPA). We treated with PSL 40mg/day and hyponatremia improved accordingly, which may suggest possible correlations between MPA and SIADH.

P1-121

A case of spontaneous remission of ANCA positive RPGN with precedent pneumonia

Toshiyuki Watanabe¹, Kenji Oku^{1,2}, Makoto Furukawa¹, Hirohiko Kitakawa¹

¹Kushiro Red Cross Hospital, Internal Medicine, ²Hokkaido University Graduate School of Medicine, Internal Medicine II

A 64-year-old woman presented to the outpatient clinic with a chief complaint of fever and cough. She was diagnosed as pneumonia and had recovered soon after starting antibiotic treatment. However, she suddenly became anuric with positive serum MPO-ANCA and pauci-immune crescentic glomerulonephritis proven by renal biopsy. We diagnosed her as ANCA-associated RPGN. Her anuria and laboratory data improved spontaneously. In a part of RPGN, there is a group of patients with benign prognoses that develop the disease secondary to infection (postinfectious RPGN). There are few reports on postinfectious RPGN patients that became ANCA positive. Thus, even when a diagnosis of ANCA-positive RPGN had been made, spontaneous remission may occur in the case with typical history of precedent infection.

P1-122

RPGN with anti-GBM antibody in 3 patients with MPO-ANCA related vasculitis

Hirohisa Kawai, Shogo Banno, Yukihiro Kimura, Kunihiro Maeda, Mari Ogawa, Hitoshi Watanabe, Masahiro Yamamura, Hirokazu Imai

Department of Internal Medicine, Division of Nephrology and Rheumatology, Aichi Medical University, Aichi, Japan

Case 1: a 75-year-old woman with RPGN was exhibited both MPO-ANCA (66 EU) and anti-GBM antibody (920 IU/ml). During

hemodialysis, she developed TTP and CMV infection. Necropsy revealed crescentic glomerulonephritis with linear IgG deposition along capillary loop. Case 2: a 69-year-old woman has treated by PSL for ANCA related vasculitis (MPO-ANCA 547 EU). Two years later, her renal function aggravated with a positive GBM antibody (115 UE) and a negative ANCA. Hemodialysis was started after the therapy of IVCY and PSL. Case 3: a 67-year-old woman had RPGN and pulmonary hemorrhage with ANCA (358 EU) and GBM antibody (95 EU). Regular hemodialysis was induced, even her pulmonary hemorrhage was improved by plasma exchange and PSL treatment.

P1-123

Three cases of ANCA-associated vasculitis with cranial nerve dysfunction

Motoko Kanemoto, Misako Uehara, Taro Karahashi

Department of Rheumatology, Fujieda Municipal General Hospital, Shizuoka, Japan

All of 3 cases had developed fever, anorexia, and weight loss at onset, without apparent organ involvement. After diagnosed as probable ANCA-associated vasculitis with positive MPO-ANCA, they were treated for oral administration with moderate dose steroids. Steroids were effective at first, however, were neurological problems such as dysphagia and hoarseness were appeared after the start of steroids 6~7 months later. On MRI images, the hypertrophic pachymeningitis was observed in case1, no abnormal findings in case2, and in case3, small brainstem infarction was recognized. It might be important to note that the expression of cranial nerve dysfunction in the course of ANCA associated vasculitis with steroid monotherapy and with non-organ involvement at first diagnosis.

P1-124

Efficacy and safety of pulse cyclophosphamide in ANCA-Associated Vasculitis

Hiroshi Oiwa, Kazuhiko Kumagai, Eiji Sugiyama

Department of Clinical immunology and Rheumatology, Hiroshima University, Hiroshima, Japan

To investigate efficacy and safety of European protocol of pulse cyclophosphamide (pCY), we retrospectively investigated 4 Japanese cases with AAV, treated with pCY during recent 14 mos. Administration of pCY and prednisolone were according to European protocol (Ann Intern Med;150: 670-, AR;57:686-). Remission (%), time to remission, adverse events were assessed. Remission was defined as 0-1 of BVAS, assessed with new or worse signs of vasculitis every 6 wks. The average \pm SD of follow up were 43 ± 19 (wk). Remission was achieved in 4/4 and time to remission was 9.0 ± 3.5 (6-12 wks). Leukopenia, oral candidaris, upper airway infection and lung cancer were found all in 1/4. In conclusion, remission was achieved in all of 4 Japanese cases with AAV within 3 mos by European protocol of pCY.

P1-125

Thrombotic microangiopathy in the course of systemic sclerosis: a case report

Takuro Sunada, Ryuichi Sada, Yukio Tsugihashi, Teruhisa Azuma, Hiroyasu Ishimaru, Kazuhiro Hatta

A 73-year-old woman had been suffering from scleroderma of skin and multiple joint swellings for a half year. She was diagnosed with systemic sclerosis (SSc), and successfully treated with PSL and MTX. A month later, she was urgently hospitalized for acute renal failure and hypertension. On admission, she received ACE-I because of suspicious renal crisis. But she was diagnosed as having a diffuse alveolar hemorrhage from the finding of diffuse ground glass opacity in chest X-ray and BALF. Although steroid pulse therapy and plasma transfusion, she got worse rapidly and died on the next day. Autopsy revealed multiple TMA in both lungs and kidneys. The cause of TMA might be associated with steroids. That is why we should consider the risk of TMA in the use of steroids for patients with SSc.

P1-126

Examination of the efficacy of the Tocilizumab treatment for patients with RA

Takahiko Wada, Yoshio Ozaki, Yonsu Son

Department of Rheumatology and clinical Immunology, Kansai Medical University, Osaka, Japan

[purpose] We examined efficacy and safety in 57 patients who introduced TCZ in this hospital during from June, 2008 to May, 2010. [background] Sex:men 13,women 44. Average age: 59.6 years. A contraction of a disease period:9.6 years. Changed by TNF: IFX 12, ETN 13, ADA 4. [results] It was Moderate response 24.5%, Good response 64.9%, about the efficacy. Cancellation by the adverse event was four cases. (Infusion reaction, erosive enterocolitis, elevated blood pressure, arthralgia exacerbation). [conclusion] It was effective for the TNF preparation invalidity case and was extremely high about the overall efficacy with GR 64.9%. Many cases were intractable cases, but a high utility of the TCZ treatment for the RA patients was found.

P1-127

The Efficacy and Safty of Tocilizumab in Patents with Rheumatoid Arthritis

Shuji Ohta, Seiji Mogi

Department of Rheumatology, Taga General Hospital, Hitachi Co. Ltd.,Ibaraki, Japan

Object; To investigate the safty and efficacy of tocilizumab (TCZ) in patients with rheumatoid arthritis(RA). **Method;** The efficacy is investigated by DAS28 in 52 week. To evaluate safety, we extract and examine the all adverse event. **Result;** Total patient number was 33. Mean age was 58 years old. Mean disease duration was 7.1 years. 15 cases (45%) were received TNF inhibitor, previously. DAS28 at baseline was 6.1. In 52 week, DAS28 was improved to 2.4. In DAS category, high disease activity was 0% (91% at baseline), moderate disease activity was 13% (4.5%), low disease activity was 23% (4.5%), remission was 64% (0%). 18 cases (82%) archived good response. Severe adverse event were observed in 3 cases, and all of them were infection of connective tissue.

P1-128

The efficacy and safety of tocilizumab therapy in patients with RA

Kazuyoshi Kubo¹, Toshihiko Hidaka¹, Shota Sakaguchi¹, Hiroshi Kuroda¹, Kunihiro Umekita², Akihiko Okayama²

¹Institution of Rheumatology, Zenjinkai Shimin-no-Mori Hospital, ²Internal Medicine, Department of Rheumatology, Infectious diseases and Laboratory medicine, University of Miyazaki

We assessed the efficacy and safety of tocilizumab (TCZ) in patients with rheumatoid arthritis (RA).Seventeen of drug-resistant RA patients were administered TCZ. We evaluated responses to TCZ therapy based on disease activity score (DAS)28 over 6 months, and 12 month treatment period. The mean levels of DAS28 decreased from 4.15 to 2.49 (6 months, P<0.01) and 2.32 (12 months, P<0.01). Based on EULAR response criteria, 82% and 89% of patient exhibited better than a moderate response to therapy after 6 and 12 months, respectively. Serious adverse events were seen in 2 cases. These data indicate that TCZ therapy is clinically effective for RA.

P1-129

Two effective cases switching from TNF- α inhibitor to IL-6 inhibitor early .

Mamoru Kanazawa

Ajisu dohjin hospital

[Introduction]I experienced two cases switching from TNF- α inhibitor to IL-6 inhibitor early because of TNF- α insensitivity. [Result]The case 1 is a 64 year old female. IFX administered from January 8 to February 19, 2010. When she visited us for the fourth administration of IFX on April 21, RA activity was not good. I started to administer TCZ on that day. After 28 weeks, DAS28-ESR dropped from 6.5 to 2.9, MMP-3 from 320ng/ml to 22, CDAI from 142 to 22, and MHAQ from 1.375 to 0.75.The case 2 is a 61 year old female. ETN administered from April 2 to April 26, 2010 but found RA activity control was not good. I started to administer TCZ on April 28. After 28 weeks, DAS28-ESR dropped from 5.52 to 1.64, MMP-3 from 209ng/ml to 37, CDAI from 127 to 3, and MHAQ from 1.375 to 0.25.

P1-130

Successful treatment of membranous nephropathy with tocilizumab in RA patient

Ryutaro Yamana¹, Koji Takasugi¹, Misuzu Yamashita¹, Kayo Ezawa¹, Masamitsu Natsumeda¹, Kazuhiko Ezawa¹, Yoshihisa Nasu²

¹Department of Internal Medicine, Kurashiki Kosai Hospital, Kurashiki, Japan, ²Department of Orthopaedic Surgery, Kurashiki Kosai Hospital, Kurashiki, Japan

A 69-year-old man diagnosed as RA in 2005 was treated with SASP. He visited our hospital and was introduced to administering MTX in July 2006. Proteinuria was shown from May 2008. Renal biopsy was performed in November 2008. Pathological finding was membranous nephropathy. MTX was stopped and he recieved 40mg/day of PSL. Proteinuria was improved from 7g/day to 1g/day. PSL was tapered from 20mg/day to 18mg/day in April 2009, and then arthritis was getting worse. Therefore tocilizumab was started in July 2009.Disease activity of RA was improved, and proteinuria was maintained in less than 1g/gCr ,though PSL was tapered until 8mg/day. We experienced a case of RA complicated with membranous nephropathy successfully treated with tocilizumab.

P1-131

3 cases of rheumatoid arthritis with systemic sclerosis treated with tocilizumab

Masao Katayama¹, Michita Suzuki¹, Kyoko Takano¹, Eiji Nagasawa¹, Atsushi Kaneko²

¹Division of Rheumatology, Department of Internal Medicine, Nagoya Medical Center, National Hospital Organization, Nagoya, Japan, ²Department of Orthopedic Surgery and Rheumatology, Nagoya Medical Center, National Hospital Organization, Nagoya, Japan

We report 3 cases of rheumatoid arthritis (RA) with systemic sclerosis (SSc) successfully treated with tocilizumab (TCZ). Case 1; A 29-year-old female has had SSc since 2000. She also have had RA since 2005, and bucillamine or tacrolimus (Tac) had not enough effects. TCZ was started from 2008. Case 2; A 71-year-old female with SSc complicated with RA was treated with prednisolone and salazosulfapyridine and Tac without enough effects. TCZ was started in May, 2009. Case 3; A 68-year-old female with polyarthritis and Raynaud's phenomenon since 2005. She was diagnosed as SSc in January, 2006. Polyarthritis was exacerbated and diagnosed as being complicated with RA. Tac had no effects and TCZ was started in April, 2010. In these 3 cases TCZ showed effective response to control disease activity.

P1-132

Successful use of Tocilizumab to treat in dialysis patient with heart failure

Yoshinari Hattori, Yoshifumi Ubara, Tatsuya Suawabe, Noriko Hayami, Keiichi Sumida, Rikako Hiramatsu, Masayuki Yamanouchi, Eiko Hasegawa, Junichi Hoshino, Naoki Sawa, Kenmei Takaichi
Toranomon Hospital Kajigaya

We report two cases of rheumatoid arthritis (RA) on hemodialysis with Tocilizumab treatment.

Two cases of RA were receiving Tocilizumab therapy after induction of dialysis treatment. After Tocilizumab therapy, cardiothoracic ratio reduced and left ventricular mass decreased. Each cases presented AA protein deposits in gastrointestinal tract, administration of Tocilizumab deposits regressed. Therefore Tocilizumab might be related improving of myocardial hypertrophy and intradialytic hypotension. Tocilizumab may be effective and therapeutic strategy in heart failure undergoing hemodialysis with AA amyloidosis secondary to RA.

P1-133

Two cases re-introduction of TCZ could achieve control over disease activity.

Mamoru Kanazawa
Aijis dohjin hospital

[Introduction]I experienced two cases in which patients obtained a remission and broke away from IL-6 inhibitor (TCZ) and I re-introduced TCZ when they relapsed to obtain improvement in symptoms. [Result]The case 1 is an 81 year old female. I administered TCZ and she obtained a remission and broke away from TCZ. Because of relapsed, I restarted TCZ on September 10, 2010. After 8 weeks, DAS28-ESR decreased from 5.9 to 2.1, MMP-3 from 552ng/ml to 97, CDAI from 132 to 24, and MHAQ from 2.215 to 1.375. The case 2 is an 84 year old male. I administered TCZ and he obtained a remission and broke away from TCZ. Because of relapsed, I restarted TCZ on September 8, 2010. After 8 weeks, DAS28-ESR decreased from 3.87 to 1.05, MMP-3 from 84ng/ml to 74, CDAI from 98 to 22, and MHAQ from 0.625 to 0.375.

P1-134

A case of RA with SSc effectively treated with tocilizumab (TCZ)

Masato Isobe, Jun Fukae, Akemi Kitano, Yuko Aoki, Fumihiko Sakamoto, Mihoko Henmi, Akihiro Narita, Takeya Ito, Akio Mitsuzaki, Megumi Matsubishi, Masato Shimizu, Kazuhide Tanimura
Hokkaido Medical Center for Rheumatic Diseases, Sapporo, Japan

A 57-year-old woman had suffered from Raynaud's phenomenon and finger edema since 1992. She was diagnosed as SSc from diffuse sclerosis of skin, ankyloglossia, positive anti-nuclear antibody and anti-Scl-70 antibody in 1993. She had polyarthritis since 2005, and NSAIDs didn't inhibit progress of finger polyarthralgia at the PIP and MP joints. The diagnosis of RA with SSc was established from positive anti-CCP antibody and bone destruction. PSL and DMARDs were prescribed, but BUC and SASP had primary and secondary failure, and CYA and TAC had side actions. She didn't apply for MTX because of her pulmonary fibrosis with restrictive respiratory dysfunction. In view of the influence on SSc, TCZ was started in 2010, and her clinical symptoms and laboratory data recovered in response to TCZ.

P1-135

The effectiveness of Tocilizumab on skin ulcers as complications of MRA

Tomohiko Yoshida¹, Syougo Eguma², Mariko Oota¹, Sayori Suzuki¹
¹Setagaya Rheumatology Center Yoshida Naika Clinic, ²Setagaya Rheumatology Center IORY

We report 3 cases where the conditions were improved by tocilizumab (TCZ) medication. 【Case1】56-yo M 【PH】Angina 【PI】A stent placement in his right coronary artery in Apr/07. Skinulcers in his left lower leg in Feb/10. IFX 's been replaced by TCZ since Mar/10. 【Case2】70-yo F 【PH】Myocardial infarction. 【PI】Developed skinulcers in her right lower leg in 2003. TCZ was introduced for the purpose of treating skinulcers in 2010. 【Case3】46-yo F 【PI】RA onset in 1988. Developed skinulcers in her right lower leg in Jul/09. Exacerbated after IFX. IFX 's been replaced by TCZ since Oct/09. 【Discussion】We saw three cases where skin ulcers following MRA were improved by TCZ medication. TCZ may be an effective option in this condition that does not respond to the conventional treatment.

P1-136

TCZ-induced severe neutropenia in a RA patient with AA amyloidosis:A case report

Daisuke Kambe, Yukio Tsugihashi, Ryuichi Sada, Teruhisa Azuma, Hiroyasu Ishimaru, Kazuhiro Hatta
Tenriyorodousoudansho Hospital

In 2008, a 67-year old man with RA receiving MTX visited our hospital due to bilateral leg edema, which proved to be due to nephrotic syndrome complicated by AA amyloidosis by rectal biopsy. We started tocilizumab (TCZ) at the dose of 8mg/kg/week. Two days later, the neutrophil count (NC) decreased (370/ μ L) but 10 days later, the NC recovered. Then, we administered TCZ at a dose of 4mg/kg/2w. Although the NC decreased again, we continuously treated him for 1 year without infection. After that, we have been administering TCZ at the previous dose without any problems. DAS28 changed as follows: 5.07 (baseline), 1.99 (52week), 1.20 (120week). Bilateral leg edema has also recovered with improve-

ment in urine and serum protein. We have successfully treated him with TCZ despite grade 4 neutropenia.

P1-137

Tocilizumab may be useful for treatment of RA patient with demyelinating disease

Megumi Hiida

Machida Municipal Hospital

A 80yo. Japanese female RA patient had re-treated which infliximab 10 month after last injection. 20 days later, she had stroke like symptom and diagnosed as demyelinating disease by neurologist. She had treated with high dose prednisolon. A year later, her DAS score became 5.6.

Because IL6 blockade inhibits the induction of experimental autoimmune encephalomyelitis and rituximab was not available in Japan, she was treated with Tocilizumab.

Since then, two years had passed without demyelinating symptom while she was treated with Tocilizumab. And DAS28 become lower than 2.6.

Tocilizumab may be useful for treatment of RA patient with demyelinating disease which caused by anti-TNF α therapy.

P1-138

Thermotherapy for Sjögren's syndrome

Naotoshi Sugimoto¹, Yoshimasa Fujita², Yasufumi Masaki², Hisanori Umehara²

¹Graduate School of Medical Science, Kanazawa University, Kanazawa, Japan, ²Department of Hematology & Immunology, Kanazawa Medical University, Uchinada, Japan

Salivary gland secretion is reduced in Sjögren's syndrome. In previous studies, decrease in the expression of aquaporin5 (AQP5) has been suggested to contribute to the glandular dysfunction in Sjögren's syndrome. Recently, we demonstrated that heat stress increased the expression of AQP5 *in vitro* and *in vivo*. In this study, we investigated whether warming salivary glands increases the volume of saliva in healthy humans. Human volunteers were allowed to warm their cheek by disposable body warmer for 1 hour a day and for consecutive seven days. The volume of saliva was measured by saxon test before and after the warming. Saliva excretion was significantly increased after the warming. Our results suggest that thermotherapy may improve the glandular dysfunction in Sjögren's syndrome.

P1-139

Effect of Sodium Azulene Sulfonate on drymouth in patients with Sjogren syndrome

Hitoshi Kobayashi¹, Nobuhito Sasaki¹, Kouko Kowata¹, Kohei Yamauchi¹, Yukari Ninomiya²

¹Iwate Medical University, ²Ninomiya Naika Clinic

Purpose: To examine the effects of Sodium Azulene Sulfonate (AZ) on dry mouth associated with Sjogren syndrome (Sjs). Method: 15 patients (one man, 14 women, age: 56.1 \pm 12.3) were enrolled. The diagnosis of Sjs was established according to the criteria of the Ministry of Health (1999). Each of them gargled with tap water for 4 weeks followed by gargling with AZ for another 4 weeks. During the treatment they were evaluated for oral dryness, anxious feeling in drinking water, oral pain and easiness of speaking using visual analog scale (VAS). Results: The VAS of oral dryness, oral pain and anxious feeling in drinking water decreased significantly ($P < 0.05$)

by gargling with AZ compared with tap water. Conclusion: These results suggest that the gargling with AZ is effective for the patients with Sjs.

P1-140

A case of Primary Sjögren syndrome with pulmonary hypertension.

Hidetaka Shiraiwa, Hirotake Inomata, Yoshikazu Kuwana, Masaaki Shiozaki, Natsumi Ikumi, Takamasa Nozaki, Hiromi Karasawa, Noboru Kitamura, Yoshihiro Matsukawa, Takashi Hayama, Shigemasa Sawada, Masami Takei

Division of Hematology and Rheumatology Nihon University School of Medicine

Primary Sjögren's Syndrome (pSS) is a chronic, slowly progressive inflammatory autoimmune disorder, characterised by lymphocytic infiltration of the exocrine glands, leading to decrease of glandular secretion. Pulmonary hypertension are not frequent in pSS. We present the case of a patient with pulmonary hypertension in the course of pSS.

P1-141

A case of Primary Sjogren syndrome accompanied with MPGN due to cryogloblinemia.

Akimasa Uehara, Kimihiko Nakatani, Osamu Asai, Hirokazu Sakan, Yasuhiro Akai, Masayuki Iwano

First Department of Internal Medicine, Nara Medical University, Kashihara, Nara, Japan

Glomerulonephritis complicating primary Sjogren's syndrome is extremely rare. We report on a 69-year-old woman with a history of dryness of the mouth and eyes and purpura in legs, who was found to have nephritic syndrome. Extensive investigations indicated primary Sjogren's syndrome. She had hypocomplementemia and cryogloblinemia. Renal biopsy revealed a membranoproliferative glomerulonephritis. Treatment with prednisone resulted in complete remission of nephritic syndrome and cryogloblinemia was disappeared. The pathogenesis of glomerulonephritis appears to be due to deposition of cryogloblins, which may be caused by primary Sjogren's syndrome.

P1-142

Patient with pernio-like erythema who was given diagnosis of Sjogren's syndrome

Hiromi Karasawa¹, Yoshikazu Kuwana¹, Masaaki Shiozaki¹, Natsumi Ikumi¹, Takamasa Nozaki¹, Hirotake Inomata¹, Hidetaka Shiraiwa¹, Noboru Kitamura¹, Takashi Hayama¹, Yoshihiro Matsukawa¹, Masami Takei¹

¹Hematology and Rheumatology, Nihon University School of Medicine, Tokyo, Japan, ²Dermatology, Surugadai Nihon University Hospital, Tokyo, Japan

A 41-years-old woman presented chilblains on her hands in the winter of 2009. On the dermatologist's examination, the diagnosis was uncertain and collagen disease was suspected for unusual pernio. Afterward, the patient was referred to the department of rheumatology in our institution. Although the patient did not present evident dry mouth or dry eye, her clinical findings were well consistent with Sjogren's syndrome (SjS); positivity of serum anti-SSA/SSB antibody and focus score 1 in lip biopsy. Result of gum test was 23ml, and KCS was not detected. A diagnosis of SjS was consequently established. The patient has been on observation without

sicca syndrome. We conclude that SjS might be one of the differential diagnoses among patients presenting such pernio-like erythema.

P1-143

Renal involvement in the long-term course of primary Sjögren's syndrome (pSS)

Tomohiro Oka, Tamaki Sasaki, Naoki Kashihara

Nephrology and Hypertension, Kawasaki Medical School, Kurashiki, Japan

Case1: A 66-year-old woman, who already had been diagnosed as pSS since 1998. She was admitted to our hospital with asymptomatic proteinuria. Renal biopsy revealed diffuse mesangial cell proliferation and a spike formation of the GBM, resembling MPGN. Especially, intraluminal thrombi and diffuse giant deposits were detected. Case2: A 63-year-old woman with long-standing pSS presented with progressive renal dysfunction. 25 years before, renal biopsy revealed tubulointerstitial nephritis (TIN) but did not identify specific immune deposits. Present renal biopsy revealed TIN with vascular injury with large subendothelial deposits. The renal involvement in long-term course of pSS may be more guarded, especially in the presence of the accompanying development of lymphoproliferative disorders.

P1-144

A case of sjogren's syndrome diagnosed as Macroglobulinemia one year after onset

Hideko Nakahara, Yoshimasa Hamano, Takashi Hosokawa, Masayuki Nishide, U Rin, Keisuke Kawamoto, Shinji Higa, Tsuyoshi Igarashi, Taro Kuritani, Keiji Maeda

Division of Allergy, Rheumatology and Connective Tissue Diseases, Department of Internal Medicine, NTT West Osaka Hospital

62-year old woman with sjogren's syndrome presented with fever, dyspnea and edema in June, 2008. She was diagnosed sepsis with acute renal failure. She was treated with antibiotics, prednisolone (50mg/day) and hemorrhage dialysis (HD). Blood examination revealed cryoglobulin. In renal biopsy, PAS positive deposits were found in the endocapillary in glomerulus. The origin of cryoglobulin was unclear. In November 2009, she presented with fever and edema again. PSL (50mg/day) and HD improved her symptom and laboratory abnormalities. Blood examination revealed IgM-k type of M-protein and urinary examination showed Bence-Jones protein (k-type). She was diagnosed as macroglobulinemia 1 year after onset.

P1-145

Mononeuropathy multiplex with Sjögren's syndrome and systemic sclerosis

Tetsuya Saito, Fumihito Suzuki, Hiroyuki Hagiya

Department of Internal Medicine, Minato Red Cross Hospital, Yokohama, Japan

A 40-year-old woman was diagnosed as Sjögren's syndrome (SS) and systemic sclerosis (SSc) with keratoconjunctivitis sicca, digital skin thickening, and positive anti-SS-A and anti-centromere antibodies in 2007. She developed numbness in her left hand in February 2008. She was diagnosed as mononeuropathy multiplex by nerve conduction studies (NDS) showing a reductive action potential in left radial and medial nerves. Treatment with prednisolone (PSL) 30mg failed and numbness appeared in her both feet on admission in June. NDS revealed an asymmetric and patchy distribution of neuropathy. A sural nerve biopsy was consistent with a vasculitic neuro-

pathy. Increase of PSL to 50mg with cyclophosphamide pulse therapy, followed by maintenance therapy of cyclosporine, improved her symptoms.

P1-146

Comparison of therapy for RA patients associated with chronic IP and without IP

Shigeki Makino, Takuya Kotani, Koji Nagai, Daisuke Wakura, Kentaro Isoda, Shuzo Yoshida, Kenichiro Hata, Tohru Takeuchi, Toshiaki Hanafusa

Department of Internal Medicine (I), Osaka Medical College, Takatsuki, Osaka, Japan

Background: We aim to clarify the difference between therapeutic regimens for RA patients with IP and for RA patients without IP. Methods: On September 30, 2010, we reviewed clinical data of RA patients of our department including IP association and treatment. Results: Total RA patients were 380 with 84 male. Among them, those with IP were 61 with 32 male. The prescribed rate of MTX for patients with IP is 39%, that for patients without IP is 69% (MTX 39%/69%). The prescribed rate of corticosteroid is 43%/40%, that of biologics is 18%/23%, that of tacrolimus is 49%/14%, that of sarpopyrine is 31%/31%, that of bucillamin is 13%/17%. Conclusions: We cannot prescribe MTX for 60% of RA patients with IP. On the other hand we are favorite to prescribe tacrolimus for them.

P1-147

Rheumatoid arthritis with multiple pulmonary nodules due to rheumatoid nodules

Hideyuki Tachibana, Mutsuto Tateishi, Sayuri Kataoka, Yumiko Seno, Akiko Tochimoto, Manabu Tanabe, Takashi Ogasawara, Takashi Yamada

Tokyo Metropolitan Ohtsuka Hospital

A 78-year-old woman has been treated for rheumatoid arthritis from 1998. Treatment with DMARDs including BUC, SASP, ACT, GST, and TAC had been stopped because of inefficacy or adverse events, and she has been treated with prednisolone (6mg per day). She was pointed out multiple pulmonary nodules on chest computed tomography in September 2009. Bronchoscopy and CT-guided needle biopsy were performed to rule out malignancy, which showed no histological features of malignancy or infections. And other studies including CT scan, MRI imaging, gastrointestinal scopy, colonoscopy, and garium scan showed no malignancy as well. Finally we consider multiple pulmonary nodules as rheumatoid nodules.

P1-148

A case of rheumatoid arthritis with multiple pulmonary rheumatoid nodules

Satoshi Yamaguchi, Masayoshi Hirata

Department of Rheumatology, Takaoka City Hospital, Toyama, Japan

We report a case of pulmonary rheumatoid nodules diagnosed histologically, and the nodules reduced after steroid treatment. A 59-year-old man had been diagnosed with rheumatoid arthritis (RA) and being treated with methotrexate and celecoxib for 5 months. When he was diagnosed, multiple subpleural pulmonary nodules were pointed out in chest computed tomography (CT). The patient was admitted to our hospital for evaluation of multiple nodules of both lungs on X-ray film, and the nodules had grown in CT. Video-assisted thoracic surgery was performed. Histologically, the resected

nodule consisted of necrotizing granuloma, and it was diagnosed as rheumatoid nodule because the patient exhibited RA. After treatment with prednisolone, the lung nodules shrank and cavitation of the nodule was noted.

P1-149

Acute exacerbation of interstitial pneumonia (IP) with rheumatoid arthritis (RA)

Kengo Akashi¹, Megumi Nakata¹, Misako Uehara², Yumiko Nobuhara¹, Shunzo Namiuchi¹

¹Department of Rheumatology, Saiseikai Nakatsu Hospital, ²Division of Rheumatology, Fujieda Municipal General Hospital

A 66-year-old man with RA, treated with prednisolone, salazosulfapyridine, bucillamine, and mizoribine admitted to our hospital because of progressive dyspnea. On chest X-ray, IP was confirmed in both lungs. Endotracheal intubation was performed because of no improvement in respiratory status despite of antibiotics and methylprednisolone (mPSL) pulse therapy. In spite of three times of mPSL pulse therapy, enteral administration of cyclosporin A, and three times of intermittent intravenous cyclophosphamide therapy, IP was deteriorated. Furthermore, he developed cytomegalovirus pneumonia and pneumothorax. Finally he died of respiratory failure. IP accompanied with RA usually show slow progression. This is a rare case of life-threatening acute exacerbation of IP.

P1-150

Outcome of ILD after Biologics in Patients with Pre-existing ILD

Tamao Nakashita, Akira Inoue, Natsuki Fujio, Shinji Motojima
Rheumatology and Allergy, Kameda Medical Center, Chiba, Japan

Post-marketing surveillance reports of biologic DMARDs (BLGs) show the exacerbation/development ratio of ILD to be 0.5 %. However, the ratio has not been known when BLGs are applied to RA patients with pre-existing ILD. In this study we restricted the follow-up period to 9 months after introduction of BLGs to pick up ILD exacerbation likely to be induced by BLGs. Subjects were 25 patients with pre-existing ILD, and the BLGs administered were INF in 7, ETN in 17 and ADA in 1, respectively. ILD exacerbation was noticed in 7/25 (28%), and duration until the exacerbation was from 1 to 9 months with the median of 2 months. BLGs administered were IFX in 3 and ETN in 4, respectively. BLGs were stopped in 6/7 and 2 patients died due to respiratory failure.

P1-151

A Case of Rheumatoid Arthritis Preceded by Pulmonary Hypertension

Masakazu Matsushita, Kentaro Minowa, Hirofumi Amano, Naoto Tamura, Yoshinari Takasaki
Department of Internal Medicine and Rheumatology, Juntendo University, School of Medicine

Around the age of 22 years old, the patient had begun to notice dyspnea on exertion and visited our hospital at the age of 27. Blood test, echocardiography, CT, Tc-99m MAA scintigraphy, etc were performed. However, anti-CL β -2-GP I-antibody was positive, and there was no evidence of thrombosis. Then she was diagnosed with pulmonary arterial hypertension (PAH) based on the right heart catheterization. Thereafter, beraprost and warfarin were started. A few years later, because her symptom was getting worse, bosentan was added. At age 31 years, the symptoms of finger polyarthritis al-

lowed the diagnosis of rheumatoid arthritis (RA). It is well known that PAH can often become apparent in patients with SSc and MCTD, but RA preceded by PAH is supposed to be rare.

P1-152

A case of rheumatoid arthritis with pulmonary artery hypertension

Takashi Fujimoto¹

¹Department of General Medicine, Nara Medical University School of Medicine, Kashihara, Japan, ²First Department of Internal Medicine, Nara Medical University School of Medicine, Kashihara, Japan

We describe a case of rheumatoid arthritis (RA) with pulmonary artery hypertension. A 48-year-old woman was diagnosed as RA in 2003. She was admitted to the hospital suffering from increasing dyspnea, chest pain, and edema in October 2010. Radiographs of chest disclosed cardiac enlargement and pleural effusions. Echocardiogram showed pulmonary artery hypertension (estimated pulmonary artery pressure (PAP) of 74 mmHg), and pulmonary arteriography revealed a PAP of 78 / 40 mmHg. A ventilation-perfusion lung scan showed reduced perfusion in multiple segmental patterns. The pulmonary artery hypertension was most likely caused by chronic pulmonary thromboembolism. The delivery of oxygen, warfarin, furosemide, and beraprost resulted in improvement of the dyspnea, pleural effusions, and PAP.

P1-153

Does higher CRP progress coronary arteriosclerosis in rheumatoid arthritis ?

Toshiaki Ohnishi

Ohnishi Naika Clinic

Objective: The aim of the study is to examine whether the longer duration of high CRP levels are associated with more severe coronary artery stenosis (CAS). **Methods:** We first performed multi-detector computed tomography (MDCT) on 10 female RA patients to screen for CAS. If significant coronary stenosis was observed with MDCT, coronary catheterization was performed to confirm the severity of coronary stenosis. Duration of high levels of CRP (>5mg/dl) was then compared to the severity of coronary stenosis. **Results:** Although significant coronary stenosis was observed in 4 patients, there was no significant correlation between the severity of coronary stenosis and the duration of high levels of CRP (>5mg/dl). However, there was a weak association between coronary stenosis and the duration with RA.

P1-154

13 cases of rheumatoid arthritis complicated with lymphoproliferative disease

Kumiko Shimoyama^{1,2}, Jin Sawada², Osamu Kimoto¹, Daisuke Suzuki¹, Hiroyuki Ohashi², Noriyoshi Ogawa¹

¹Third Department of Internal Medicine, Hamamatsu University School of Medicine, Hamamatsu, Japan, ²Omaezaki Municipal Hospital

Purpose: To investigate the characteristics of rheumatoid arthritis complicated with lymphoproliferative disease (LPD-RA).

Object: 13 cases of LPD-RA and 83 cases of non LPD-RA were subjected for the study.

Results: In 13 LPD-RA (9 were females). 4 were diffuse large B cell lymphoma, 3 were polymorphic LPD. 7 were EBER-ISH positive.

All cases were treated with methotrexate. In LPD-RA, CRP 7.0 ± 8.7 mg/dL, DAS28 (CRP) (4.5 ± 1.5) were significantly higher and body mass index (19.3 ± 1.3) , serum albumin (3.3 ± 0.6) g/dL were significantly lower ($P < 0.001$) compared with non-LPD-RA. There was no significant difference in tender/swollen joint count, duration of RA, MTX dosage between the two groups.

Conclusions: Because LPD is important complication of RA, early treatment and the early diagnostics are necessary.

P1-155

Recurrent cerebellar infarctions associated with atlanto-axial subluxation in RA

Shiro Ohshima, Eriko Kudo-Tanaka, Yuichi Maeda, Soichiro Tsuji, Yoshinori Harada, Yoshinori Katada, Masato Matsushita, Yukihiro Saeki, Shosuke Akita

NHO Osaka Minami Medical Center

A 69-year-old man with RA. Although disease activity was well controlled, he presented dizziness, vomiting and double vision. MRI confirmed cerebellar multiple small infarction. Anticoagulant therapy was performed with heparin, but recurrent infarctions occurred in the short term. No evidence of thrombosis in heart and carotid arteries were revealed with ultrasonography. Radiographs of the cervical spine diagnose as atlanto-axial subluxation (AAS). Doppler ultrasonography and angiography revealed transient occlusion of left vertebral artery (VA) when his head position placed in both sides rotation, and retroflexion respectively. As a result, recurrent cerebellar infarctions were induced by insufficient flow of VA associated with AAS in RA.

P1-156

A case of rheumatic meningitis

Megumi Matsuhashi, Masato Isobe, Masato Shimizu, Mihoko Henmi, Yuko Aoki, Fumihiko Sakamoto, Akemi Kitano, Akihiro Narita, Takeya Ito, Jun Fukae, Akio Mitsuzaki, Kazuhide Tanimura

Hokkaido Medical Center for Rheumatic Diseases

Although RA with concomitant nervous system complication is rare, recent advent of imaging techniques allowed some reports. We herein report a case of rheumatic meningitis (RM) with cataplexy and transient conscious disturbance along with peculiar MRI findings. A 62 years-old woman had high blood pressure, hyperlipidemia and Sjogren's syndrome. Her RA symptoms appeared in 1994 and worsened despite MTX treatment commenced in 2007. In 2010 after she experienced transient cerebral ischemic attack she was admitted to a cerebral surgeon. Albeit suspected acute cerebral infarction, poor treatment response prompted transfer to a general hospital, where she was diagnosed as RM after brain MRI signals and biopsy. After she was transferred to our hospital her RA improved with steroid pulse therapy.

P1-157

A case of rheumatoid arthritis with lung patchy consolidations on chest CT scan.

Yasuhiro Kato, Yoshiyuki Mori, Kumiko Kobayashi, Hiroshi Fujiwara

Division of Rheumatology, Osaka General Medical Center, Osaka, Japan

A 66-year-old man with rheumatoid arthritis had longstanding refractory leg ulcers. We started etanercept (ETN) treatment since Mar, 2009. Then, the ulcers were healed completely. However, the

ulcers relapsed in 2010. Since concomitant infection of the ulcers was suspected, ETN treatment was stopped and admitted to our hospital. Computed tomography on the lungs revealed multiple patchy consolidations predominantly in the peripheral subpleural regions. Septic embolism of the lungs was suspected. However, antibiotic therapy was ineffective. We increased the dose of PSL to 0.5mg/kg/day. This resulted in the improvement of his clinical findings. We present this case of rheumatoid arthritis with interstitial pneumonia that had to be differentiated by pulmonary embolism.

P1-158

A huge Baker's cyst in a patient with RA

Hiroaki Hamada¹, Takashi Ohhira³, Koichiro Saisho², Etsuo Chosa¹, Tomohisa Sekimoto¹, Takero Sakamoto¹

¹Department of Orthopedic Surgery, Faculty of Medicine, University of Miyazaki, ²Department of Orthopaedic Surgery, National Hospital Organization, Miyakonojo Hospital, ³Ohira orthopaedic and rheumatism clinic

【Patient】A patient is 67 years old female.

【chief complaint】the tumor of left thigh in popliteal region. 【present illness】In April of 2010 it occurred secondarily invalid, so the medication was changed Infixmab to Tocilizmab. Tumors are noticed May, 2010 on the popliteal region, and she visited our department first medical examination in June.

【Findings】In left thighs on the popliteal region it has no inflammatory sign. < CT・MRI>A huge and cotyledon cyst was seen and the edge of cyst was reinforced. <operative findings> Lots of debris was in the cyst and no PVS findings was there.

【 diagnosis 】A huge Baker's cyst 【 consideration 】The gastro-semimembraneous bursa was made huge and a rare synovial bursitis. It seems that poor control of RA made it hugely.

P1-159

CX3CL1/CXCR1 axis is a crucial target for ETN therapy

Michihito Sato, Tsuyoshi Odai, Kumiko Otsuka, Hidekazu Furuya, Ryo Takahashi, Kuninobu Wakabayashi, Takeo Isozaki, Nobuyuki Yajima, Yusuke Miwa, Masao Negishi, Hiroshi Ide, Tsuyoshi Kasama

Division of Rheumatology, School of Medicine, Tokyo, Japan

Objective. To examine the relationship between serum chemokine levels and patient responsiveness in RA patients to etanercept (ETN) and the influence of ETN administration on serum chemokine levels.

Methods. Serum levels of the chemokines CX3CL1, CXCL8, CXCL10 and CCL3 were quantified prior to (at baseline) and after 14 weeks of treatment with ETN in 20 patients using enzyme-linked immunosorbent assays.

Results. By 14 weeks, a significant reduction in CX3CL1 was observed in the responsive group, although ETN treatment had no significant effect on the serum levels of the other three chemokines. In addition, the mRNA expression of CX3CR1 in peripheral blood mononuclear cells were significantly decreased after ETN treatment.

Conclusion. CX3CL1/CX3CR1 axis plays a crucial role in RA.

P1-160

Elevated CSF levels of CX3CL1 in patients with NPSLE

Nobuyuki Yajima, Hidekazu Furuya, Michihito Sato, Kumiko Otsuka, Ryo Takahashi, Kuninobu Wakabayashi, Tsuyoshi Odai, Yusuke Miwa, Masao Negishi, Hirotsugu Ide, Tsuyoshi Kasama

(Purpose)To assess the role of CX3CL1 in NPSLE. (Method) CSF was obtained from 19NPSLE and 10 non-NPSLE patients. The relationship of CSF levels of CX3CL1 to CSF levels of IL-6, IgG-index and anti-ribosomal P Ab was examined. In addition, The comparison of CSF level of CX3CL1 in Neurologic syndrome and in Diffuse psychiatric/neuropsychological syndromes was examined. (Result) CSF levels of CX3CL1 were significantly higher in patients with NPSLE as compared with non-NPSLE. Significant correlation was observed between CSF levels of CX3CL1 and of CSF levels of IL6. CSF levels of CX3CL1 were significantly higher in patients with Neurologic syndrome than with Diffuse psychiatric/neuropsychological syndromes. (Conclusion) These findings suggest that CX3CL1 may be a diagnostic tool of NPSLE.

P1-161

Contribution of CXCL16 to plasmacytoid dendritic cell activation

Hidekazu Ikeuchi^{1,2}, Noriyuki Sakurai¹, Ken Kayakabe¹, Akito Maeshima¹, Toru Sakairi¹, Takashi Kuroiwa¹, Keiju Hiromura¹, Yoshihisa Nojima¹

¹Department of Medicine and Clinical Science, Gunma University Graduate School of Medicine, Gunma, Japan, ²National Cancer Institute, MD, USA

Evidence suggests that IFN- α influences the pathogenesis of SLE. In humans, plasmacytoid dendritic cells (pDC) are a primary source of IFN- α . They produce large amounts of IFN- α when triggered via their TLR. We previously reported that CXCL16 contributes to pDC recognition of Type D CpG ODN, and that this interaction promotes IFN- α production via the TLR9 signaling pathway. Recent studies show that the level of CXCL16 is elevated in urine from patients with SLE. We therefore investigated the effect of CXCL16 on the CAL-1 human pDC cell line. Using shRNA targeting CXCL16, and anti-CXCL16 antibodies, we found that depletion of CXCL16 increased TLR9 ligand induced IFN- α expression. This results indicates that the CXCL-16 signaling pathway plays an important role in CpG triggering of pDC.

P1-162

Clinical efficacy and IL-17 level of early stage RA treated with tight control

Eiji Torikai, Motohiro Suzuki, Yukihiro Matsuyama
Department of Orthopaedic Surgery, Hamamatsu University School of Medicine

IL-17 plays a crucial roll in rheumatoid arthritis (RA). The aim of the present study was to evaluate clinical efficacy and IL-17 serum levels of patients with early stage RA treated with tight control therapy. Fourteen early stage RA patients (<12 months disease duration, 2 men and 12 women) were followed up. As soon as they were diagnosed as RA, they were treated with DMARDs. All patients underwent clinical examinations and routine blood analysis every 3 months. When their DAS28CRP scores were > 2.7, DMARDs were changed. The IL-17 serum level was measured by ELISA at the baseline, 3 months, 6 months and 12 months after the initial treatment. Tight control therapy for early stage RA was very efficacious. The mean IL-17 serum level from RA patients decreased significantly.

P1-163

Effect of IL-6 on the production of chemokine in macrophage by adiponectin

Miho Suzuki, Masahiko Mihara
Product Research Department, Chugai Pharmaceutical Co., Ltd.

THP-1 cells activated by PMA (THP-1 macrophages) were stimulated with full-length adiponectin (fAd) or globular adiponectin (gAd) and then the production of chemokine was examined. GAD stimulation increased the production of chemokine compared with fAd at the same concentration. THP-1 macrophages were stimulated with fAd, IL-6 or fAd+IL-6 and then the production of chemokine was measured. fAd+IL-6 stimulation increased synergistically the expression of chemokine compared with fAd and IL-6 alone. In addition, IL-6 stimulation increased the expression of MMP-12 which cleave fAd into gAd in THP-1 macrophages. In conclusion, IL-6 might induce ptoinflammatory gAd from fAd via the induction of MMP-12 expression in macrophage.

P1-164

Anti-IL-6R antibody prevent antibody production by suppressing of IL-6 signaling

Hiroto Yoshida, Miho Suzuki, Misato Hashizume, Masashi Shiina, Masahiko Mihara
Product Research Department, Chugai Pharmaceutical Co., Ltd., Shizuoka, Japan

We examined the effects of IL-6 on the production of antibody (Ab) against Ab. Firstly, BALB/c mice received anti-mouse IL-6 receptor Ab (MR16-1) or rat IgG or human IgG1 weekly. The production of anti-MR16-1 Ab was suppressed when a large amount of MR16-1 was injected at first time. However, without a large amount injection at first time, anti-MR16-1 Ab was induced. Interestingly, in the case of rat IgG and human IgG1, Ab production was induced, even if a large amount of Ab was injected at the first time. Next, human IgG1 was injected weekly into mice in which IL-6 signaling were blocked by the pre-treatment of MR16-1. Anti-human IgG1 Ab was not produced in this mice. In conclusion, MR16-1 suppressed production of Ab to itself by inhibiting IL-6 signaling.

P1-165

Impact of adipocytokines on disease activity in RA -TOMORROW study-

Yuko Sugioka¹, Shigeyuki Wakitani¹, Masahiro Tada¹, Tadashi Okano¹, Kenji Mamoto¹, Tatsuya Koike²

¹Department of Orthopaedic Surgery, Osaka City University Medical School, Osaka, Japan, ²Department of Rheumatology, Osaka City University Medical School, Osaka, Japan

[Purpose] We conducted a prospective cohort study to evaluate risk factors in RA patients for disease activity (TOMORROW study). Two hundred eight RA patients (112 patients received biologic agents) and 205 healthy volunteers were enrolled in the study. We evaluate adiponectin and leptin concentrations in relation to disease activity and bone metabolism. [Result] Serum levels of both leptin and adiponectin in RA patients are higher than that of volunteers ($p < 0.05$). In RA patients, leptin concentrations were significantly correlated with % of fat rate ($r = 0.719$), but not correlated with disease activity and bone mineral density. Adiponectin concentration were positively correlated with DAS28 ($r = 0.392$ in men) and inversely correlate with leg bone mineral density ($r = 0.392$).

P1-166

The combined effect of hyaluronic acid and cytokine inhibitors

Misato Hashizume, Masashi Shiina, Hiroto Yoshida, Miho Suzuki, Masahiko Mihara

Product Research Department, Chugai Pharmaceutical Co., Ltd., Gotemba, Japan

Cytokines play roles in the cartilage destruction in RA. However, it has been reported that cytokine inhibitors do not show sufficient effect on the weight-loading large joints. Whereas HA is widely used for the therapy of OA and RA by the injection into large joints. We examined the combined effect of HA and cytokine inhibitors on joint destruction factor production. HA inhibited the MMP-3, RANKL and ADAMTS4 inductions by IL-1 and IL-6 in part, but not by TNF- α at all. RA synovial fluid induced these molecules. Cytokine inhibitors partially inhibited these inductions, showing that multiple cytokines involved in the joint destruction factor expression. This study suggested that the co-administration of HA and the cytokine inhibitors may be effective on the preventing the joint destruction.

P1-167

IL-32 expression increased on Oc and α IL-32Ab inhibits human osteoclastogenesis.

Toru Yago, Yuki Nanke, Manabu Kawamoto, Tsuyoshi Kobashigawa, Naomi Ichikawa, Hisashi Yamanaka, Shigeru Kotake
Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Objective. To investigate the expression of IL-32 on osteoclasts (Oc) compared to monocytes (Mo) and the effect of anti-IL-32 antibody (Ab) for inhibiting osteoclastogenesis.

Methods. 1) Human Mo were cultured with M-CSF for 3 days. Then, Mo were cultured with IL-32 and/or anti-IL-32 Ab for 10 days. Oc were stained for anti-CD51/61 (vitronectin receptor) antibody. 2) mRNA expression of IL-32 was evaluated on Mo, pre-Oc, Oc by RT-PCR.

Results. Anti-IL-32 Ab dose-dependently inhibited human osteoclastogenesis induced by IL-32. Moreover, as Mo differentiated into Oc, mRNA expression of IL-32 was increased.

Discussion and Conclusions. These results suggest that anti-IL-32 Ab has the potential to inhibit human osteoclastogenesis and Oc also express IL-32 as well as T cells.

P1-168

RANK expression and osteoclast formation in human monocytes in RA

Yuki Nanke, Toru Yago, Manabu Kawamoto, Tsuyoshi Kobashigawa, Naomi Ichikawa, Hisashi Yamanaka, Shigeru Kotake
Institute of Rheumatology, Tokyo Women's Medical University

Receptor activator of NF κ B (RANK) is a member of the TNF receptor superfamily and a receptor for RANKL. We have been reported that the expression of RANK on monocyte in non-treatment RA was elevated. Moreover, high expression of RANK on CD 14+ cells may induce the osteoclastogenesis. Aim: To study an effect of IL-17A on expression of RANK on human monocytes in peripheral bloods. Methods: Peripheral bloods were obtained from normal volunteers. Human monocytes were cultured with M-CSF and/or IL-17A for 2, 4, or 24 hours. Levels of RANK mRNA were measured by RT-PCR. Results: IL-17 did not influence the expression of

RANK on monocytes. Discussion: IL-17 may not contribute the expression of RANK on monocytes.

P1-169

A peptide from TCTA protein inhibits human osteoclastogenesis –the 4th report-

Shigeru Kotake, Yuki Nanke, Toru Yago, Manabu Kawamoto, Naomi Ichikawa, Tsuyoshi Kobashigawa, Hisashi Yamanaka
Institute of Rheumatology, Tokyo Women's Medical University

Objective: We have demonstrated that a novel peptide from T cell leukemia translocation-associated gene (TCTA) protein inhibits human osteoclastogenesis (JCR2008, Bone, 2009). The peptide inhibits the total and mean area of human osteoclasts (JCR2010). In the current study, we examined the pit of a single osteoclast using scanning electron microscope (SEM). Methods: Human peripheral monocytes were cultured in the presence of RANKL with or without the peptide on dentine slices. The area and depth of a pit resorbed by a single osteoclast were measured by SEM. Results: The peptide inhibited the area and depth of the pits. Conclusions: The peptide inhibits human osteoclastogenesis. The peptide may be used for the therapy of human osteoporosis or rheumatoid arthritis.

P1-170

Histomorphometric analysis of joint lesions in rheumatoid arthritis

Rikako Hiramatsu¹, Yoshifumi Ubara¹, Naoki Sawa¹, Masayuki Yamanouchi¹, Eiko Hasegawa¹, Kenmei Takaichi¹

¹Nephrology Center, Toranomon Hospital, Tokyo, Japan, ²Ito Bone Histomorphometry institute

A 54-year-old woman on hemodialysis due to a secondary amyloidosis suffered from rheumatoid arthritis for 30 years performed a total knee arthroplasty. The specimen was investigated with histomorphometric analysis on undecalcified sections. The trabecular bone under the sites of normal cartilage formed lamellar pattern to the loading direction. However, the bone under the sites of destruction of cartilage formed woven architecture occurred from minimodeling. The role of cartilage is considered to transmit the loading signal to subcartilaginous bone, and maintain lamellar architecture. In patients with rheumatoid arthritis, cartilage is destructed with chronic inflammation and minimodeling-mediated woven bone formation might arise and contribute to pain and discomfort at their joints.

P1-171

Bone resorption inhibitors drop serum ucOC in elderly rheumatoid arthritis women

Sho Mokuda, Naoya Sawada, Masashi Takebayashi, Kenichiro Matoba, Akihiro Yamada, Makoto Onishi, Kazuo Jouyama, Yasuaki Okuda, Kiyoshi Takasugi

Department of Internal Medicine, Center for Rheumatic Diseases, Dohgo Spa Hospital, Matsuyama, Ehime, Japan.

Serum undercarboxylated osteocalcin, ucOC, provides an index of vitamin K deficiency in bone. Some bisphosphonates affect the serum ucOC level in primary osteoporosis. The goal of this study was to investigate the relationship between serum ucOC and bone resorption inhibitors in rheumatoid arthritis patients. This study measured the serum ucOC level in 99 postmenopausal women with low rheumatoid arthritis disease activity. The serum ucOC cutoff value was set at 4.5 ng/ml; the positive rate was 52.6% in the untreated group, 16.7% in the raloxifene group and 14.0% in the alendro-

nate group. A χ^2 test indicated a significant difference between these groups ($p=0.0078$). Therefore, bone resorption inhibitors decrease the positive rate for serum ucOC in rheumatoid arthritis patients.

P1-172

Osteogenesis and osteoclast inhibition effects of bisphosphonates in RA patients

Masakazu Nagashima, Hiroshi Takahashi, Kohichi Wauke, Nobuyuki Suzuki, Yoshiyuki Yamazaki

Department of Rheumatology, Tokyo Metropolitan Bokutoh Hospital

To investigate the effects of bisphosphonates (Bis) on bone loss and osteogenesis in patients with rheumatoid arthritis (RA). Eighty-three RA patients administered Bis for over 4 years (average age, 65.7 years; average disease duration, 23.4 years; average prednisolone dose, 2.6 mg) were included in this study. BMD levels at the radius, lumbar spine, and femoral neck were measured by using QDR. Serum levels of NTX, TRACP, PICP, and RANKL were measured by ELISA. YAM values of the radius, lumbar spine, and femoral neck were 80.2%, 103.8%, 92.7% respectively. The mean levels of NTX, TRACP, and PICP were 16.1 nmol BCE/l, 348.9 μ U/dl, and 600.4 ng/ml. BMD and bone absorptional markers of RA patients administered Bis for long time improved and the marker of osteogenesis increased significantly.

P1-173

Clinical results of alendronate with menatetrenon (VitK2) in postmenopausal RA

Kouji Suzuki¹, Shigeyoshi Tsuji¹, Takao Iwai¹

¹Department of orthopaedic surgery, Hoshigaoka Koseinenkin Hospital, ²Seikeikai Hospital Oosaka Trauma Microsurgery Center

A total of 62 postmenopausal RA patients with osteopenia (YAM<80%) or osteoporosis were classified into two groups; alendronate with menatetrenone (Vit K2) group (ALN+K ; ucOC >4.5mg/dl, n=39) and alendronate group (ALN; ucOC <4.5mg/dl, n=23). In all patients, we evaluated in comparison with 57 patients who could continue to take medicine over 1 year. In conclusion, lumbar bone mineral density (BMD) in both group increased significantly (ALN+K : +5.3%, ALN: +4.3%). Femoral neck BMD in only ALN+K group increased significantly (ALN+K:+3.3% ($p<0.05$), ALN :+0.2% (NS)). In ALN+K group, all cases serum ucOC improved within normal level. Recently several studies have reported that Vit K2 improved bone strength, additionally our study suggested that Vit K2 was able to improve also femoral neck BMD.

P1-174

Mir-31 contributes to bone resorption by osteoclasts

Fumitaka Mizoguchi^{1,2}, Nobuyuki Miyasaka^{1,2}, Hitoshi Kohsaka^{1,2}

¹Department of Medicine and Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan, ²Global Center of Excellence Program, International Research Center for Molecular Science in Tooth and Bone Diseases

MicroRNAs (miRNAs) are endogenous noncoding RNAs, which suppress the expression of genes by binding to 3'-UTR of the target mRNAs. We showed previously the importance of miRNAs in osteoclasts by analyzing osteoclast-specific dicer deficient mice. To identify individual miRNAs involved in formation and function

of osteoclasts, miRNA array was employed to analyze miRNA expression by bone marrow-derived macrophages (BMM) and by those stimulated with RANKL. We identified miR-31 as highly up-regulated miRNA by RANKL. Retroviral transfer of anti-miR-31 antagonists to BMM inhibited RANKL-induced generation of TRAP positive multinucleated cells, bone resorption and actin ring formation. These results indicate that miR-31 plays an important role in osteoclast regulation.

P1-175

Proteomic analysis of bone marrow-derived adherent cells in RA and OA

Toshikazu Kamada¹, Manae S. Kurokawa², Tomohiro Kato², Kenji Takenouchi¹, Kenji Takahashi¹, Kazuki Okamoto², Kazuo Yudo³, Hiroshi Nakamura¹

¹Department of Rheumatology, Nippon Medical School, Tokyo, Japan, ²Clinical Proteomics and Molecular Medicine, St. Marianna University Graduate School of Medicine, Kawasaki, Japan, ³Department of Frontier Medicine, Institute of Medical Science, St. Marianna University Graduate School of Medicine, Kawasaki, Japan

To elucidate the pathophysiology of rheumatoid arthritis (RA) and osteoarthritis (OA), we analyzed protein profiles of bone marrow-derived adherent cells (BMACs). Proteins in BMACs from 3 RA and 3 OA patients were comprehensively analyzed by 2-dimensional electrophoresis, and were identified by mass spectrometry. As a result, expression of 340 protein spots out of more than 1,600 spots detected was significantly altered between the diseases (≥ 1.5 folds: RA>OA, 26 spots; OA>RA, 314 spots). The identified 11 spots included vimentin and annexin A5 (RA>OA), and collagen VI α , a membrane anchor for acetylcholine esterase, heat shock protein 27, caldesmon, and cytoskeletal proteins (OA>RA). The altered protein profiles of BMACs may reflect the different pathophysiology between RA and OA.

P1-176

Cross-sectional data analysis of distribution of joints involved in RA

Teruhisa Kanazawa¹, Jinju Nishino², Toshihiro Matsui³, Shigeto Tohma³, Sakae Tanaka²

¹Department of Rheumatology, Tokyo Medical University Ibaraki Medical Center, Ibaraki, Japan, ²Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, ³Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami-hara National Hospital, National Hospital Organization

[Obj. &Methods] To identify the characteristics of involved joints in RA patients by large-cohort cross-sectional analysis, the involvement of 68 joints were investigated in 6408 RA. **[Results]** The frequently affected areas were intermediate/large joints by tenderness, but small joints of upper limbs by swelling. Classified involved joints as tenderness-only, swelling-only, or combination type, swelling was predominant in hands, and tenderness in feet. Classified joints in 34 symmetrical regions by unilateral or bilateral involvement, "unilateral" was predominant throughout the course of disease. **[Conclusion]** There are frequently affected joints in RA. Joints frequently affected with swelling are different from those with tenderness. Symmetry of involved joints is not characteristic to RA.

P1-177

Importance of E3 ubiquitin ligase Synoviolin in fibrogenesis

Naoko Yagishita¹, Satoko Aratani², Tomoo Sato¹, Ryoji Fujii¹, Yoshihisa Yamano¹, Kusuki Nishioka², Toshihiro Nakajima²

¹Institute of Medical Science, St.Marianna University School of Medicine, ²Institute of Medical Science, Tokyo Medical University

The symptoms of rheumatoid arthritis (RA) are based on the many processes; chronic inflammation, overgrowth of synovial cells, bone destruction and fibrosis. We recently cloned Synoviolin and confirmed that this molecule regulates the outgrowth of synovial cells. Furthermore, *synoviolin* deficient mice exhibited severe anemia caused by enhancement of apoptosis in fetal liver. To understand the role of Synoviolin in fibrosis, one of the symptoms of RA, we explored the involvement of Synoviolin in liver fibrosis because of simplicity of its development. We applied the CCl₄-induced hepatic injury model to *synoviolin* heterozygote mice, and demonstrated that these mice are resistant to onset of liver fibrosis. This result suggests that Synoviolin is a novel target for the fibrosis process.

P1-178

Aseptic meningitis related to EBV infection in a patient with MCTD

Satoshi Suzuki¹, Shoko Tohyama², Souichiro Nakano², Yuko Shimura¹, Yoshinori Kanai¹, Kenjiro Yamanaka¹, Yoshinari Takasaki²

¹Department of Internal Medicine and Rheumatology, Kyoundo Hospital of Sasaki Foundation, ²Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine

Patient was a 30-year-old woman. In Feb 2007, the patient was diagnosed with MCTD. On Sep 28, 2010, she developed lymph node swelling accompanied by persistent fever. Symptoms of meningeal irritation appeared on Oct 13, and lumbar puncture revealed meningitis. Later examinations showed positive anti-EA IgG antibodies against the *Epstein-Barr* (EB) virus in the serum, and positive EB virus DNA, positive anti-U1-RNP antibodies, and a high level of IL-6 in the cerebrospinal fluid. [Conclusion] Molecular homology between U1-RNP antigen and EB virus proteins is known. We herein report this relatively rare case in which anti-U1-RNP antibodies were detected in the cerebrospinal fluid, despite scant findings suggestive of MCTD activation.

P1-179

A case of mixed connective-tissue disease complicated by aseptic meningitis

Hiroshi Sato, Atsushi Masuyama, Isamu Yokoe, Hitomi Haraoka
Division of Rheumatology, Itabashi Chuo Medical Center

A 29-year-old woman diagnosed with MCTD had parotitis with a high level of inflammatory response. She was treated by antibiotic therapy. Although she appropriately took oral loxoprofen at the onset of fever, her headache tended to become exacerbated, and her body temperature rose as high as 40°C. Meningitis was also suspected, and lumbar puncture was performed. The cell count mildly increased to 34/3, and IL-6 in the cerebrospinal fluid (CSF) showed an abnormally high value of 1,460 pg/ml. On the other hand, positive anti-RNP antibodies in the CSF were confirmed, and MCTD-associated aseptic meningitis was diagnosed. The symptoms improved after PSL treatment. We report a case in which measurement of anti-RNP antibodies in the cerebrospinal fluid was useful for diagnosis.

P1-180

A rare case of patient with MCTD who had fasciitis and was cured by tacrolims

Yoshikazu Nakashima¹, Satoshi Yamasaki¹, Tomoki Origuchi², Hideki Nakamura¹, Mami Tamai¹, Shin-ya Kawashiri¹, Tomohiro Koga¹, Junko Kita¹, Akitomo Okada¹, Eriko Isomoto¹, Takahisa Suzuki¹, Atsushi Kawakami¹

¹The First Internal Department in Nagasaki University Hospital, Nagasaki, Japan, ²The Department of Health in Nagasaki University

Fasciitis is a relatively rare complication in mixed connective tissue disease (MCTD). We experienced a case of fasciitis in a patient with MCTD. A 49-year-old woman presented with 11 months history of swollen hand and muscle pain in her legs. Laboratory data revealed the elevation of creatine phosphokinase and positive anti-U1-RNP antibody. MCTD was diagnosed based on these physical and laboratory findings. SjS was confirmed by a biopsy of small salivary gland. Computed tomography demonstrated interstitial pneumonia. She was treated with 500mg methyl prednisolone for 3 days followed by oral prednisolone and tacrolims. Her muscle and respiratory symptoms were improved by the treatments. The present case suggested that tacrolims is useful treatment for fasciitis complicated with MCTD.

P1-181

Early diagnosis and clinical intervention improved PH with MCTD, a case report.

Kayo Oku, Yuko Kurihara, Atsushi Suzuki, Yasuo Ohsone
Department of Rheumatology, Kawasaki Municipal Ida Hospital, Kawasaki, Japan.

A 37-years old woman was admitted to our hospital due to polyarthralgia, fever and Raynaud's phenomenon. The laboratory findings were as follows: lymphocyte (600/μl), serum C-reactive protein (CRP) (10.74mg/dl), antinuclear antibody (ANA) (1:1280 speckled pattern) and antiRNP antibody (500U/ml). After admission, she had acute cardiac failure due to pulmonary hypertension, bilateral pleurisy and pericardial effusion. Her systolic PA pressure was about 40mmHg in echocardiogram. The diagnosis was PH, pleurisy and pericardial effusion with MCTD. M-PSL pulse followed by 50mg/day of PSL was initiated. On the day 40 after admission, right cardiac catheterization was performed. Her PA pressure was improved to PA17/5 (10)mmHg. In this case, early diagnosis and clinical intervention improved PH with MCTD.

P1-182

Postoperative pain in TKA is greater than that in THA

Kunio Yamada, Takaaki Hasuo, Masahiro Nishino, Tetsuya Takenaga, Tsukasa Imaizumi

Department of Orthopaedic Surgery, Komaki City Hospital, Komaki, Japan

We compared the intensity of postoperative pain in patients who underwent TKA and those who underwent THA managed by intravenous patient-controlled analgesia (PCA) with fentanyl. Forty patients who underwent unilateral primary TKA (n = 20) or THA (n = 20) were included in this study. All operations were performed under general anesthesia. Pain at rest was assessed using a visual analog scale at 1, 24, 48, and 72 h after the operation. Pain scores obtained at 24 h and thereafter were significantly higher in the TKA group than in the THA group. Further, patients in the TKA group demanded a significantly greater number of PCA boluses and more

supplemental analgesics than those in the THA group. The results of this study suggest that postoperative pain in TKA is greater than that in THA.

P1-183

Survival ratio differences after total joint arthroplasties in RA patients

Hiromu Ito, Hiroyuki Yoshitomi, Shinichiro Nakamura, Takashi Nakamura

Department of Orthopaedic Surgery, Kyoto University Graduate School of Medicine

We evaluated survival ratio of rheumatoid arthritis (RA) patients undergone three types of arthroplasties. Consecutive patients for 68 total hip (THA), 75 total knee (TKA), and 43 total elbow arthroplasties (TEA) were followed up to 15 years, and the survival ratios were calculated. In the patients undergone THA, the average age was 61.2, and the survival ratios after 5, 10 and 15 years were 83.1, 54.9, and 28.2 %, respectively. In the patients undergone TKA, the average age was 59.1, and the survival ratios were 89.0, 77.8, and 22.2%, respectively. In the patients undergone TEA, the average age was 64.0, and the survival ratios after 5 and 10 years were 89.7 and 55.0 %, respectively. We conclude that THA, TKA, and TEA did not cause any difference in survival ratios in RA patients.

P1-184

The RA patient's results of reconstruction with combined multiple operation

Ko Kato¹, Makoto Kowada¹, Daichi Hirano¹, Seiya Kawamura¹, Makoto Okada², Shinichi Yoshino³, Naoya Gunji⁴

¹Department of Orthopaedics Tokyo Hakujuji Hospital, ²Department of Internal medicine Tokyo Hakujuji Hospital, ³Yoshino memorial clinic, ⁴Gunji clinic

It is known that some rheumatic patients (RA) suffer from joints pain and severe deformities. our aim is to improve on these patients' problems with multiple joints operations. RA patients were 14 women, 21 lower legs were checked. The evaluation items are as follows: 1) With X-rays 2) Pain control 3) The evaluation with AOFAS score 5) Post operative complications 6) Re-operation after discharge etc. Results: It was noticed that two staples were loose, pain controlled with painkiller as usual, AOFAS score was improved on all patients. postoperative complications were staple loose, skin re-suture, infection, flare up due to rest of biologics, sepsis. The re-operation after discharge were one femur-loosening and one additional ankle dissection. Our results were good as we expected even if some problems occurred.

P1-185

Stress analysis of the acetabular reinforcement ring in total hip arthroplasty

Koji Totoribe, Etsuo Chosa, Hiroaki Hamada, Takero Sakamoto, Tomohisa Sekimoto

Department of Orthopaedic Surgery, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan

The acetabular support ring can be considered in total hip arthroplasty (THA) depending on the areas of bone grafting for protrusion of acetabulum in rheumatoid arthritis. Finite element analysis of the support ring in the THA was performed. 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. In the cup model, comparatively uniform stress distribution was observed. In the Ganz ring model, hook and screw showed stress concentration, and the stress of bone graft area showed low tendency. Bone grafting with Ganz ring can be expected to provide stress dispersion.

P1-186

Cemented total hip arthroplasty for rheumatoid arthritis of the hip

Tetsuo Masui

Hamamatsu Medical Center

The purpose of the present study was to assess the results of cemented total hip arthroplasty (THA) for rheumatoid arthritis of the hip. Fourteen patients (16 hips) were included in the current study: two males and 12 females with mean age at surgery of 64 years (range 37-84 years). The mean duration of follow-up was 3 years (1-6 years). Exeter stem and polyethylene socket (Stryker Japan) were used in all cases. Bulk structural bone graft was performed in one hip and impaction bone graft 7 hips for acetabular bone deficiencies. The mean JOA score improved from 48 (range 31-66) before surgery to 81 (range 50-95) at the final follow-up. No radiological loosening was seen in any case. Cemented THAs showed good clinical results in patients both with and without acetabular bone deficiencies.

P1-187

Total knee arthroplasty in patients with coxitis knee

Hiroshi Yonezu

Department of Orthopaedic Surgery, Mitoyo General Hospital

Coxitis knee is a condition defined as secondary osteoarthritis of the knee joint due to contralateral or ipsilateral hip disorder. In this study, we investigated the usefulness of TKA for coxitis knee and the early outcomes of patients undergoing this procedure. Three knees with coxitis were treated using primary TKA. One patient had fusion of the contralateral hip joint due to tuberculous arthritis, and two patients had functional leg length discrepancy due to severe osteoarthritis of the contralateral hip joint. Before surgery, the averaged FTA was 160.3°, and after surgery this was improved to 173.3°. Functional leg length discrepancy was not improved by TKA, and the two affected patients required corrective shoes. All became able to walk with cane.

P1-188

The clinical results of NRG CR/HA Total Knee Arthroplasty

Shaw Akizuki, Yoshiyuki Nakamura, Tsutomu Takizawa, Ikuya Yamazaki, Masataka Mochizuki, Tsuyoshi Toyota, Daigo Matsunaga

Department of Orthopaedic Surgery, Nagano Matsushiro General Hospital

149 knees in 87 patients were received NRG CR/HA TKA between in 2006 to 2008. Follow-up rate was 100%. ROM and Knee society score were evaluated. In addition, the radiographical evaluation was performed. There was no revised case. The mean preoperatively ROM was 96 degrees, and the mean ROM at 2 year after surgery was 128 degrees. The mean preoperative Knee society score was 27 points and the mean knee score at 2 years after surgery was 95 points. At 2 years after surgery, the initial gap at tibia remained only 3 knees (2%). There was no loosening implant in our series.

The clinical and radiographical results of NRG CR/HA TKA in 2 to 4 years after surgery were excellent. However, we thought that the long term observations would be necessary.

P1-189

The clinical results and evaluation of knee joint stability after CR-TKA in RA

Yuka Mukofujiwara, Motonobu Sakakibara

Aichi Koseiren Kainan Hospital, Department of Orthopaedic Surgery, Aichi, Japan

Objective : To investigate the clinical results and the knee joint stability of rheumatoid knees implanted with a high-flexion posterior cruciate-retaining total knee arthroplasty. **Methods :** The results were assessed for of 25 patients (70years), including 4males (6knees) and 13females (18knees) and mean follow-up period was 34months. **Results :** The mean JOA score improved from 43points preoperatively to 91points at the postoperative period. The range of motion improved from an average of 113° (flexion), -12° (extension) preoperatively to 123° , -0.8° at the postoperative period. No patients developed posterior instability. **Conclusions :** We present satisfying short term results in CR TKA for RA patients.

P1-190

Changes of the Postural Sway after Total Knee Arthroplasty

Hideyuki Aoki¹, Yoshiyasu Miyazaki¹, Takashi Nakamura¹, Ayako Kubota¹, Toru Suguro¹, Kazuaki Tsuchiya¹

¹Orthopaedic Surgery, Toho University, School of Medicine, Tokyo, Japan, ²Toho University, School of Medicine, Dept. of Rehabilitation, Tokyo, Japan

Objective: To investigate how the stability of postural sway would differ before and after Total knee arthroplasty (TKA). **Methods:** The patients for this study were who had rheumatoid arthritis and done bilateral TKA. The equipments used were FINE ® Total Knee System. For majoring stability of postural sway, PDM System by Zebris Medical was used. The items are; 1) length (mm), 2) rectangle area (mm²), and 3) envelop area (mm²) to compare the measurements with the data before and after surgeries. **Results:** Total length and a rectangular area increased, while there were no significant difference on envelop area compared before and after TKA. **Discussion and Conclusion:** The data would imply postural sway becomes worse right after the bilateral TKA, but recovery cycle might be shorter.

P1-191

Two RA cases with simultaneous bilateral TKA for severe flexion contracture.

Junji Hayashi

Joint Reconstruction and Rheumatic Center, Niizashiki Central General Hospital, Saitama, Japan

Flexion contracture is a common deformity encountered during total knee arthroplasty. Some patients with rheumatoid arthritis show gait disturbance caused by severe flexion contracture of bilateral knee joints. To avoid prolonged admission period, we tried simultaneous bilateral total knee arthroplasty for two patients of rheumatoid arthritis with severe flexion contracture. The flexion contracture of both patients was improved less than 10 degrees. One patient can walk without cane, and the other needs single T-cane. The simul-

taneous bilateral total knee arthroplasty was efficient for rheumatoid arthritis patients with severe flexion contracture.

P1-192

A case of revision TKA using a modular resection system for the Charcot knee

Shintaro Tsuge¹, Arata Nakajima¹, Koichi Nakagawa¹, Masato Sonobe¹, Yoshifumi Shibata¹, Yasuchika Aoki¹, Yu Sasaki¹, Manabu Fujino¹, Teruo Furufu¹, Toru Suguro²

¹Department of Orthopedic Surgery, Toho University Sakura Medical Center, ²Department of Orthopedic Surgery, Toho University Omori Medical Center

[Introduction] The Charcot joint is neuropathic arthritis, where deep and/or position sense is impaired, resulting in abnormal instability and destruction of joints. We present a patient who had a large bone defect at the femoral condyle after TKA for the Charcot joint then underwent a revision TKA using a modular resection system. [Case report] 80yrs, male. He has a history of primary amyloidosis but not DM, syringomyelia or tabetic neurosyphilis. He underwent a TKA for the Charcot joint of his left knee and has been doing well for 7 years. However, he got unable to walk due to the femoral condyle fracture following the implant loosening. Eventually, he underwent a revision TKA using a modular resection system (Kotz) and has been doing well, but careful follow up is needed.

P1-193

Patellar clunk syndrome developed after trauma: a case report

Hiromi Kondo, Daisaku Tokunaga, Yuji Arai, Ryo Oda, Ryu Terauchi, Eigo Otakara, Toshikazu Kubo

Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

A 70year-old lady with rheumatoid arthritis underwent right TKA. In 2010, severe clunk around patella occurred after she fell down and got a blow with the right knee. A surgical treatment was done under suspicious of loosening of the patellar component. For the perioperative findings, no loosening of the patellar component was found, although small damage of the bone cement existed. Hard fibrous tissue with deposition of prosthetic particles was found. After resection of this fibrous tissue, the clunk disappeared. Patellar clunk syndrome is reported to be caused by the formation of a fibrous nodule at the articular side of junction of superior pole of patella, especially after posterior stabilized TKA. In this case, bleeding and edema around the fibrous nodule might cause this phenomenon.

P1-194

Five cases of continuous hydroarthrosis after TKA in RA patients

Hideki Date¹, Kazue Hayakawa¹, Harumoto Yamada¹, Kenji Nakagawa²

¹Department of Orthopaedic surgery, Fujita Health University, ²Nissin Orido Hospital

[Purpose] The main cause of continuous hydroarthrosis after TKA is considered by deterioration of RA. We investigated the cause of hydroarthrosis. [Patients and Methods] Five patients were operated, whose mean age at primary TKA was 52.0 y and mean interval between primary TKA and re-operation was 6.3 years. In all cases, total synovectomy and polyethylene insert exchange were performed. [Results] Histological findings in three cases showed the appearance of active synovial proliferation in relation with inflam-

mation markers. Another two cases showed the appearance of high density histiocytes compatible with foreign body reaction. **Conclusions** Three cases were due to deterioration of RA activity and two cases were due to foreign body reaction as the cause of continuous hydroarthrosis

P1-195

Rheumatoid arthritis with intra-patellar geode: two cases report

Hiroshi Tamai, Jin Miyagi, Eiichi Itadera, Tomoko Kobayashi
Department of Orthopedics, Kashima Rosai Hospital, Ibaraki, Japan

Case 1: 67 years old woman, diagnosed with rheumatoid arthritis (RA) in other clinic from 2002, was treated in our hospital from 2007 for bilateral knee pain. Her right knee pain was very severe and was difficult to walk. She admitted in our hospital on March 2010. Her preoperative CRP was 7.53. The right knee showed severe destructive change (Larsen grade IV) and intra-patellar geode was observed on the x-ray. Total knee arthroplasty was done. There was no postoperative pain and the walking difficulty was not observed. Intra-patellar geode is rare relatively. In both cases preoperative CRP was high, and poor control of RA seemed to be related to the formation of geode

P1-196

Effect of JAK inhibitor on serum amyloid A expression in RA synoviocytes

Kiyoshi Migita¹, Yasumori Izumi¹, Taiichiro Miyashita¹, Tomohiro Koga², Satoshi Yamasaki², Takafumi Torigoshi¹, Satoru Motokawa¹

¹Department of Rheumatology Nagasaki Medical Center, ²Department of Rheumatology Nagasaki University Hospital

Objective: We investigated the influence of JAK/STAT inhibition on the induction of serum amyloid A (SAA) in RA-FLS. **Methods:** IL-6-stimulated gene expression of the acute-phase serum amyloid A genes, (A-SAA; encoded by SAA1+SAA2) and SAA4 were analyzed by RT-PCR. **Results:** IL-6 trans-signaling induced A-SAA mRNA expression in RA-FLS. IL-6 stimulation did not affect the SAA4 mRNA expression, which is expressed constitutively. IL-6 stimulation elicited the rapid phosphorylation of JAK2 and STAT3, which was blunted by CP690,550. CP690,550 abrogated IL-6-mediated A-SAA mRNA expression in RA-FLS. **Conclusions:** Our data indicated that inhibition of IL-6-mediated pro-inflammatory signaling pathways by CP690,550, may represent a new anti-inflammatory therapeutic strategy for RA and AA amyloidosis.

P1-197

Evaluation of SAA and apoE metabolism in murine AA amyloidosis

Toshiyuki Yamada
Department of Clinical Laboratory Medicine

SAA and apoE in sera and spleen of mice during the period from amyloidogenesis to amyloid resorption were focused. Amyloidosis was generated by AEF and silver nitrate. Sera and spleen were taken at day 2, 5, 21, and 55. No significant findings were seen in serum SAA or apoE. Immunostaining and immunoblotting for spleens revealed the followings. SAA was detected at day 2 and molecular sizes of SAA fragments were constant during the period observed. The size of these fragments differed from those seen in serum, suggesting that specific degradation may lead to amyloidogenesis.

ApoE behaved almost the same as SAA. Both SAA and apoE are able to be therapeutic targets in AA amyloidosis.

P1-198

Improvement of amyloidosis with rheumatoid arthritis by biologics: 2 cases

Shuichi Nakabo, Takao Fujii, Yuki Ishikawa, Seiko Ishikawa, Naoichiro Yukawa, Hajime Yoshifuji, Daisuke Kawabata, Takaki Nojima, Koichiro Ohmura, Tsuneyo Mimori

Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan.

Case 1: 52 year old male whose rheumatoid arthritis (RA) duration was 17 years (Stage IV, Class I). Biopsy specimen of gastric mucosa revealed AA amyloidosis, and then etanercept was administered. Abnormal serum creatinine level was decreased and proteinuria was disappeared a few weeks after etanercept treatment. His follow-up endoscopic biopsy showed no amyloid deposition.

Case 2: 62 year-old RA female (Stage III, Class 2). She had chronic diarrhea and biopsy specimen from rectal mucosa revealed AA amyloidosis. Infliximab was started but lost efficacy 4 months later. After switching to tocilizumab, her diarrhea disappeared and follow-up biopsy specimen showed significantly less amyloid deposition.

These 2 cases suggest that RA-associated AA amyloidosis can be treated by biologic agents.

P1-199

Cases with AA amyloidosis and end stage kidney disease treated with tocilizumab

Yoko Shimizu, Hiroshi Kajiyama, Muneo Ota, Akinori Yamamoto, Yuki Shimada, Yasufumi Shindo, Kazuhiro Yokota, Yuji Akiyama, Toshihide Mimura

Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University

Background) The evidence for safety and efficacy of tocilizumab is not enough in RA patients with AA amyloidosis and end stage kidney disease (ESKD).

Case 1) A 64-year-old female RA patient with ESKD underwent gastroendoscopic biopsy for appetite loss, and congo red staining revealed AA amyloid deposition in the stomach. Monthly 310mg of Tocilizumab improved appetite loss and arthritis.

Case 2) A 67-year-old female RA patient under hemodialysis, whose congo red staining had revealed AA amyloid deposition in the glomeruli, was treated with 300mg of tocilizumab. Appetite loss and numbness in the limbs were improved without infection in three months.

Conclusion) Tocilizumab improved arthritis and appetite loss in RA patients with AA amyloidosis and ESKD without significant adverse effects.

P1-200

Rheumatoid Arthritis with AA amyloidosis

Tatsuya Suwabe, Yoshifumi Ubara, Keiichi Sumida, Noriko Hayami, Rikako Hiramatsu, Masayuki Yamanouchi, Eiko Hasegawa, Naoki Sawa, Kenmei Takaichi

Department of Rheumatology, Toranomon Hospital, Tokyo, Japan

22 RA patients with AA amyloidosis who were referred to our hospital from 1985 to 2010 were enrolled. 16 patients were induced HD despite treatment with steroids. Among the 16 patients on HD, 10 patients died and 4 patients are alive. Among the alive 4 patients,

3 patients are still receiving bio-DMARD. Among the 6 non-HD patients, 3 patients died of Gastrointestinal perforation, 2 patients with chronic renal dysfunction are receiving bio-DMARD and 1 patient with normal renal function is receiving MTx.

None of the 22 patients with AA amyloidosis had received MTx before diagnosis of AA amyloidosis. The number of new occurrence of AA amyloidosis has been only two cases since 2005. We guess that MTx and bio-DMARD is very useful for preventing onset and progress of AA amyloidosis.

P1-201

Successful treatment of Amyloidosis by adult Still's disease with tosilizumab.

Kiyoshi Matsui, Masayasu Kitano, Masahiro Sekiguchi, Naoto Azuma, Aki Nishioka, Mai Morimoto, Naoaki Hashimoto, Hajime Sano

Division of Rheumatology, Department of Internal medicine, Hyogo College of Medicine

A-38-year-old female was admitted to our division for diagnosing and treating with fever and pharyngo pain in 1992. She was diagnosed of adult onset Still's disease by rash, slightly splenomegaly, lymphadenopathy, fever, negative-auto-antibodies and hyper-ferritinemia. She was tried to treated with steroid-pulse therapy, plasmapheresis, cyclophosphamide, methotrexate, cyclosporine and etanercept, but not suffered from negative CRP, SAA and ESR. In 2006, she has been diagnosed of amyloidosis by gastric fiber. She was administered of intravenously tosilizumab, and suffered from inflammation and amyloidosis. Following the successful treatment, tosilizumab was given and it maintained amyloidosis remittance for two years.

P2-202

Study on the effectiveness and safety of biologic DMRADS introduced after 2008/4

Tamao Nakashita, Akira Inoue, Natsuki Fujio, Shinji Motojima
Rheumatology and Allergy, Kameda Medical Center, Chiba, Japan

We have learned a lot about the tips of the use of biologic DMARDs (BLGs) after the introduction of the first BLGs, IFX. Therefore simple comparison of BLGs may not be appropriate. We here compared the effectiveness and safety of BLGs for 9 months introduced after April 2008 when ADA and TCZ became available in Japan. The BLGs used were ADA in 28, ETN in 38 and TCZ in 25, respectively. DAS28/ESR decreased in the 3 BLGs, but the decrease was significantly greater in TCZ. MMP-3 decreased in ETN and TCZ, but not in ADA. Drug survival rates were the same in these 3 drugs and discontinuation by adverse events was also the same. We noticed some bias in the selection of BLGs, but they seemed to have been used appropriately.

P2-203

Characteristics of RA patients who are treated with biologics in our hospital

Hideyuki Watanabe, Nobuhisa Hirase, Hideaki Goda, Hiroshi Nishikawa, Shoichiro Ikuyama
Kyushu University Hospital at Beppu, Oita, Japan

We characterized patients under biologics therapy, who were given either infliximab (IN)(54 cases), etanercept (ET)(45), adalimumab (AD)(9) or tocilizumab (TO)(4). RA stage was; Stage I 7.1, II 28.6, III 26.8, and IV 37.5%. Mean disease duration was 120< mo in IN, ET and AD groups, while it was 61 mo in TO group. Rate of

continuity of IN, ET, AD and TO at 15 mo after introduction was comparable; 75.9, 75.5, 77.7, and 75.0%, respectively. Patients in IN and ET groups were divided by the time when the therapy started (before/after April, 2008 when AD/TO generally available). After the point, IN was applied in much younger patients, while ET in older patients. DAS28 was lower in After than Before group both in IN and ET.

P2-204

Study of clinical sequel of the treatment for patients with rheumatoid arthritis

Teppe Hashimoto¹, Akira Hashiramoto¹, Yoshitada Sakai^{1,2}, Yoshiko Kawasaki¹, Chihiro Tanaka^{1,3}, Maki Kagitani¹, Nao Shibamura^{1,4}, Shunichi Shiozawa¹

¹The Center for Rheumatic Diseases, Kobe University Hospital,

²Faculty of Health Science, Himeji Dokkyo University, ³The Rheumatic Disease Center, Konan Kakogawa Hospital, ⁴Orthopedic surgery, Kobe Kaisei Hospital

(Objective)To evaluate clinical sequel of the treatment of rheumatoid arthritis (RA) patients at out-patient clinic of Kobe University, The Center for Rheumatic Disease. (Method) A total of 125 patients with active RA were enrolled. Patients' profile was age 56.5±15.0, female 99, male 26, DAS28-3CRP 3.73±1.12. (Result) DAS28 was changed to 2.67±1.10, 2.66±1.14 and 2.94±1.13 at 3, 6 and 12 months period after treatment. Patients introduced to disease-remission were 47.3%, 49.1% and 42.5%, respectively. At the point of final evaluation, 74 of 125 patients intake MTX (59.2%, 7.0±2.1mg), and biologics were introduced to 39 of 125 patients (31.2%, IFX8, ETN18, ADA8, TCZ6)

P2-205

Therapeutic Effect of 4 Biological Agents for Rheumatoid Arthritis

Yukio Yonemoto¹, Kimihiko Takeuchi², Koichi Okamura¹, Masatoshi Matsushita³, Tsutomu Kobayashi¹, Tetsuo Aramaki³, Tetsuya Kaneko¹, Tsuyoshi Ichinose¹, Kenji Takagishi¹

¹Department of Orthopaedic Surgery, Gunma University Graduate School of Medicine, ²Department of Rheumatology, Isesaki Fukushima Hospital, ³Department of Orthopaedic Surgery, Isesaki Fukushima Hospital

Objective: We compared the therapeutic effect of 4 biological agents (Bio)—infliximab (IFX), etanercept (ETN), tocilizumab (TCZ), and adalimumab (ADA)—in Bio-naïve rheumatoid arthritis (RA) patients concurrently initiated on treatment. **Methods:** DAS-28 ESR and EULAR response criteria at Month 12 were evaluated in 133 Bio-naïve RA patients (36 on IFX, 36 on ETN, 26 on TCZ, and 35 on ADA) who began treatment in July 2008. **Results:** For all 4 Bio, DAS28-ESR at Month 12 was significantly lower than at baseline. The DAS28-ESR of TCZ was significantly lower than IFX. Significantly more TCZ patients satisfied the EULAR remission criteria at 69.2% than IFX (25.0%), ETN (23.3%), and ADA (21.4%). **Conclusions:** TCZ had a therapeutic effect in Bio-naïve RA patients comparable to or better than TNF-α inhibitors.

P2-206

Comparison of 4 biologics - LUNDEX from 1-year observation

Koji Takasugi¹, Misuzu Yamashita¹, Masamitsu Natsumeda¹, Ryutaro Yamanaka¹, Kayo Ezawa¹, Kazuhiko Ezawa¹, Yoshihisa Nasu², Keiichiro Nishida³, Shinichiro Fujita⁴, Sanae Ishii⁵, Wataru Yamamoto⁶

¹Department of Internal Medicine, Kurashiki Kosai Hospital, Kurashiki, Japan, ²Department of Orthopaedic, Kurashiki Kosai Hospital, Kurashiki, Japan, ³Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, ⁴Department of Rehabilitation, Kurashiki Kosai Hospital, Kurashiki, Japan, ⁵Department of Nursing, Kurashiki Kosai Hospital, Kurashiki, Japan, ⁶Department of Health Information Manage, Kurashiki Kosai Hospital, Kurashiki, Japan

【Purpose】The clinical study of ETN, IFX, TCZ, and ADA. **【Method】**Two hundred fifty seven patients (ETN:78, IFX:90, TCZ:52, ADA:37) were initiated for 12 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 1 year were 83.3% (ETN), 73.0% (IFX), 66.0% (TCZ), 52.4% (ADA). DAS28 remission:34.6% (ETN), 28% (IFX), 42.6% (TCZ), 23.8% (ADA). LUNDEX-DAS28 remission:28.8 (ETN), 20.4 (IFX), 28.1 (TCZ), 12.5 (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 at effectiveness and the continuance rate.

P2-207

Comparison of anti-TNF therapy and anti-IL-6 therapy after 1st anti-TNF therapy

Yuji Hirano, Yukiyooshi Oishi

Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan

The aim is to compare anti-TNF therapy and anti-IL-6 therapy after failure of 1st anti-TNF therapy. We investigated clinical outcomes (DAS28-ESR, CDAI, MMP-3, mHAQ, TJC+SJC) in patients with RA receiving etanercept (ETA: 16cases) or tocilizumab (TCZ: 16cases) as 2nd or 3rd biologics (BIO) after failure of 1st BIO (TNF inhibitor). DAS28-ESR was significantly decreased in both groups and DAS28-ESR in TCZ group was significantly lower than that in ETA group after 12 weeks. Other parameters were also significantly decreased in both group and there were not significant differences between two groups. Both ETA and TCZ were effective in patients with RA after failure of 1st BIO. These results suggested that DAS28-ESR should not be used when TCZ was compared with other BIO such as TNF inhibitors.

P2-208

Clinical results of tocilizumab and etanercept in bio-naïve patients none of MTX

Masatoshi Matsushita¹, Kimihiko Takeuchi¹, Tetsuo Aramaki¹, Yukio Yonemoto²

¹Orthopedic Department of Isesaki-Fukushima Hospital, Isesaki, Gumma, Japan, ²Department of Orthopedic Surgery, Gumma University Graduate School of Medicine, Maebashi, Gumma, Japan

Objective: 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. **Subjects:** Bio-naïve RA patients who cannot take MTX observed for at least 6 months divided into 16 in the TCZ group and 30 in the ENT group. **Results:** At the start, the mean disease activity score 28 (DAS28) with c-reactive protein (CRP) was 5.16 in the TCZ group and 4.63 in the ENT group; that in the TCZ

group was significantly higher. After 6 months, DAS28 CRP was significantly reduced to 3.19 in the TCZ group and 3.22 in the ENT group, and no significant difference was seen between the two groups. **Conclusion:** TCZ and ENT show about the same excellent effects in patients who cannot use MTX.

P2-209

Comparison of effects between tocilizumab and infliximab therapy for RA patients

Satoshi Jodo

Tomakomai City Hospital, Hokkaido, Japan

Purpose: We compared the therapeutic utility between tocilizumab (TCZ) and infliximab (IFX) treatment for RA patients.

Subject and Method: We retrospectively investigated the outcome in 14 patients treated with TCZ and 20 patients treated with IFX at 24 weeks.

Results: The continuation rate in TCZ group was 86% and that in IFX group was 50%. The rate of DAS28<2.6 in TCZ group was 50.0% and that in IFX group was 12.5%. A patient treated with TCZ developed acute bronchiolitis and stopped the treatment. 9 patients treated with IFX exhibited side effects/complications and 5 patients were excluded from the study.

Discussion: In view of the continuation rate, therapeutic effects, and adverse events, TCZ may be more useful agent as the first line biologic for RA patients.

P2-210

Comparison of efficacy and predictive factors of tocilizumab and infliximab

Tamami Yoshitama

Department of Rheumatology and Internal Medicine, Yoshitama Clinic, Kagoshima, Japan

Objective: To compare efficacy and predictive factors of TCZ and IFX.

Subjects: 27 TCZ and 43 IFX patients.

Methods: Efficacy of TCZ and IFX was compared for DAS28 and clinical disease activity index (CDAI). Patients showing remission in 6 months (m) were predicted from characteristics.

Results: The 6 m remission rates were 36% for TCZ and 28% for IFX for DAS28, and 9% for TCZ and 12% for IFX for CDAI. Predictive factors for remission were no history, low RF and HAQ for TCZ and short duration, Class <II, and low HAQ, inflammatory reaction, DAS28 and CDAI for IFX.

Conclusion: In a comparison for CDAI with no inflammatory reaction, TCZ and IFX had about the same effects. With TCZ, remission was more likely in patients with long duration and strong inflammatory reaction than with IFX.

P2-211

Effectiveness of switching therapy to adalimumab.

Masahiro Nishino, Kunio Yamada, Takaki Hasuo, Tsukasa Imaizumi, Tetsuya Takenaga, Hiroki Yamada, Ryouji Tsuda
Komaki City Hospital, Aichi, Japan

This study consisted of 10 patients with RA, all treated with adalimumab. (n=10; male/female,4/6; mean age, 54.1 y.o.; mean duration of disease, 9 y. and 3 mo.) At baseline 5 patients (50%) had been previously treated with infliximab (IFX), and 4 (40%) were treated with etanercept (ETA), and 1 (10%) was treated with IFX, ETA and tocilizumab. Disease activity was assessed using disease

activity score in 28 joints-CRP (DAS28-CRP) and European league against rheumatism (EULAR) criteria response. At week 24, 40% of patients had a moderate and 30% had a good EULAR response. For patients with rheumatoid arthritis after failure of other biologic therapies, switching to adalimumab can restore a good clinical response.

P2-212

Analysis for continuation rate and switching patterns of four biologics

Michihiro Ogasawara, Michiaki Kageyama, Makio Kusaoi, Shin Onuma, Kaoru Sugimoto, Fumio Sekiya, Takayuki Kon, Kazuo Kempe, Ken Yamaji, Naoto Tamura, Yoshinari Takasaki
Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine

Three hundreds and sixty-five rheumatoid arthritis patients had been treated with biologics(Bio) (Infliximab IFX 167cases, Etanercept ETN 142 cases, Adalimumab 34 cases, Tocilizumab TOC 22 cases) in our hospital by 2009. We compared those continuation rates using Kaplan-Meier method and three bio, IFX, ETN and TOC showed the rate about 60% at 2years. Although ADA showed lower continuation rate than those 3 Bios, in patients with class I, concomitant with MTX, Bio-naïve and switching from IFX showed not significantly different continuation rate with other Bios. Moreover, by studying tendency of switching among 4 Bios and continuation rate after switching, we discuss the recommended order of use and how to select those Bios as the situation demands.

P2-213

Estimation of the increase or the switch of biologics by RA patients

Ryutaro Matsumura¹, Kei Ikeda², Tsuyoshi Umibe³, Takao Sugiyama⁴, Yasushi Nawata⁵

¹Clinical Reserch Center, Chiba East National Hospital, Chiba, Japan, ²Department of allergy and clinical immunology, Chiba University, Chiba, Japan, ³Department of internal medicine, Matsudo municipal hospital, Chiba, Japan, ⁴Department of Rheumatology, Shimotsu National Hospital, Chiba, Japan, ⁵Center of Rheumatism, Saiseika Narashino Hospital, Chiba, Japan

Strict treatment with biologics came to be requested for rheumatic arthritis. If the effect of biologics of the start is insufficient, the increase and the change of the medicine are positively needed. The increase and the change have the possibility of giving birth to the patient to a change in use and a new economical load. The questionnaire survey was enforced to 50 patients whose biologics were increased or changed. The cases of Infliximab increase were 1/3, and the cases changed to Tocilizumab were 1/2. By the increase or the change by the biologics, the symptom of almost patients was improved. Moreover, in the half of patients, the time possible to work was increased. However, in sixty percent of patients there was an increase of the load of medical expenses.

P2-214

Cytokine measurement in whole blood cultures to predict response to biologics

Ken Kayakabe, Takashi Kuroiwa, Noriyuki Sakurai, Hidekazu Ikeuchi, Toru Sakairi, Akito Maeshima, Keiju Hiromura, Yoshihisa Nojima

Department of Medicine and Clinical Science, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan

Objective : To predict response to biologics in RA patients by examining proinflammatory cytokine production in whole blood cultures (WBC). **Methods:** We measured density of TNF- α , IL-1 β , and IL-6 in supernatants of LPS-stimulated WBC obtained from RA patients (n=53) before biological therapy (IFX 10, ETN 27, ADA 2, TCZ 14). Response to the therapy was defined by EULAR response criteria. **Results:** Among patients examined, 41 were responders (good and moderate), and 12 were non-responders. In WBC stimulated by LPS, cytokine production was lower in non-responders than in responders (TNF- α 434 vs 776, p=0.12; IL-1 β 106 vs 246, p=0.15; IL-6 2617 vs 6210 pg/ml, p=0.22). **Conclusion:** Proinflammatory cytokine measurement in LPS-stimulated WBC may be useful to predict response to biologics in RA.

P2-215

Adalimumab maintains MMP-3 normalization in rheumatoid arthritis for a long term

Yukitomo Urata¹, Ryoko Uesato², Dai Tanaka², Hiroshi Tsushima³, Kenji Kowatari², Taisuke Nitobe², Yoshihide Nakamura⁴

¹Department of Rheumatology Seihoku Chuo Hospital, Gogyogawara, Japan, ²Department of Orthopaedic Surgery, Seihoku Chuo Hospital, Gogyogawara, Japan, ³Department of Rehabilitation, Seihoku Chuo Hospital, Gogyogawara, Japan, ⁴Department of Orthopaedic Surgery, Hirosaki University Graduate School of Medicine, Hirosaki, Japan

[Purpose] Comparing the MMP-3 normalization rate of each biological drug in rheumatoid arthritis (RA). **[Methods]** We compared how infliximab (INF), etanercept (ETN), adalimumab (ADA) and tocilizumab (TCZ) did normalized of serum MMP-3 (male<121ng/ml, woman<59.7ng/ml) of 330 RA patients at 0weeks, 24weeks and 56 weeks. **[Result]** For MMP-3 normalization rate, 0 weeks INF20.4 %, ETN24.7, ADA31.6, TCZ26.3; 24 weeks 40.9, 57.0, 62.5, 15.8; 56 weeks, 48.7, 54.2, 66.7, 33.3

[Conclusion] ADA maintain the MMP-3 normalization in RA patient for a long term.

P2-216

Pulmonary Cryptococcus in patient receiving abatacept and MTX for RA

Asa Hotta¹, Taichi Minami¹, Akiko Suda¹, Kenji Ohmura¹, Shohei Nagaoka^{1,2}, Yoshiaki Ishigatsubo²

¹Department of Rheumatology, Minamikyosai Hospital, Yokohama, Japan, ²Department of Internal Medicine and Clinical Immunology, Yokohama, Japan

A 62-year-old woman was diagnosed RA in December 2009. Treatment with Abatacept was initiated in mid May due to inadequate responses to MTX. Dry coughs and fever occurred in late October. Chest X-rays showed an infiltrative shadow in the right lung. Test results were positive for Cryptococcus antigen (x256). The diagnosis of Cryptococcus pneumonia was made based on these findings, and administration of 400 mg of fosfomycin was started. **Discussions:** Although Cryptococcus pneumonia has not been reported in any patient under treatment with Abatacept, close attention should be paid to opportunistic infections such as Cryptococcus pneumonia during the treatment with any biologic drugs.

P2-217

Treatment of biologics in rheumatoid arthritis patients with blood dyscrasia

Hisato Ishikawa¹, Kaneyuki Furihata², Toshihisa Kanamono¹

¹Department of Orthopedics, Nagano Red Cross Hospital, ²Department of Respiratory Medicine, Nagano Red Cross Hospital

Anti-TNF biologics use has been reported to be risk factors for developing malignancy. We report about the treatment of the biologics in RA patients of blood dyscrasia. Biologics treatment of 4 patients with a history of malignancy was determined in consultation with the hematologist, 3 of them have the past of the malignant lymphoma and one has anaplastic anemia. In 3 patients, the disease activity was improved. In addition, there were neither a relapse nor deterioration of the blood dyscrasia in all the 4 patients. Treatment of biologics with blood dyscrasia in rheumatoid arthritis should be considered enough to risk and benefit, obtain a patient's informed consent, followed closely with biologics treatment. Biologics treatment considered as one of the last options.

P2-218

Local community-based treatment of RA by biological

Ryuki Shinohe¹, Masao Sato²

¹Department of Orthopaedic Surgery, Nishimino Welfare Hospital,

²Department of Reconstructive Surgery for Bone and Joint, Gifu University School of Medicine

107 RA patients (male 22, female 85) were received biological treatment whose age was 61.1 years old average, and 81 patients were kept on being administration biological, and showed the effectiveness of biological (DAS28-CRP value improved 5.764 average (high activity) before administration biological to 1.798 (remission) at the end of observation. CRP value as inflammation marker (3.471 to 0.81) and MMP-3 also indicates the effect of biological (278.1 to 135.2). But, 23 patients changed a kind of biological, because of ineffectuality. In observation, harmful event was occurred in 24 patients including died 10 patients. It is clear that the treatment by biological is most effective way to cure RA. Even in local community-based care.

P2-219

Efficacy of tocilizumab evaluated by DAS-28 and CDAI compared with infliximab

Kenji Takahashi¹, Kenji Takenouchi¹, Toshikazu Kamada², Hiroshi Kaneko³, Masahito Koiwa⁴, Sanshiro Hashimoto⁵, Hiroshi Nakamura¹

¹Department of Rheumatology, Nippon Medical School, Tokyo, Japan, ²Hara Orthopaedic Hospital, Tokyo, Japan, ³Department of Rheumatology, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan, ⁴Department Rheumatology and Orthopaedics, Syuwa General Hospital, Saitama, Japan, ⁵Hashimoto Clinic, Tokyo, Japan

Purpose: We studied the efficacy of tocilizumab (TCZ) treatment for RA compared with infliximab by DAS-28 and CDAI. **Subjects:** Twelve cases treated with TCZ and 100 cases treated cases IFX were investigated. **Results:** There were no differences in DAS28 and CDAI between cases treated with TCZ and IFX at the baseline. At month 6, DAS-28 was 2.88 and 3.73 in TCZ and IFX respectively, while CDAI was 26.7 and 26.3 respectively. **Conclusion:** TCZ had good efficacy even for cases unresponsive to other TNF antagonists or cases without MTX. However, the effects of

TCZ treatment tend to be overestimated by DAS-28 comparing IFX treatment.

P2-220

Induction of Remission with Non-Biological DMARDs during Clinical Practice

Ko Katayama

Katayama Orthopedic Rheumatology Clinic

(Methods) In 555 patients with RA newly registered in 3.5 year, the outcome of induction of remission by mono or combination therapy with non-biological DMARDs (non-Bio) was analyzed retrospectively. (Results) Following mono therapy, 58 cases achieved remission, with DAS28 being improved from 4.54 to 1.87. Mean age was 58 years. Mean duration of sickness was 32 months. The drug used was SASP; 20, Bu; 19, MTX; 18 and LEF; 1 cases. Following combination therapy, 29 cases achieved remission, with improvement of DAS28 from 4.70 to 1.89. Mean age was 52.6 years. Mean duration of sickness was 38 months. The drug used in combination with MTX was Bu; 14, LEF; 8, TAC; 6 and SASP 1 cases. (Conclusion) Positive application of non-Bio under the T2T strategy is expected to improve the remission rate.

P2-221

Evaluation of new remission criteria for rheumatoid arthritis

Toshihiro Matsui^{1,6}, Yoshiaki Kuga^{2,6}, Jinju Nishino^{3,6}, Atsushi Kaneko^{4,6}, Yoshiyuki Arinuma^{1,6}, Shigeto Tohma^{5,6}

¹Department of Rheumatology, Sagami National Hospital, National Hospital Organization (NHO), Kanagawa, Japan, ²Department of Orthopedic Surgery, Wakaba Hospital, Saitama, Japan, ³Nishino Clinic, Orthopedics and Rheumatology, Tokyo, Japan, ⁴Department of Orthopedic Surgery, Nagoya Medical Center, NHO, Nagoya, Japan, ⁵Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami National Hospital, NHO, Kanagawa, Japan, ⁶iR-net

[Aim] To evaluate the new remission criteria (TJC28, SJC28, CRP, PtGA ≤ 1) for RA. [Methods] Data of 5610 RA patients registered in NinJa2009 were analyzed. [Results] Remission rates of each criteria were as follows; 15.4% in new criteria, 24.9% in DAS28, 20.9% in SDAI, and 20.1% in CDAI. Among 1395 patients classified as DAS28-remission, rate of patients with SJC ≥ 2 [2-8] was 5.5%, TJC ≥ 2 [2-11] was 9.5%, CRP >1 mg/dl was 2.2%, PtGA >1 was 24.9%, and remission rate was 47.5% in new criteria, 63.3% in SDAI, and 60.6% in CDAI, respectively. Among 866 patients classified as new criteria-remission, remission rate was 76.6% in DAS28, 92.0% in SDAI, 90.3% in CDAI, and mean ESR (mm/hr) was higher and CRP (mg/dl) was lower in female (22.2 and 0.20) than those in male (16.9 and 0.25), respectively.

P2-222

Bucillamine study of holding remission after infliximab dose-off (BuSHIDO) trial

Takahiko Kurasawa¹, Koji Nishimura¹, Tsuneo Kondo¹, Ayumi Okuyama¹, Eiko Nishi¹, Hirofumi Takei¹, Hayato Nagasawa¹, Koichi Amano¹, Tsutomu Takeuchi², Hideto Kameda²

¹Saitama Medical Center, Saitama Medical University, Kawagoe, Japan, ²Division of Rheumatology and Clinical Immunology, De-

Objective: To examine the efficacy of bucillamine (BUC) on holding remission in RA patients after infliximab (IFX) withdrawal. **Methods:** RA patients who had been receiving 6 or more infusions of IFX with DAS28-ESR3.2 or DAS-CRP2.6 for more than 6 months were randomized to either BUC 200 mg/day (group 1) or not (group 2) upon the withdrawal of IFX. Primary endpoint included flare rate within 2 years. MTX was continued in all. **Results:** At present, 24 and 31 patients were assigned to group 1 and 2, respectively. Four have experienced flares in group 1, while 15 patients showed flare-up so far. Six patients in group 1 discontinued BUC because of rash (n=5) and proteinuria (n=1). **Conclusion:** BUC may be useful for maintaining disease remission after the withdrawal of IFX.

P2-223

Background feature of the reaching HAQ remission by biologics for RA patients

Yusuke Miwa¹, Kumiko Otsuka¹, Michihito Sato¹, Ryo Takahashi¹, Kuninobu Wakabayashi¹, Tsuyoshi Odai¹, Takeo Isozaki¹, Nobuyuki Yajima¹, Hidemazu Furuya¹, Tsuyoshi Kasama¹, Michio Hosaka²

¹Division of Rheumatology Department of Medicine, Showa University School of Medicine, ²Katsuyama Clinic

Objective: We examined the factor which reached the HAQ remission for RA patients. **Method:** Age, sexuality, dosage of steroid, DAS28, HAQ, Short Form (SF)-36 and depression scale (HAM-D and SDS) were assessed in 75 RA pts used biologics. HAQ remission was defined as less than 0.5 point after 12 weeks. **Result:** In the HAQ remission group, younger age (52.9 ± 14.1 vs. 62.1 ± 13.6 , $p=0.014$), lower dosage of steroid (3.4 ± 3.2 vs. 5.6 ± 3.5 mg, $p=0.013$), lower HAQ (0.32 ± 0.37 vs. 1.05 ± 0.34 , $p<0.001$), higher SF36 (all categories, $p<0.05$), lower SDS (39.5 ± 9.6 vs. 44.2 ± 10.1 , $p=0.04$) and HAM-D (5.3 ± 4.0 vs. 8.1 ± 5.5 , $p=0.025$) before treatment and high efficacy of the drugs ($p=0.018$) compared with others. **Conclusions:** Younger age, lower steroid dosage, higher QOL and lower depression are the important factor for HAQ remission.

P2-224

Pulmonary Function Test of Systemic Sclerosis without Interstitial Pneumonia

Tohru Takeuchi, Takuya Kotani, Kenichiro Hata, Shuzo Yoshida, Koji Nagai, Daisuke Wakura, Kentaro Isoda, Shigeki Makino, Toshiaki Hanafusa

Department of Internal Medicine (I), Osaka Medical College

Objective: To evaluate pulmonary function in SSc patients without IP. **Method:** This study comprised a total of 78 SSc patients: 54 patients with IP and 24 without IP (non-IP). We analyzed the comparison of PFT and laboratory findings between IP and non-IP patients. **Results:** IP patients showed the increased percentages of men, diffuse cutaneous type, positive anti-Scl-70 Ab and positive anti-RNP Ab. Seven patients had pulmonary hypertension (PH) in IP and 1 had in non-IP. %TLC (IP vs non-IP: 91.1% vs 117.2%), %VC (89.0% vs 103.5%), and %DLco (47.7% vs 56.7%) were significantly decreased in IP patients. Moreover, %DLco was decreased in almost half of patients without IP and PH. **Conclusion:** PFT maybe a useful tool for the early diagnosis of IP and PH in SSc patients with these complications.

P2-225

Peripheral blood eosinophil in patients with RA and SSc

Tamao Nakashita, Akira Inoue, Natsuki Fujio, Shinji Motojima
Rheumatology and Allergy, Kameda Medical Center, Chiba, Japan

Peripheral blood eosinophil (PB-EOS) was measured in patients with RA and SSc and relation to the disease pathogenesis was investigated. Subjects were 44 RA and 36 SSc patients without PSL. PB-EOS was measured 3 times and the mean value was used. Interstitial lung disease (ILD) was graded using chest CT images. In RA, PB-EOS was inversely correlated with RF titer, ILD grade and MMP-3 concentration. In SSc, PB-EOS was significantly higher in diffuse SSc than in limited SSc and showed a positive correlation with ILD grade. These results suggest that in RA, although the mechanisms have not been clarified, higher PB-EOS % indicates better prognosis. On the other hands, it was suggested that eosinophils directly relate to the pathogenesis of ILD by releasing TGF- β and other cytokines.

P2-226

Efficacy of sildenafil for vasculopathy in systemic sclerosis (SSc)

Akiko Tochimoto^{1,2}, Yasushi Kawaguchi¹, Chikako Fukasawa¹, Kae Takagi¹, Yuko Ota¹, Sayuri Kataoka¹, Hisashi Yamanaka¹

¹Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, ²Department of Rheumatology, Tokyo Metropolitan Ohtsuka Hospital, Tokyo, Japan

In previous reports, sildenafil was shown to improve not only pulmonary arterial hypertension (PAH) but Raynaud's phenomenon and digital ulcers (DUs) in SSc. We report 3 cases with SSc which were treated with sildenafil. Case 1: A 66 year-old woman complicated by PAH was treated with sildenafil 60 mg daily. She was in WHO functional class II at baseline. Sildenafil decreased the RVSP from 75.6 mmHg to 43.6 mmHg. Case 2 and 3: 38 and 41 year-old women complicated by DUs resistance to bosentan and beraprost was treated with sildenafil 60 mg and 40 mg daily respectively. Sildenafil decreased DUs after 2 month. Sildenafil will be effective on early PAH and refractory DUs in SSc. In conclusion, sildenafil may be a novel treatment for intractable DUs as well as PAH in patients with SSc.

P2-227

Efficacy of bosentan on SSc-associated pulmonary arterial hypertension

Yuko Ota, Yasushi Kawaguchi, Manabu Kawamoto, Kae Takagi, Akiko Tochimoto, Yasuhiro Katsumata, Takahisa Gono, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University

Objectives. Pulmonary arterial hypertension (PAH) is one of the most severe complications in patients with SSc and contributed to a poor prognosis of SSc. Recently, endothelin-1 has been strongly implicated in the pathogenesis of SSc and PAH. The aim of this study was to investigate the effects of bosentan on SSc-associated PAH. **Methods.** A prospective analysis of 10 SSc-associated PAH patients treated with bosentan was performed. The clinical outcome was estimated using WHO functional class, RVSP and BNP at 0, 3, 6, 12, 24, 36, and 48 months after treatment. **Results.** At 3, 6, 36 and 48 months, there were significant improvements in RVSP. There were also significant improvements in BNP at 3 and 36 months. **Conclu-**

sions. Our results suggest bosentan may be effective for SSc-associated PAH.

P2-228

Long term prognosis in patients with scleroderma.

Tomoya Miyamura, Yoshiro Horai, Karin Shimada, Motoko Ishida, Soichiro Takahama, Rumi Minami, Masahiro Yamamoto, Eiichi Suematsu

Department of Internal Medicine and Rheumatology, Clinical Research Center, National Hospital Organization, Kyushu Medical Center, Fukuoka, Japan

To clarify the long term prognosis in patients with systemic sclerosis (SSc), we investigated mortality, cause of death and comorbidities of 168 patients in our hospital, retrospectively. The patient's median ages were 59.2 years old, and 72 patients were diffuse coetaneous SSc (dSSc), while 96 were limited coetaneous SSc (lSSc). Their median disease durations were 4.1 years. Sixty one patients showed interstitial pneumonia, 10 patients showed pulmonary arterial hypertension and 8 patients showed renal crisis. Sixteen patients died during the follow up period. All dead patients were dSSc and 13 patients showed interstitial pneumonia. Our studies showed higher mortality rate in patients with dSSc. These results suggested the necessity of early treatment in patient with poor prognosis.

P2-229

Successful treatment of scleroderma-related digital ulcer with leukocytapheresis

Risa Yamada¹, Makio Kusaoi¹, Misa Yasui¹, Go Murayama¹, Keisuke Oda¹, Katsura Hohtatsu¹, Michiaki Kageyama¹, Toshio Kawamoto¹, Takayuki Kon¹, Fumio Sekiya¹, Kaoru Sugimoto¹, Kazuo Kempe¹, Michihiro Ogasawara¹, Ken Yamaji¹, Hiroshi Tsuda², Yoshinari Takasaki¹

¹Department of Rheumatology and Internal Medicine, Juntendo University School of Medicine, Tokyo, Japan, ²Department of Geriatric General Medicine, Juntendo Tokyo Koto Geriatric Medical Center, Juntendo University School of Medicine

A 46-year-old woman who has been treated for scleroderma and Sjogren syndrome for 19 years progressively manifested digital ischemic ulcers after cancellation of monthly leukocytapheresis (LCAP) 2 years ago. Her digital ulcers were exacerbated despite of empirical therapy including steroid, prostaglandin and antiplatelet therapy. Recently, we tried LCAP therapy again and acquired good response. So, we restarted LCAP twice per month. Her digital ischemic ulcers were gradually improved with pain relaxation. To clarify a mechanism of the healing, we investigated population of CD34, CD133 and CD117-positive cells before and after LCAP by using flow cytometry. The result suggested that the mobilization of endothelial progenitor cells from bone marrow associate with tissue regeneration.

P2-230

A case of NSF (nephrogenic systemic fibrosis) occurred in the course of RA

Kazuhiro Hatta, Ryuichi Sada, Teruhisa Azuma, Hiroyasu Ishimaru
General Medicine, Tenri Hospital

A 82-year-old man was referred to our clinics because of bilateral leg edema. Except well controlled RA and CKD stage 3, he was rather well until two months after he was operated on by neurosurgeon of another hospital due to the RA cervical lesions, when he no-

ticed edema with red colorization in his legs, which he thought due to change of drugs (diuretics). But edema continued after changing back to previous diuretics. Further examination of skin biopsy and Bone scintigraphy suggested that the leg edema was due to NSF (nephrogenic systemic fibrosis). This pathologic condition is rather rare in Japan, especially CKD stage 3 patient, we are going to observing him carefully. We should pay much attention to subclinical renal dysfunction of RA patients.

P2-231

Pulmonary-renal syndrome in systemic sclerosis.

Ryosuke Hara, Kenta Hoshi, Takeo Kudo, Eisuke Ogawa, Junichi Tanaka, Tatsuo Nagai, Sumiaki Tanaka, Akira Ishikawa, Shunsei Hirohata

Department of Rheumatology and Infectious Disease, Kitasato University School of Medicine, Kanagawa, Japan

A 59 year-old-woman diagnosed as SSc a year ago, was referred to our hospital because of severe hypertension, acute renal failure, hemolytic anemia and thrombocytopenia. Based on elevation of plasma renin activity and the absence of ANCA, she was diagnosed as scleroderma renal crisis (SRC). She was immediately treated with captopril, but her renal function did not improve, requiring hemodialysis. After two months on hemodialysis, she suddenly suffered from dyspnea. Chest CT revealed diffuse ground glass opacity lesions, suggesting diagnosis of diffuse alveolar hemorrhage (DAH). She was treated with steroid pulse therapy and positive pressure ventilation. After 13 days, she improved and mechanical ventilation was withdrawn. SRC and DAH are rare but serious complications of SSc.

P2-232

A case of pneumocephalus associated with systemic sclerosis

Takuya Hino¹, Naoaki Hashimoto¹, Masahiro Sekiguchi¹, Kazuyuki Fujita¹, Mika Okabe¹, Mai Morimoto¹, Aki Nishioka¹, Naoto Azuma¹, Masayasu Kitano¹, Takenori Hashimoto², Hajime Sano¹

¹Division of Rheumatology, Department of Internal Medicine, Hyogo college of Medicine, Nishinomiya, Japan, ²Hashimoto Clinic for Rheumatic Diseases, Osaka, Japan

A 55 years old man was diagnosed as systemic sclerosis 19 years ago and he had interstitial pneumonia and esophageal disorder. In May 2010, he admitted our hospital because of inability to move and fatigue. Laboratory data showed elevated CRP, hypoxemia and reduction in blood pressure. We diagnosed bacterial pneumonia caused septic shock and treated with antibiotics. His consciousness was disturbed and he had neck rigidity. He had pneumocephalus and retropharyngeal abscess. We considered the air flowed into spinal subarachnoid space through the retropharyngeal abscess from pharynx. There are few case reports of pneumocephalus without the trauma or sinusitis. We report this case of pneumocephalus and retropharyngeal abscess associated with gastrointestinal lesion in systemic sclerosis.

P2-233

A case of rheumatoid arthritis rapidly progressed scleroderma and TMA

Akira Furusaki¹, Izumi Yasuda², Yoshiharu Amasaki¹, Akihiro Ishizu³

¹Department of Rheumatology, Tonan Hospital, Sapporo, Japan,
²Department of Internal Medicine, Yamanote Avenue Yagi Hospital,
Sapporo, Japan, ³Faculty of Health Sciences, Hokkaido University

A 45-yr woman was diagnosed RA at July 2007 and given bucillamine. It was not as effective, MTX was started from May 2008, RA became remission. Fever and shortness of breath appeared from June 2010, and interstitial pneumonia was pointed out in a home-town. At July 9, we diagnosed scleroderma in upper and lower limbs skin hardness, trismus and pericardial effusion. She hospitalized on July 13, we suspected TMA for thrombocytopenia, hemolytic anemia, but showing no fragmented red blood cell. The next day, we diagnosed TMA with fragmented red blood cells, and started plasmapheresis, but there were disturbance of consciousness, progress of liver renal dysfunction. She died on July 15. It was the findings of the scleroderma kidney in the pathology.

P2-234

Mitochondrial encephalomyopathy with systemic sclerosis: A case report

Makoto Kubo¹, Seiko Fukuta¹, Hiroshi Nakamura², Hajime Miyazato³

¹Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine, Ube, Japan, ²Department of Community Health and Medicine, Yamaguchi University Graduate School of Medicine, Ube, Japan, ³Shunan Memorial Hospital, Shunan, Japan

The patient was a 42-year-old woman with diabetes mellitus and chronic kidney disease. Her mother had congenital hearing impairment. The patient had scleroderma, Raynaud's phenomenon, and polyarthralgia for several years. In 2009, she was diagnosed with systemic sclerosis (SSc) and treated with prednisolone and intravenous cyclophosphamide. However, she developed congestive heart failure. Thus, she was admitted to our hospital on December 2009. Skin biopsy findings were compatible with SSc. Echocardiogram revealed diastolic heart failure. Molecular genetic test showed the presence of m.3243A>G mutation in MT-TL1, which suggested mitochondrial encephalomyopathy. The results of electromyography and muscle and endomyocardial biopsy were compatible with mitochondrial encephalomyopathy.

P2-235

Systemic sclerosis presented as congestive heart failure: an autopsy case

Hiroyuki Kanno, Takashi Sawai

Department of Pathology, Iwate Medical University School of Medicine, Morioka, Japan

We report an autopsy case of systemic sclerosis (SSc) with myositis lesions in skeletal muscles and myocardium. A 69-year-old woman developed congestive heart failure and died due to respiratory failure showing restrictive hypoventilation. The case showed apparent scleroderma of the trunk but no sclerodactyly even at autopsy. The heart showed dilated ventricular hypertrophy, and histopathology of the heart exhibited diffuse replacement fibrosis resembling the lesion of ischemic heart diseases, in addition to patchy fibrosis around myocardial fibers suggesting post-myocarditis-like fibrosis. The case gives insight into pathologic changes of myocardial diseases of SSc and polymyositis patients, and might suggest the

possible relationship between dilated cardiomyopathy and collagen diseases.

P2-236

A case of systemic sclerosis with pericarditis and PAH

Tetsushi Aita¹, Susumu Nishiyama¹, Yasuhiko Yoshinaga¹, Shoji Miyawaki¹, Hiroki Kishimoto², Michio Toda², Yoshiki Yoshihara², Shinya Miyoshi², Akira Manki³

¹Rheumatic Disease Center, Kurashiki Medical Center, ²Department of Orthopedics, Kurashiki Medical Center, ³Department of Pediatrics, Kurashiki Medical Center

A 62-year-old limited systemic sclerosis was admitted because of exertional dyspnea. Chest X-ray, CT and UCG revealed pleural effusion, pericardial effusion and right heart failure. Pleural effusion was expulsive and she was treated with diuretics. Pleural effusion was decreased, but pericardial effusion (exudative) was remained. She was treated with prednisolone(20mg) with marked improvement of pericardial effusion. But estimated systolic pulmonary artery pressure (PAP) by UCG was 62mmHg and mPAP measured by right heart catheterization was 29 mmHg. She was diagnosed as pulmonary arterial hypertension(PAH). Oxygen therapy, beraprost and bosentan were added and her PAH has been in good condition. We reported the interesting case of systemic sclerosis associated with pericarditis and PAH.

P2-237

A case of scleroderma with progressive IgA nephropathy

Masayuki Yamanouchi, Yoshifumi Ubara, Keiichi Sumida, Rikako Hiramatsu, Rikako Hasegawa, Tatsuya Suwabe, Naoki Sawa, Kenmei Takaichi

Institute of Nephrology Center, Toranomon Hospital, Tokyo, Japan

The case is 67-year old man. Polyarticular pain and dyspnea appeared in February, 2007. PSL was started by another doctor. In July, he visited our office and was diagnosed scleroderma by skin biopsy. Because he had interstitial pneumonia, tacrolimus 2mg/day was started. Urine blood 3+ and urine protein 1+ appeared in July 2008. Renal impairment with Cre 0.7→1.0mg/dL was observed in April 2009 and kidney biopsy revealed tacrolimus nephropathy and mild IgA nephropathy with striped interstitial fibrosis and mesangial proliferation with IgA deposition in the mesangium. Hypertension appeared in December, and the kidney biopsy is enforced again with Cre 1.0→1.7 in March, 2010. Though there was no crescent nor adhesion, mesangial IgA deposition was increased and the steroid pulse was enforced.

P2-238

Pneumomediastinum and malfixation of duodenum confirmed by autopsy in SSc

Shinichiro Nakachi¹, Shigeko Inokuma¹, Hiromitsu Asashima¹, Yoshimi Matsuo¹, Ryo Rokutanda¹, Shoko Kobayashi¹, Kiyofumi Hagiwara¹, Tamiko Takemura¹

¹Japanese Red Cross Medical Center, Tokyo, Japan, ²The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan

A 62-year-old male patient had a 3-year history of systemic sclerosis with interstitial lung disease. During corticosteroid therapy, recurrent severe pneumomediastinum and pneumothorax developed. Also, he suffered from recurrent ileus and the cause was suspected to be malfixation of duodenum. Aspiration pneumonia related to

ileus resulted in septic shock, of which he died. Autopsy revealed malfixation of duodenum and lung fibrosis. Pneumomediastinum in connective tissue diseases usually complicated with dermatomyositis, and although that related with interstitial pneumonia is known, that with systemic sclerosis is seldom reported. Ileus in systemic sclerosis is usually considered to relate to disperistalsis, and malfixation of duodenum has been scarcely reported.

P2-239

Investigation of discontinued infliximab to rheumatoid arthritis with remission

Takashi Imagama¹, Hiroshi Tanaka², Atsunori Tokushige¹, Ryo Date¹, Toshihiko Taguchi¹

¹Department of Orthopedic Surgery, Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan, ²Department of Orthopedic Surgery, Yamaguchi Grand Medical Center, Yamaguchi, Japan

Remission was achieved as a result of infliximab (IFX) to rheumatoid arthritis and the outcomes of cases where administration was discontinued were investigated. **[Subjects]** Remission had been sustained, and follow-up studies were carried out for over one year on seven cases. The mean period of time since beginning IFX was 136months and DAS28-CRP was at 4.72. In Steinbrocker Stages, there were three cases in stage II, and four in stage IV. **[Results]** Remission was able to be sustained in two cases for one year, two for two years, and two for over three years. **[Discussion]** It is suggested that the long-term remission after discontinuation of infliximab is possibly sustained in cases where the joint destruction has not progressed in a relatively short period since the emergence of the disease.

P2-240

Infliximab (IFX) dose increase in 26 RA patients with insufficient response

Hiroshi Sawano

Shimizu Public Welfare Hospital, JA Shizuoka Kouseiren, Shizuoka, Japan

Objectives: To evaluate the effect of increasing the dose and/or reducing the dosing intervals of IFX in RA patients with insufficient response. **Methods:** Twenty-six of 41 patients were evaluated for dose escalation on the basis of DAS28-CRP after 54 weeks. **Results:** Before IFX treatment, 24 of the 26 patients had high DAS28-CRP scores (>4.1) and 2 had medium scores (2.7-4.1). At the time of dose escalation 7 patients had high scores, 18 had medium scores, and 1 had a low score (2.3-2.7). After 54 weeks, 0 patients had high scores, 2 had medium scores, 1 had a low score, 17 were in remission, and 6 were switched to other drugs. IFX was interrupted in 1 patient (CR) and a successful dose reduction in 2 patients. **Discussion:** Dose escalation was beneficial in RA with insufficient response to IFX.

P2-241

Evaluation of Infliximab treatment with a shortened period by every 4 week

Kiichiro Ando, Hidenori Muro, Reou Ohguchi, Hironari Sakurai
Tosei general hospital

OBJECTIVE: We evaluated the efficacy of Infliximab treatment with a shortened period by every 4 week. **METHOD:** Two patients with Rheumatoid arthritis, who had insufficient effect for usual In-

fliximab therapy, undergone Infliximab treatment with a shortened period by every 4 week, from June 2009 to September 2010, were analyzed over 6 months. The amount of Infliximab was 3mg/kg. **RESULTS:** In case 1. DAS28ESR decreased significantly from 5.92 to 2.87 at 48 week. In case 2, DAS28ESR decreased significantly decreased from 4.81 to 2.94 at 28 week. **CONCLUSION:** These results demonstrated that Infliximab therapy with a shortened period by every 4 week was effective choice for patients with rheumatoid arthritis who were not responded to usual Infliximab therapy.

P2-242

Influence of the joint destruction on the HAQ-DI by IFX in patients with RA

Hayato Nagasawa¹, Koji Nishimura¹, Takahiko Kurasawa¹, Tsuneo Kondo¹, Ayumi Okuyama¹, Eiko Nishi¹, Hirofumi Takei¹, Koichi Amano¹, Hideto Kameda², Tsutomu Takeuchi²

¹Department of Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan, ²Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Faculty of Medicine, Keio University, Tokyo, Japan

Objective. We clarify the influence of the joint destruction on the HAQ-DI by infliximab treatment in patients with RA. **Methods.** Among 130 patients treated with infliximab, the HAQ-DI and the vdH-Sharp score (erosion, JSN, total score) were investigated, at 0 and 102 weeks. **Results.** Pre yearly progression and post yearly progression of vdH-Sharp score (erosion, JSN, total score) were 4.7 vs. 1.1, 5.2 vs. 1.1, and 9.9 vs. 2.2. Erosion, JSN, and total score at 0 week significantly correlated with HAQ-DI at 102 weeks. Whereas, in 40 patients with HAQ-DI ≤ 0.5 , only the JSN and total score significantly correlated with HAQ-DI at 102 weeks. **Conclusion.** The HAQ-DI at 102 weeks was influenced the joint destruction at baseline, and HAQ remission at 102 weeks was influenced the JSN.

P2-243

Efficacy of infliximab according to the concomitant use of oral steroids

Kenji Takahashi¹, Kenji Takenouchi¹, Toshikazu Kamada², Hiroshi Kaneko³, Masahito Koiwa⁴, Sanshiro Hashimoto⁵, Hiroshi Nakamura¹

¹Department of Rheumatology, Nippon Medical School, Tokyo, Japan, ²Hara Orthopaedic Hospital, Tokyo, Japan, ³Department of Rheumatology, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan, ⁴Department Rheumatology and Orthopaedics, Syuwa General Hospital, Saitama, Japan, ⁵Hashimoto Clinic, Tokyo, Japan

Purpose: We studied the differences in the efficacy of infliximab (IFX) treatment for RA according to the concomitant use of oral steroids. **Subjects:** We comparatively studied 18 cases that did not concomitantly use prednisolone (PSL) (NS group) and 17 cases that used 10 mg or more of the drug (S group). **Results:** There were no differences in DAS28 and mHAQ at the time of commencement. At the time of the final examination, the proportion of cases of clinical remission and of cases that discontinued treatment due to insufficient efficacy were respectively 44% and 33% in the NS group and 24% and 65% in the S group. **Conclusion:** Among cases with identical disease activity, the results of IFX treatment were inferior for cases that concomitantly used high doses of PSL at the time of commencement.

P2-244

Severe thrombocytopenia induced by first infliximab administration for RA

Yoshiki Nagai¹, Mutsuhito Ui¹, Satoshi Watanuki¹, Naofumi Chinen¹, Takahiro Nunokawa¹, Katsuaki Shiroto¹, Tsuyoshi Odai², Naoto Yokogawa¹, Kota Shimada¹, Shoji Sugii¹, Shinichi Inada¹

¹Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center, Tokyo, Japan, ²Division of Rheumatology and Clinical Immunology, Showa University, Tokyo, Japan

Back ground: Thrombocytopenia due to anti-TNF agents is very rare. Case: A 68-year-old women with rheumatoid arthritis on methotrexate received infliximab (IFX) at doses of 3mg/kg. Three days after the first IFX infusion, she developed gingival bleeding, petechia and gross hematuria and was admitted next day. Her platelet count fell to 2000/ μ l from four days ago. We gave platelet transfusion and intravenous methylprednisolone (80mg/day). Three days after admission, her platelet count was 7000/ μ l. After double filtration plasmapheresis (DFPP), her bleeding stopped and platelet count recovered over two weeks. Conclusion: Thrombocytopenia is a rare but severe complication of IFX. DFPP may help to remove IFX or possible antibodies against platelet.

P2-245

A case of de novo acute hepatitis B in RA treated with infliximab

Kenya Terabe¹, Masahiro Kobayakawa¹

¹Department of Orthopaedics, Fukuroi Municipal Hospital, Fukuroi, Japan, ²Department of Gastroenterology, Fukuroi Municipal Hospital, Fukuroi, Japan

A 81-year-old female had been suffering from RA for 40 years. Since 2005, she had treated with infliximab (IFX) combined with MTX. HBsAg was negative before receiving IFX, and also one year later. At the last administration a dose of IFX was 200mg/8wk, MTX4mg/wk. In August 2010 serum transaminase level was rather increased and then IFX and MTX were stopped, but serum transaminase level were further increased. She was diagnosed as de novo hepatitis B induced by IFX, because of positive HBsAg. She was treated with antiviral drugs and steroid pulse therapy, but she died 16 days later. Recently hepatitis B reactivation is recognized in some RA patients with TNF inhibitors. It is inadequate to judge the safety for de novo hepatitis B, even if HBsAg is negative before receiving TNF inhibitors.

P2-246

Polymyositis associated with infliximab treatment for rheumatoid arthritis

Makoto Wada

Yamashiro public hospital

A 41-year-old Japanese women had a 9-year history of severe and seropositive destructive RA, had received treatment with methotrexate. The patient was started on infliximab in October 2008. After the 6th course of injection, marked clinical improvement was observed. In October 2009, the patient was admitted to our hospital due to proximal muscle weakness and pain in both lower extremities, general fatigue. The findings of physical examination, laboratory test, muscle biopsy, and electromyogram resulted in a diagnosis of PM associated with infliximab. After the diagnosis of PM, infliximab was discontinued as the probable causative agent, treatment

was continued with low dose prednisolone and abatacept. We report here the very rare case report.

P2-247

Unusual multiple subcutaneous abscesses occurred during an infliximab treatment

Hiroshi Nishikawa¹, Hideaki Gouda¹, Hideyuki Watanabe¹, Nobuhisa Hirase¹, Kazuhide Tomari², Shoichiro Ikuyama¹

¹Division of Rheumatology, Hematology, and Metabolic Diseases, Kyushu University Hospital at Beppu, Beppu, Japan, ²Department of Orthopaedics, Shin-Beppu Hospital, Beppu, Japan

A 54-year-old female had been treated with IFX for 3 years. The therapy was effective and RA symptoms improved without any adverse events. Complaining severe pain around the lt. shoulder, rt. elbow and lt. knee joints 2 weeks after 30th IFX infusion, she made an ER visit. Since infection in the above joints was suspected, she was referred to an orthopedist. MRI revealed multiple subcutaneous abscesses in these regions. Incision, drainage, and debridement were performed. Although *S. aureus* was detected in blood and synovial fluid samples, possible origins of the infection could not be identified. Several antibiotics were given for 7 months, and the infection seemed to be resolved. We should be aware of unusual infectious complications when conducting a treatment with the biologics.

P2-248

Successful treatment of myositis observed in Behcet's disease by infliximab

Yoshinobu Matsuura, Isao Murakami, Miwa Nishida, Saori Hatachi, Masato Yagita

Department of Clinical Immunology and Rheumatology, Tazuke-Kofukai Medical Research Institute, Kitano Hospital, Osaka, Japan

A 44-year old man had developed intractable uveitis since December 2007 and aortic aneurysm at right popliteal artery since March 2008. He had further developed oral aphtha and severe muscle pain of lower limbs since February 2010, and was admitted to our hospital on April, 2010. He was diagnosed as incomplete and vascular Behcet's disease because of recurrent uveitis, oral aphtha and aortic aneurysm at popliteal artery. MRI of lower limbs revealed high intensity area at muscles and fascias corresponding to the regions of muscle pain. He was treated with 5mg/kg of infliximab, and his clinical symptoms including muscle pain dramatically improved. We herein report a rare case with Behcet's disease having myositis that was successfully treated with infliximab.

P2-249

Efficacy of infliximab for patients with refractory colitis in Behcet's disease

Hidetoshi Miyakawa¹, Satoshi Hachisuka¹, Naoki Katsuyama¹, Takahito Kimata¹, Masaomi Yamasaki¹, Shoichi Ozaki²

¹Division of Rheumatology, Yokohama City Seibu Hospital, St. Marianna University School of Medicine, ²Division of Rheumatology and allergy, St. Marianna University School of Medicine

OBJECTIVE: To report 2 cases of refractory colitis due to Behcet's disease treated with infliximab. **METHODS:** Two cases of Behcet's disease complicated with colitis. Their colitis was relapsing and was resistant to the combination of colchicine, prednisone and immunosuppressants included azathioprine, cyclosporine A, tacrolimus and methotrexate. **RESULTS:** Infliximab was efficient in all two cases. The mean prednisone dose decreased from 25 mg to 5mg

daily. Both of them were performed colonoscopy before and after treated with infliximab, and it showed remission of colitis. Infliximab was well tolerated without infections and infusion reactions. **CONCLUSION:** Infliximab may be efficient in refractory colitis due to Behçet's disease.

P2-250

Four cases of Behçet's disease treated with Infliximab in our hospital

Hideki Amuro, Akihiro Tanaka, Keiko Shimamoto, Yonsu Son, Yoshio Ozaki, Tomoki Ito, Shosaku Nomura
First Department of Internal Medicine, Moriguchi, Japan

We report 4 patients with Behçet's disease treated with infliximab (IFX). All patient are male, and IFX treatment was started at either 27, 30, 33, or 39 years old. Disease duration was 93 ± 70 months. All patients suffered from uveitis. Ocular inflammation with all cases were completely suppressed by the initial IFX administration, however 3 patients relapsed thereafter by upset of treatment schedules. Therefore, increased dose or shortened intervals with IFX treatment or joint use of steroid was performed in these 3 cases. An infusion reaction and infection without hospitalization occurred as adverse events. Although IFX is effective in the refractory uveitis, sustained remission requires the scheduled infusion and the dose escalation or shortened infusion intervals as the treatment for RA.

P2-251

Two-case of Behçet disease having severe arthritis treated with Infliximab

Fumiaki Nishisaka, Tohgo Nonaka, Kanji Fukuda, Chiaki Hamanishi
Department of Orthopaedic Surgery Kinki University School of Medicine, Osaka, Japan

We report two-case of Behçet disease having severe arthritis and mucocutaneous lesion treated with IFX. Case1: 42-year old woman had stomatitis and ulceration of vulnerable and severe arthritis. Some DMARDs therapy was not success for arthritis. After that, IFX treatment was started and the symptoms were improved immediately. Case2: 32-year old male had severe hydro-arthritis of bilateral knee joints with dermatitis. Some treatment were not success. IFX treatment was started and hydro-arthritis of the knee were improved immediately. Discussion: For arthritis in BD dose not advanced to bone erosion and destructive changes, BD patients were usually administrated NSAIDs and glucocorticoids, but they were often ineffective. We recommend IFX treatment for severe arthritis with Behçet disease.

P2-252

Clinical evaluation of infliximab in patients with Behçet's disease

Takuma Wada, Yuji Akiyama, Muneo Ota, Mayuko Sakamoto, Yuki Shimada, Akinori Yamamoto, Yasufumi Shindo, Yoshihiro Yoshida, Kazuhiro Yokota, Yasuto Araki, Haruhiko Akiba, Hiroshi Kajiyama, Kyoichi Nakajima, Kojiro Sato, Yu Asanuma, Toshihide Mimura

Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University

Objective We reviewed the efficacy and safety of infliximab (IFX) therapy in patients with Behçet's disease (BD) in our hospital,

retrospectively.

Patients 3 males and 4 females. Average age; 47.0 ± 16.0 years old, Average disease duration; 8.0 ± 7.7 years. symptoms; uveitis 2, entero-BD 4, both 1.

Result 1) Four patients were effective in uveitis or entero-BD and had been continuing for more than 2 years. Three patients were discontinued the therapy due to adverse events or secondary failure. 2) One pulmonary tuberculosis and one infusion reaction were investigated as adverse events. 3) Oral aphtha and arthritis were improved in all patients that could continue treatment.

Conclusion It was suggested that IFX therapy would be effective to refractory BD, especially oral aphtha and arthritis.

P2-253

Bach1 regulates expression of heme oxygenase-1 in monocytes

Mitsumiro Takeno, Yohei Kirino, Reikou Watanabe, Sei Samukawa, Maasa Hama, Yoshiaki Ishigatsubo
Department of Internal Medicine and Clinical Immunology, Yokohama City Graduate School of Medicine

We previously showed that defective expression of heme oxygenase (HO)-1, an anti-inflammatory protein, is associated with increased TLR4 expression in PBMC, leading to inflammation in Behçet's disease. Regulatory roles of the transcriptional repressor, Bach1 in HO-1 expression of monocytes were investigated. We found that peripheral monocytes expressed substantial amounts of HO-1, along with nuclear Nrf2 and cytoplasmic Bach1. LPS, a TLR4 ligand, induced translocation of Bach1 into nuclei and binding to the MARE motif, resulting in suppressed HO-1 expression. Bach1 siRNA canceled LPS dependent HO-1 reduction. The results suggest that Bach1 is a possible therapeutic target leading to upregulation of HO-1, in inflammatory diseases including Behçet's disease.

P2-254

A case of Neuro-Behçet's disease which occurred during pregnancy

Hideto Oshikawa¹, Tatsuo Kobayashi¹, Kazuki Yoshida¹, Masako Utsunomiya¹, Makiko Yamamoto¹, Mitsumasa Kishimoto², Kazuo Matsui¹

¹Department of Rheumatology, Kameda Medical Center, Chiba, Japan, ²Section of Allergy and Rheumatology, St Luke's International Hospital, Tokyo, Japan

A 38-year-old woman had often suffered from oral ulcer since her childhood, and genital ulcer for 4 years. Two years ago, she gave birth to her first child, and developed acneiform lesions. After that, she became pregnant, and developed genital and oral ulcer at 14 weeks of gestation. She had developed impaired memory since 21 weeks of gestation. MRI revealed abnormal intensity in caudatum, hippocampus, and putamen. CSF showed increase of IL-6. She had no ocular involvement and HLA-B51 was negative. Neuro-Behçet's disease was diagnosed, and mPSL pulse was started.

It has been reported that Behçet's disease tend to improve during pregnancy, and there have been few reports of a case with neurological manifestations occurring during pregnancy. We review our case and the relevant literature.

P2-255

A Case of Behçet's Disease Accompanied with Suspected of Multiple Sclerosis

Kentaro Susaki, Tomohiro Kameda, Shusaku Nakashima, Hiromi Kizu, Yohei Takeuchi, Miharuru Izumikawa, Hiroaki Dobashi

A 37 year-old woman was admitted to our hospital with a complaint of sudden left lower limb paralysis. She had been suffered from recurrent painful oral and genital ulcers and she was pointed out uveitis. She was diagnosed with incomplete type Behcet's disease (BD) and treated in a nearby hospital. On admission, brain MRI revealed multifocal and spatial ovoid lesion perpendicular to the ventricle and extending outward. She was suspected of multiple sclerosis (MS) by these MRI findings. She was administered m-PSL pulse therapy. Clinical symptoms have improved and ovoid lesion in the brain reduced. Her brain MRI findings were typical of MS but atypical of neuro-BD. BD was rarely accompanied with multiple sclerosis. It is difficult to differentiate of these diseases in this case.

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Unilateral abducens nerve palsy as an unusual complication of Behcet syndrome

Satoko Ueda¹, Yoshinori Taniguchi¹, Yoshiko Shimamura¹, Koji Ogata¹, Kosuke Inoue¹, Toru Kagawa¹, Yoshitaka Kumon², Yoshio Terada¹

¹Department of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Nankoku, Japan, ²Department of Laboratory Medicine, Kochi Medical School, Nankoku, Japan

76-year-old woman with bilateral autoimmune otitis interna with sensorineural deafness and intractable oral, gastric and colonic aphthous ulcers both of which lasted for more than 10 years, developed double vision. She had been suffered from the repeated autoimmune scleritis and Achilles tendonitis. The abduction of right eye was affected on the right gaze. Cerebrospinal fluid and brain MRI evaluation were normal. Unilateral abducens nerve palsy due to Behcet syndrome was clinically diagnosed. Abducens nerve palsy responded to the daily administration of PSL 40mg, and returned to normal on the right gaze after the treatment. Bilateral deafness, and oral and digestive aphthous lesions were also improved. To our knowledge, abducens nerve palsy with Behcet syndrome is extremely rare.

P2-257

Myelodysplastic syndrome mimicking Behcet's disease; A case report.

Ryuichi Sada, Yukio Tsugihashi, Teruhisa Azuma, Hiroyasu Ishimaru, Kazuhiro Hata
Tenri Hospital, Department of General Internal Medicine, Nara, Japan

A 39-year-old man had been suffering from recurrent fever and sore throat for 6 weeks. At the time of our consultation, he had injected eyes, blurred vision, oral ulcer, bilateral polyarthralgia, back pain, acneform skin on his back and subcutaneous abscess on his right leg. He fulfilled two major criteria (oral ulcer / skin disease) and one minor criteria (arthralgia) of Behcet's disease. Therefore, he was strongly suspected of having a Behcet's disease. However, his laboratory data showed remarkable leukocytosis with left shift, and a few blasts. Dysplasia of granulocytic and megakaryocytic series was detected in his bone marrow smear. Some blasts included Auerbody. He was finally diagnosed as having a myelodysplastic syndrome with mucosal and skin damage.

P2-258

A patient manifesting visual loss due to neuro-Behcet disease

Tomoko Kawabata, Ken-ei Sada, Noriko Toyota, Mariko Takano, Yoshinori Matsumoto, Ryutaro Yamanaka, Koichi Sugiyama, Hiroshi Wakabayashi, Hirofumi Makino
Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

The patient was a 43-year-old man with ocular involvement of Behcet disease (BD). He was also diagnosed as having the acute type of neuro-BD (NBD) in April 2009. He was treated with high-dose glucocorticoids with a tapering scheme and the neuro-symptoms disappeared. However, his right vision failed and he underwent surgery for right cataract. At surgery, atrophy of right optic nerve was demonstrated. Thereafter, ophthalmologic examination demonstrated inflammation of the anterior chamber cells and vitreous opacity. Treatment with infliximab (IFX) for ocular involvement was started. Before the first IFX injection, the IL-6 level in cerebrospinal fluid was very high (183pg/ml). It was difficult to determine which form of BD was the leading cause of the loss of visual acuity in this case.

P2-259

Proteomic analysis of peripheral blood mononuclear cells from Behcet's disease

Takuya Yoshioka¹, Manae S. Kurokawa¹, Yukiko Takakuwa², Hiromasa Nakano², Seido Ooka², Kouhei Nagai¹, Mitsumi Arito¹, Kazuki Okamoto¹, Noboru Suzuki³, Tomohiro Kato¹

¹Clinical Proteomics and Molecular Medicine, St. Marianna University Graduate School of Medicine, Kawasaki, Japan, ²Division of Rheumatology and Allergy, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan, ³Department of Immunology and Medicine, St. Marianna University School of Medicine, Kawasaki, Japan

To elucidate the pathophysiology of Behcet's disease (BD), we comprehensively analyzed protein profiles of peripheral blood mononuclear cells (PBMCs). Proteins, extracted from PBMCs from 3 BD patients and 3 healthy controls (HC), were separated by 2-dimensional gel electrophoresis. In 1,362 protein spots detected, intensity of 161 spots was altered in BD ($^2\pm 1.5$ folds; BD>HC, 64 spots; HC>BD, 97 spots; $p<0.05$). The 19 protein spots ($^2\pm 2.0$ folds), identified by mass spectrometry, included an inhibitor of neutrophil function, anti-oxidant enzyme, heat shock protein, precursor of coagulation factor, and cytoskeletal proteins. The protein profile of BD-PBMCs were characterized by the alteration of proteins associated with inflammation, which may be involved in the pathophysiology of BD.

P2-260

Skewed CD4 T cell development in Behcet's disease

Jun Shimizu, Noboru Suzuki
Department of Immunology and Medicine, St. Marianna University School of Medicine

Purpose: We have demonstrated that the IL-23/IL-17 pathway was skewed in Behcet's disease (BD). This study was designed to observe Th17 development in BD. Methods: We observed the ability of cytokine production of naive CD4 T cells, under Th0, Th1, Th2 or Th17 polarizing condition, and also memory CD4 T cells, comparing with healthy volunteers (HV). Results: Memory CD4 T

cells produced IFN-gamma and TGF-beta in BD as much as in HV, while naïve CD4 T cells didn't produce enough, especially under Th1 condition. Conclusion: We revealed skewed CD4 T cell development which may play a critical role in the recurrent acute inflammation in BD.

P2-261

Serum adalimumab concentrations and AAA: clinical efficacy of ADA, 1st report

Misuzu Yamashita¹, Masamitsu Natsumeda¹, Koji Takasugi¹, Ryutaro Yamanaka¹, Kayo Ezawa¹, Kazuhiko Ezawa¹, Yoshihisa Nasu², Keiichi Nishida³

¹Department of Internal Medicine, Kurashiki Kosai Hospital, Kurashiki, Japan, ²Department of Orthopaedic Surgery, Kurashiki Kosai Hospital, Kurashiki, Japan, ³Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Objective: To compare the efficacy of adalimumab (ADA) among concomitant drugs (methotrexate (MTX) or tacrolimus (TAC)) including associations between serum ADA concentrations and anti-adalimumab antibodies (AAAs). **Methods:** We assessed DAS28, CDAI, ACR improvement and EULAR response in MTX combination arm (16 cases), TAC combination arm (22 cases) and monotherapy arm (8 cases). We further measured serum trough ADA levels and AAAs. **Results:** In MTX arm and TAC arm, mean DAS28 and CDAI were significantly improved after 4 weeks. Both arms showed better response in ACR improvement and EULAR response than monotherapy arm. There were no significant differences in formation of AAAs and serum ADA levels among three arms. **Conclusion:** TAC combination therapy is useful for patients intolerant to MTX.

P2-262

The 1 year results of 175 patients in TBC with RA treated with adalimumab (ADA)

Atsushi Kaneko^{1,6}, Yuji Hirano^{2,6}, Kenya Terabe^{3,6}, Takayoshi Fujibayashi^{4,6}, Yosuke Hattori^{5,6}, Toshihisa Kojima^{5,6}, Naoki Ishiguro^{5,6}

¹Department of Orthopaedic surgery and Rheumatology, Nagoya Medical Center, NHO, Nagoya, Japan, ²Toyohashi Municipal Hospital, ³Fukuroi Municipal Hospital, ⁴Konan Kosei Hospital, ⁵Department of Orthopaedic surgery, Nagoya University, Graduate School & Faculty of Medicine, Nagoya, Japan, ⁶Tsurumi Biologics Communication

This purpose of this study is to analyze the data of 21 institutes of the TBC. We investigated the drug survival rate, the mean of DAS 28ESR, the remission rates of DAS28, and the reasons for discontinuation. Results. The drug survival rate was 61.1% throughout 1 year. The mean score of DAS28 was 5.54 in the beginning, decreasing to 3.27 after a year. Overall remission rate over 1 year was 19.6%. Within 1 year 71 patients dropped out; 56 patients within 6 months; and 15 patients discontinued after more than 6 months. The reasons for discontinuations were as follows: 20 patients for primary failure; 19 for secondary failure; 18 patients dropped out for safety reasons, including 7 patients with related infection, 8 patients with skin allergies, and 3 patients with cytopenia.

P2-263

Examine of effectiveness of adalimumab on rheumatoid arthritis

Kosaku Oda

Department of Orthopedic Surgery, Takatsuki Red Cross Hospital

<Purpose> Clinical use of ADA to RA began from August, 2008 was examined. <Object> the RA included to this study was 24 weeks or more after ADA began 17 cases. Also the patient were 58.4 years old on average and duration rate was 10.1 years. MTX was administered to 17 patients and dosage average was 6.4mg and 1male / 17 female was gender. The naïve and switch were 11 / 6 cases. <Result> 11 cases were Good Response and 3 cases were Moderate Response and No Response was 1 case. For the case of Moderate Response, 2 of 3 patients were switching. The DAS28 mean value has been improved from 5.78 to 2.86. <Discussion> ADA shown the effect on the early phase, and especially biological naïve patients shown excellent progress effect. More early add on treatment of ADA with MTX thought to be effective.

P2-264

Short-term use results of adalimumab in our department

Takahiko Wada^{1,2}, Akihiro Tanaka^{2,3}, Yonsu Son^{2,3}, Katsuyuki Kawakami^{2,3}, Hirokazu Sawai^{1,2}, Yoshio Ozaki^{2,3}, Shosaku Nomura³, Hirokazu Iida¹

¹Department of Orthopaedic Surgery, Kansai Medical University Hirakata Hospital, ²Department of Rheumatology and Clinical Immunology, Kansai Medical University Hirakata Hospital, ³First Department of Internal Medicine, Kansai Medical University

Aim: To investigate short-term use results of adalimumab (ADA) in our department.

Subjects and Methods: We administered ADA 40mg sc in 29 rheumatoid arthritis (RA) patients (female, n=25; male, n=4) visiting our department and followed up for 24 weeks. There were differences in dose (every-other-week, n=19; every-three-week, n=2; every-four-week, n=8). Some patients switched from other biologics (infliximab, n=5; etanercept, n=5; tocilizumab, n=2). DAS28-ESR, MMP-3 etc were used to assess the efficacy.

Results: Changes of mean (beginning/16 weeks) for DAS28-ESR and MMP-3 were 4.6/3.9 and 183.2/80.4 (ng/mL), respectively. Major adverse event was not seen for this period. **Conclusion:** Efficacy of ADA in RA patients was confirmed although this was a short-term study.

P2-265

Evaluate the clinical utility of adalimumab in dairy practice.

Kanako Iwata¹, Toshihiro Matsui¹, Shinichi Nogi¹, Hidekazu Futami¹, Hirokazu Takaoka¹, Tatsuoh Ikenaka¹, Yoshiyuki Arinuma¹, Atsushi Hashimoto¹, Akiko Komiya², Hiroshi Furukawa², Hisanori Nakayama¹, Shigeto Tohma²

¹Department of Rheumatology, Sagami National Hospital, National Hospital Organization, Kanagawa, Japan, ²Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami National Hospital, National Hospital Organization, Kanagawa, Japan

【Objective】To evaluate the clinical utility of adalimumab (ADA) in dairy practice.

【Method】Using data of 58 patients treated with ADA, we analyzed their background, pretreatment, combined therapy, and efficacy of ADA.

【Result】At 12 weeks, 46 cases (79%) had continued ADA, 4 cases discontinued by unresponsiveness and 5 cases discontinued by adverse events. Average of DAS28 was improved significantly (5.03 to 4.28). Sub-analysis showed TNF-blockade-naïve cases treated

with ADA+MTX were significantly more common in good or moderate response cases than in no response cases. 22 cases achieved low activity, and 3 cases had maintained low activity with prolonged administration interval.

【Conclusion】This study showed the possibility that efficacy of ADA depends on the background of patients.

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Clinical features of ADA cases administered continuously for more than 2 years

Toyomitsu Tsuchida¹, Ayako Kubota²

¹Institute of Rheumatic Disease, Tsuchida Clinic, ²Department of Orthopaedic Surgery, Toho University School of Medicine, Tokyo, Japan

2 years have passed since Adalimumab (ADA) was introduced and has been administered in more than 100 cases in the hospital. Objective To consider clinical features of continuous administration group. 18 Naïve cases (Group N); ADA combined with MTX in 12 cases and ADA alone in 6 cases. 14 Switch cases (Group S) Results The continuation rates of Group N and S were 55.6% and 28.6% respectively, the continuation rates of ADA combined with MTX (Group A) and ADA alone (Group B), were 38.9% and 16.7% respectively. In Group S, on the other hand, the continuation rates of ADA combined with MTX (Group C) and ADA alone (Group D) were 21.4% and 7.1%. Conclusion It was suggested the highest continuation rate can be obtained by administering ADA combined with MTX in Naïve cases.

P2-267

Evaluation of patients with rheumatoid arthritis treated with adalimumab

Katsumitsu Arai¹, Junya Ajiro², Naoki Kondo³, Junichi Fujisawa³, Takahiro Netsu³, Naoko Kudo¹, Takeshi Tojo¹, Naoto Endo³

¹Niigata Prefectural Central Hospital, Department of Orthopedic Surgery, ²Niigata Prefectural Central Hospital, Department of Internal Medicine, ³Division of Orthopedic Surgery, Niigata University, Graduate School of Medical and Dental Sciences

Evaluation of 25 RA cases treated with adalimumab for more than 12 weeks is performed. There were 22 cases treated with MTX and 6 cases had been treated with biologics previously. The average age was 56±15 years old. Average of DAS28-ESR (4) was 5.3. It was changed to 3.9 at one month, 4.0 at three months. Two in 25 cases had become a remission in three months. Four in 6 cases who had another biologics previously, had dropped out with no effect by adalimumab. Two cases dropped out with side effect. There were 16 cases who had adalimumab as 1st biologics and treated with MTX which dose was more than 8mg/w, 7 cases had good response at 12 weeks.

P2-268

The continuance rate of adalimumab treatment among RA patients

Hiroki Wakabayashi¹, Yousuke Nishioka², Masahiro Hasegawa¹, Akihiro Sudo¹, Kusuki Nishioka³

¹Department of Orthopaedic Surgery, Mie University Graduate School of Medicine, Japan, ²Nishioka Clinic, Mie Japan, ³Institute of Medical Science, Tokyo Medical University, Japan

We investigated to the continuance rate of adalimumab (ADA) treatment among patients with rheumatoid arthritis (RA). This retro-

spective study investigated 17 patients with RA who were treated with ADA. Nine patients (52.3%) completed 24 weeks of ADA treatment. Six (75%) of the 8 naïve patients and 3 (33.3%) of the 9 switched completed 24 weeks of ADA treatment. Four (80%) of the 5 patients with methotrexate (MTX) and 5 (35.7%) of the 14 without MTX completed 24 weeks of ADA treatment. In conclusions, the continuance rate of ADA treatment was better in the naïve or with MTX.

P2-269

The efficacy of Adalimumab not combined with MTX for patients of RA from TBC.

Kenya Terabe¹, Toshihisa Kojima², Atsushi Kaneko³, Yuji Hirano⁴, Takayoshi Fujibayashi⁵, Yosuke Hattori², Masahiro Kobayakawa¹, Naoki Ishiguro²

¹Department of Orthopaedics, Fukuroi Municipal Hospital, Fukuroi, Japan, ²Department of Orthopaedic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan, ³Department of Orthopaedic Surgery and Rheumatology, Nagoya Medical Center, Nagoya, Japan, ⁴Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan, ⁵Department of Orthopaedics, Konan Kosei Hospital, Konan, Japan

We evaluated efficacy of Adalimumab not combined with Methotrexate for patients of Rheumatoid arthritis. These results are derived from multicenter study from TBC. Efficacy was evaluated based on DAS28-ESR and survival rate at 52 weeks in 39 RA patients. We investigated the various baseline characteristics between good response group (G group) and not good response group (N group). The ratio consecutive rate after 52 weeks period was 46.2%. Average of DAS28 improved 5.61±1.11 at baseline to 4.62±1.71 after 52 weeks later. 8 patients (21%) were in G group and 31 patients (79%) were in N group. Comparison of baseline characteristics between G group and N group, average of RA duration was significantly shorter in G group than N group and rate of class one or two was higher in G group.

P2-270

Disseminated nontuberculous Mycobacterial infection in a patient with SLE

Naoko Ueki, Kensuke Oryoji, Fumihiko Konishi, Kazuo Kamada, Shinichi Mizuki, Eisuke Yokota
Matsuyama Red Cross Hospital, The Center for Rheumatic Disease

A 58-year-old woman with systemic lupus erythematosus developed swelling and pain in her right wrist. She was diagnosed as having a synovitis by MRI findings and received MTX therapy. A month later, she was admitted to our hospital due to high fever. Whole-body CT scanning revealed abscess formations adjacent to bilateral shoulder joints and a hematoma or an abscess in the spleen. We punctured her both shoulder joints and right knee joint, and confirmed that she was infected with nontuberculous mycobacterium (NTM, *M. intracellulare* was isolated from all joint fluids). Since anti-mycobacterial drug therapy was not effective, she underwent the splenectomy resulting in the isolation of NTM from the splenic tissue. She became better and has stayed in a good condition under the drug therapy.

P2-271

A cases of peritoneal tuberculosis which mimic Lupus peritonitis
Tatsuo Kobayashi¹, Hideto Oshikawa¹, Kazuki Yoshida¹, Masako Utsunomiya¹, Makiko Yamamoto¹, Mitumasa Kishimoto², Kazuo Matsui¹

¹Department of Rheumatology, Kameda Medical Center, Chiba, Japan, ²Section of Allergy and Rheumatology, St Luke's International Hospital, Tokyo, Japan

It is difficult to diagnose ascites, especially for the elderly. Case: 92 y.o female presented with abdominal distention, low grade fever of 2 weeks duration. She had massive ascites and acid-fast stain, PCR for Tuberculosis (TB) and cytology of ascites were negative. She met classification criteria of SLE. ANA in ascites was 1:1280 and anti-DNA antibody and anti-Sm antibody in ascites were negative. SAAG were less than 1.1. Prednisolone 10mg/day was started as Lupus Peritonitis (LP). After 2 weeks, ascites culture for TB became positive. She was diagnosed as a case of peritoneal tuberculosis which mimics LP. Although some reports say ANA in ascites is positive in LP, it is not established. We should rule out other disease in treating patients with LP like disease.

P2-272

A case of PCP appeared with recovery from agranulocytosis due to AZP in SLE

Yuichiro Taguchi, Rei Itoh, Toshiaki Miyamoto
Seireihamamatsu Hospital

A 43 years old woman with RA and SLE, who received methylpredonison 16mg per day and azathioprine (AZP) 125mg per day, was admitted to our hospital due to general fatigue and high fever since a week. Her clinical examination revealed pancytopenia and agranulocytosis in bone marrow which were suggested to side effect of AZP. Acute respiratory distress suddenly onset accompanied with white blood cell improvement by G-CSF administration, typical CT imaging and high beta-D glucan indicated pneumocystis jirovecii pneumonia (PCP). Then, she received high dose steroid and trimethoprim-sulfamethoxazole and she was recovered. This interesting case made us consider that inapparent PCP covered by leukocytopenia appeared accompanied with reconstruction of immunity.

P2-273

A case report of neuropsychiatric SLE successfully treated with low dose IVCY.

Wataru Fujii, Masataka Kohn, Amane Nakabayashi, Aihiro Yamamoto, Takahiro Seno, Kaoru Nakamura, Ken Murakami, Hidetake Nagahara, Takashi Kida, Hidetaka Ishino, Yutaka Kawahito

Inflammation and Immunology, Kyoto Prefectural University of Medicine, Kyoto, Japan

A 23-year-old woman was diagnosed as systemic lupus erythematosus (SLE), who had malar rash, hematologic and immunologic disorder 3 months before. We started the treatment of 20mg/day of oral PSL. But, the increase of dose of PSL, methylprednisolone pulse therapy, and plasma exchange were needed because of flare-up of liver dysfunction. After these treatments she came down with psychosis, spastic paraplegia, and bladder bowel disturbance. We diagnosed her as neuropsychiatric SLE by brain and spinal MRI, and lumbar puncture. We treated her with intravenous cyclophosphamide pulse therapy (IVCY) of 6mg/kg/m² biweekly, and she got improved. NPSLE is generally treated with IVCY of 500-1000mg/

body monthly. In this case frequent IVCY of low dose was effective, without major side effect.

P2-274

A case of SLE with PAH complicated with TM and scattered encephalitis

Takeo Kudo¹, Junichi Tanaka¹, Ryosuke Hara¹, Eisuke Ogawa¹, Yoshihiro Tono¹, Kenta Hoshi¹, Tatsuo Nagai¹, Sumiaki Tanaka¹, Akira Ishikawa¹, Shunsei Hirohata¹

¹Department of Rheumatology and Infectious Disease, Kitasato University School of Medicine, Kanagawa, Japan, ²Department of Pathology, Kitasato University School of Medicine, Kanagawa, Japan

A 42-year-old woman. She presented dyspnea and oliguria in July 2009. She was diagnosed as SLE in October, and treatment with PSL 30mg/day was started. One week later, she had PAH. In spite of mPSL pulse therapy, she developed TM in late November, and developed severe brainstem encephalitis leading to respiratory arrest. Although she was treated by mPSL pulse and IVCY, she died due to sudden cardiac arrest on February 1, 2010. Histopathological analysis on autopsy showed diffuse circumference necrosis of spinal white matter with thickening of small vessel walls, luminal narrowing, and organizing thrombus in blood vessels of spinal cord, but not with vascular inflammation. It is suggested that TM in our patient might be resulted from spinal vasculopathy.

P2-275

A patient with SLE who was presented with exuberant callus formation after ASCT

Rie Karasawa¹, Minako Murata¹, Takahiro Okazaki², Kazuo Yudo¹

¹Institute of Medical Science, St. Marianna University School of Medicine, Kawasaki, Japan, ²Division of Rheumatology and Allergology, Department of Internal Medicine St. Marianna University School of Medicine

SLE patient with lupus nephritis and thrombocytopenia was treated with prednisolone and tacrolimus. She was operated on for arthritis with ASCT. She had inactive disease and calcification in subcutaneous tissue in lower extremities. She had levels of biochemical markers of bone turnover within near-normal ranges and hadn't received administration for osteoporosis. After operation, marked callus formation was concurrent with reduction in severe swelling of left foot and was also induced in collection site. In addition to immune disorder of SLE, inflammatory cytokines and elevated concentrations of osteoprotegerin may induce to form them by suppressing differentiation of osteoclast. High expression of BMP-2 and Runx2 may result in increasing differentiation and proliferation of osteoblast.

P2-276

A case of SLE complicated by pneumatosis intestinalis and cystitis emphysematosa

Ayako Okubo, Taro Iwamoto, Yoshie Suzuki, Daiki Nakagomi, Hirotohi Kawashima, Yoshihisa Kobayashi, Yukiko Hiramatsu, Kei Ikeda, Norihiko Watanabe, Hiroshi Nakajima
Chiba University Hospital

49 year-old female with 30 year-history of systemic lupus erythematosus was transferred to intensive care unit on mechanical ventilation in June, 2010 due to lupus cardiomyositis and thrombotic thrombocytopenic purpura. Although steroid pulse and rituximab therapy was successful, severe dysphagia and muscle weakness per-

sisted. In August, she developed pneumatosis cystoides intestinalis in the whole colon, which resolved with total parenteral nutrition. In September, she had pyuria and CT scan revealed emphysema in the bladder wall, which led to a diagnosis of cystitis emphysematosa. The emphysema gradually subsided with antibiotics and urethral catheterization. Cystitis emphysematosa without diabetes is a very rare condition and the possible cause will be discussed with literature review.

P2-277

A case of protein-losing gastroenteropathy (PLGE) associated with SLE

Tsukasa Yoshida¹, Seiyo Honda¹, Shinjiro Kaieda¹, Hiroshi Maruoka², Takaaki Fukuda³, Hiroaki Ida¹

¹Division of Respiriology, Neurology and Rheumatology, Department of Medicine, Kurume University School of Medicine, ²Maruoka Internal Medicine and Rheumatology Clinic, ³Kurume University Medical Center

A 66 year old woman, who was diagnosed as having SLE for 14 years, was admitted to our hospital for investigation of peripheral edema, diarrhea and hypoalbuminemia. Chest X-ray study proved a substantial pleural effusion on admission. Serological verification demonstrated a prominent decrease in the levels of albumin (1.8g/dl) and a positivity for anti-nuclear antibody (ab) and anti-Sm ab whereas anti-dsDNA ab was not detected. Nephrotic syndrome and malignant diseases were ruled out as the cause of hypoalbuminemia. Then we performed Tc-HAS scintigraphy and it revealed the protein leakage in the intestinal tract. This finding uncovered the presence of PLGE. The combination therapy of high dose prednisolone (PSL) and tacrolimus improved peripheral edema, pleural effusion and hypoalbuminemia. (Conclusion) PLGE is an uncommon manifestation of SLE. Treatment with a combination of PSL and tacrolimus was effective in this case.

P2-278

A case of SLE with chronic peritonitis developing small intestinal hemorrhage

Ayako Nishino¹, Shin-ya Kawashiri¹, Akitomo Okada¹, Junko Kita¹, Tomohiro Koga¹, Satoshi Yamasaki¹, Hideki Nakamura¹, Tomoki Origuchi², Atsushi Kawakami¹

¹Unit of Translational Medicine, Department of Immunology and Rheumatology, Graduate School of Biomedical Sciences, Nagasaki University, ²Nagasaki University School of Health Sciences, Nagasaki University

A 50-year-old Japanese woman, who was a patient with systemic lupus erythematosus (SLE) complicated with chronic lupus peritonitis, developed massive small intestinal hemorrhage. Although she was treated with intravenous pulse of methylprednisolone, intravenous pulse of cyclophosphamide (IVCY), and immunoabsorption, peritonitis was refractory. She had subsequently continued to be treated with oral corticosteroid and tacrolimus, and IVCY monthly, but she developed massive small intestinal hemorrhage one year later. The abdominal angiography detected multiple bleeding from jejuna and ileal arteries. After operating transarterial embolism, melena was disappeared. The pathology of this case was suggested to be lupus mesenteric vasculitis.

P2-279

Extensive cerebral calcification in patients with SLE: report of three cases.

Hideki Ito, Takehiko Ogawa, Takehisa Ogura, Yuichi Izumi, Norihide Hayashi, Ayako Hirata, Reiko Miura, Rie Kujime, Ryuta Endo

Division of Rheumatology, Toho University Ohashi Medical Center

We report extensive cerebral calcification in 3 SLE patients. Case 1. A 31-year-old woman was diagnosed as SLE with finger erythema, Raynaud's phenomenon (RP), mesangial proliferative (MPLN), positive ANA, raised anti-DNA and anti-RNP Ab titers. Case 2. A 51-year-old woman was diagnosed as SLE with malar rash, finger erythema, RP, arthritis, membranous lupus nephritis, positive ANA, raised anti-DNA and anti-RNP Ab titers. Case 3. A 52-year-old woman was diagnosed as SLE with finger erythema, RP, MPLN, positive ANA, raised anti-DNA and anti-RNP Ab titers. In all 3 cases, CT of the head showed extensive calcification of the basal ganglia, thalamus, deep white matter and cerebellar dentate nuclei. The present cases suggest that extensive cerebral calcification is closely associated with SLE.

P2-280

A case of malignant lymphoma during the progress of SLE complicated APS

Kyoko Yoshihiro, Nobuyuki Ono, Daisuke Himeji, Yasufumi Kai, Akira Ueda

Miyazaki Prefectural Hospital

A 51-year-old woman with 9-year history of Systemic Lupus Erythematosus and antiphospholipid-antibody syndrome, who developed Lupus nephritis, autoimmune hemolytic anemia, neuropsychiatric syndromes of SLE, and she was treated with high dose of prednisolone, cyclophosphamide, rituximab, and plasma exchange. In 2010, her hemolytic anemia relapsed, and treated with 1mg/kg/day PSL. Hemolytic anemia was recovered, but complicated neutropenia. She medicated with G-CSF. Some tumors elapsed on gingival and skin, which were diagnosed as non-Hodgkin's lymphoma. We considered treatment with rituximab, but resigned because of her low performance status, and APS. Disease progression was very rapid, and she died half a month after diagnosis. The risk of malignancy is shown to be increased in SLE patients, those cases would increase, because lupus patients would live longer than before.

P2-281

A case of fasciitis associated with systemic lupus erythematosus

Taro Ukichi, Ken Yoshida, Kentaro Noda, Kenichiro Hirai, Isamu Kingetsu, Daitaro Kurosaka, Akio Yamada

Department of Internal Medicine, Division of Rheumatology, Jikei University School of Medicine, Tokyo, Japan

On 25 March 2010, a 33-year-old woman was admitted to our hospital due to high fever, rashes, cervical lymphadenopathy, myalgia in both femurs, splenomegaly, liver dysfunction and elevated CRP. She was diagnosed with SLE because of butterfly rash, renal dysfunction, elevated serum anti-ds-DNA antibody and a positive test for antinuclear antibody. On 9 April 2010, oral administration of high-dose prednisolone was started. After that, clinical manifestations including rashes, lymphadenopathy, renal dysfunction gradually improved, but myalgia in both femurs exacerbated. STIR images on MRI of both her femurs showed high intensity signals at the site

of fascia. En block muscle biopsy revealed fasciitis with intense sheet-like infiltration of CD68 (+) histiocytes along with fascia.

P2-282

A case of refractory thrombocytopenia associated with SLE treated with rituximab

Chiharu Imada, Hajime Hamasaki, Mikako Iwakura, Misuzu Akamine, Itomi Abe, Keisuke Maeshima, Miwa Haranaka, Midori Kumagi, Koji Ishii, Hironobu Yoshimatsu

Internal Medicine 1 Faculty of Medicine, Oita University, Oita, Japan

A 39-year-old woman had been treated for 22 years with corticosteroids and some immunosuppressants for SLE. She presented severe immune thrombocytopenic purpura in March 2009. She was unsuccessfully treated at the outset with a infusion of intravenous immunoglobulin (IVIG). Since thrombocytopenia remained, she was given rituximab 375 mg/m²/week for 4 weeks twice. Thrombocytopenia and native anti-DNA antibody levels decreased after the infusion. No side effects of treatment were observed. The patient did not experience any relapse during the 12 months following the final infusion. Rituximab appears to constitute a safe and effective treatment for refractory immune thrombocytopenic purpura associated with SLE in patients having a contraindication to or refractory to conventional therapy.

P2-283

Mycophenolate mofetil for SLE complicated with severe retinal artery occlusion

Satoshi Watanuki, Naoto Yokogawa, Mutsuhito Ui, Naofumi Chinen, Yoshiki Nagai, Takahiro Nunokawa, Katsuaki Shiroto, Kota Shimada, Shoji Sugii, Shinichi Inada

Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center

31 year old female patient was admitted with fever, malaise and joint pain for six weeks. Physical exam showed oral ulcers and palmer erythema. Laboratory findings were white blood cell 3200/ μ l, platelets 61,000/ μ l and positive serologies for ANA, anti-SSA, anti-dsDNA, anti-SS-A and low C3/C4. Three days after admission, she rapidly lost her vision with eye pain in the left eye. Funduscopy exam showed retinal edema and hemorrhage with retinal artery narrowing and fluorescein angiography revealed delayed perfusion. These findings were consistent with severe retinal vasculitis with occlusion secondary to SLE. Though her left visual loss became permanent, steroids and mycophenolate mofetil successfully induced and maintained remission over a year without side effect such as amenorrhea or infection.

P2-284

The case report; usefulness and adverse effects of biological agents

Takako Mine¹, Takao Takeuchi²

¹Mine Clinic, ²Hayaishi Hospital

88-year-old woman with treated-resistant RA was cared by NSAIDs alone, due to adverse effects of DMARDs. RA caused severe pain and restriction of wrists. Some orthopedic surgical operations were performed for upper extremities. In 2007, administration of etanercept (25mg/week) was selected, with early-administration of isoniazid (100mg) by a month. At 5th-administration, the pain disappeared. However, liver dysfunction was observed at 7th-ad-

ministration. It was diminished by the withdrawal of etanercept and isoniazids. Re-administration of etanercept alone was also effective. However, at the 22th-administration, interstitial pneumonia occurred. This case suggested the usefulness of etanercept in elderly people. However, careful observation is needed to avoid severe adverse effects.

P2-285

A case of elderly-onset RA with disease activity (DA) dependent on ETN dose

Yuichiro Kamada

kamada orthopedic clinic Kameoka city kyoto Japan

[Case] 92-yo male developed rheumatoid arthritis (RA) Jan. 2006, started 2 mg/week (W) methotrexate (MTX) treatment at nearby clinic, but was referred to our hospital due to poor control. MTX increase to 4 mg/week was insufficient and further increase was difficult due to renal impairment (RI). Jan. 12, 2007 Etanercept (ETN) 25 mg \times 2/week started. DA ameliorated and ETN was decreased to 25 mg/W followed by C-reactive protein increase; due to mild DA increase dose was unchanged. Gradual DA increase led ETN increase to 25 mg \times 2/W and DA returned to same level as before the ETN decrease. [Discussion] MTX is often not applicable in elderly-onset RA due to RI. ETN has few effects on renal function; this dose and DA clearly related case suggest considering ETN increase when DA control fails.

P2-286

Effects of Etanercept (ENT) in elderly RA patients and Adverse events

Hiroyuki Ohashi, Jin Sawada

Rheumatology Department, Omaezaki Municipal Hospital

We evaluated the effects and adverse events of etanercept (ENT) in 101rheumatoid arthritis (RA) patients who were divided between Elderly ones (K group, ≥ 65 , n=44) and Non-elderly (H group, <64 , n=57). (Method) All subjects were examined monthly. (Result) 1 K group patients were less treated with MTX compared to H group. 2 K group patients had higher values of patient assessment of pain and global status compared to H group. 3 There was no difference of clinical effects between K and H group. 4 3 patient in H group achieved ETN free clinical remission. K group had aging-related complications. (Conclusion) Our data indicate that ENT is very effective for treating elderly and young RA patients. Whereas it is necessary to notice the aging-related adverse effects of ETN in elderly patients.

P2-287

A case report of Pneumocystis Pneumonia administering Etanercept 25mg per week

Tetsuya Takenaga, Kunio Yamada, Takaaki Hasuo, Masahiro Nishino, Tsukasa Imaizumi

Department of Orthopaedic surgery, Komaki City Hospital, Komaki, Japan

[Purpose]Report on a case of pneumocystis pneumonia (PCP) while administering etanercept (ETN). [Case]A 74-year-old woman with rheumatoid arthritis (Stage IV, Class 3) received ETN 25 mg/week after joint destruction progressed despite treatment with methotrexate (MTX) and salazosulfapyridine (SASP). She had high temperature and cough after 3 months. High-resolution computed tomography revealed a diffuse ground-glass shadow. She was hospi-

talized and bronchofiberscopy was performed. PCP was the final diagnosis because PCR of bronchoalveolar lavage showed *Pneumocystis* and β -d glucan levels increased. She recovered after administration of sulfamethoxazole-trimethoprim and steroid. [Discussion] Despite the low dose of ETN, great care must be taken to avoid infection while ETN administration.

P2-288

One example of the improvement of hydrarthrus in knees by the Etanercept dosage.

Shuichiro Kitada
Orthopedics Clinic

The case is 67 years old woman. General malaise appears from 2007. More than antiCCP antibody 100, MMP-3 were 1,465.8 at first, too. Dropsy appeared to a right shoulder joint and both knees. The right shoulder, the hydrarthrus of both elbows disappear afterwards when I start MTX. However, it continued to pool immediately even if I punctured the hydrarthrus of both knees. The hydrarthrus of the right knee disappeared slowly since I begin to start Etanercept 25ml drug in July, 2009, but dropsy continues the left knee joint. I am reducing the quantity of the left water on the knee pool when I change it to 50ml drug from Etanercept 25ml drug in October, 2010. I chased process of process of the rheumatism reaction in MMP-3 under the treatment by MTX and Etanercept and the hydrarthrus decrease.

P2-289

Oldest-old case of RA with COPD and renal dysfunction markedly responded to ETN

Motohide Kaneko
kaneko clinic saitama japan

Early aggressive treatment in RA is predominant, but there is no consensus on treating the elderly. We report an oldest-old patient case that markedly responded to etanercept (ETN). 90-yo woman developed RA and was treated w/ only NSAID. She started visiting our hospital at age 93 complaining pain and insomnia. For high disease activity (DAS28, 7.08) treatment with salazosulfapyridine (SASP) was started since close examination showed COPD. RA resolved once but reaggravated 6 months later; ETN 25 mg/W was started Jul. 2009. DA steadily decreased, reaching DAS28, 2.65 in Sep. 2010. Without any AEs nutritional and respiratory status improved and activities of daily living are well-maintained. [Discussion] Aggressive treatment w/ biopharmaceuticals may also be an option for senior patients.

P2-290

Etanercept was effective in RA patient with chronic renal failure -a case report

Haruki Imura, Yoshikiyo Ohsawa, Syuichi Nakagawa, Hitoshi Nakata, Satoshi Kashiwagi
Amagasaki Medical coop Hospital

A 61-year-old Japanese man was diagnosed with rheumatoid arthritis (RA) in 2009 based on the presence of polyarthritis. There was chronic renal failure as complication, so treatment with salazosulfapyridine and prednisolone was discontinued at general practitioner. But his arthritis remains active, so he came to our hospital in 2010. Laboratory findings were C-reactive protein (CRP) 1.4mg/dl, Matrix-metaro-protease-3 599ng/ml, urea nitrogen 56mg/dl, creatinine 4.3mg/dl, 24 hour creatinine clearance 12.1ml/min and disease

activity score(DAS)28-CRP was 3.3. Treatment with etanercept was started at a dose of 25mg subcutaneously injected weekly in September 2010. It was effective and DAS28(CRP3) became 2.8. The Etanercept is one of the good drug to treat RA with chronic renal failure.

P2-291

Influence of etanercept on preexisting ILD in patients with RA.

Shinichi Mizuki, Fumihiko Konishi, Naoko Ueki, Kazuo Kamada, Kensuke Oryoji, Eisuke Yokota
The Centre for Rheumatic Diseases, Matsuyama Red Cross Hospital, Ehime, Japan

(Objective) To examine the influence of etanercept on prognosis in rheumatoid arthritis (RA) patients with preexisting interstitial lung disease (ILD). (Patients and methods) All RA patients with ILD receiving etanercept at our hospital were registered in this retrospective study. Demographic data and radiographic findings were collected. (Results) Among 27 patients, 4 patients (14.8%) with a mean follow up period of 20 months developed exacerbation of ILD and 27 patients (85.2%) showed no progression. No significant differences were found for the baseline demographic characteristics and radiographic patterns between patients with and without progression of ILD. (Discussion) It is difficult to predict which patients will progress ILD in patients with RA after initiating etanercept therapy.

P2-292

etanercept monotherapy for rheumatoid arthritis with pneumoconiosis

Shinji Hirose
Yuujin Yamazaki Hospital

A 79 year old man was diagnosed as rheumatoid arthritis two years ago. He had been treated for pneumoconiosis for about 30 years. He had suffered from high disease activity of rheumatoid arthritis. He had past history of adverse event by using MTX. We decided to treat him with etanercept monotherapy. After 24 weeks since we started etanercept monotherapy, DAS28 (4CRP) was reduced from 6.15 to 2.63. He had achieved good response by EULAR criteria. No adverse event was occurred during the period of etanercept monotherapy.

P2-293

A case of successful pregnancy in RA patient treated with etanercept

Kanako Furukawa¹, Etsuko Maeshima^{1,2}, Masakazu Ichinose¹
¹Third Department of Internal Medicine, Wakayama Medical University School of Medicine, Wakayama, Japan, ²Department of Health and Sport Management, Osaka University of Health and Sport Sciences, Osaka, Japan

A 34 year-old woman was diagnosed as RA on 1999. The administration of bucillamine was started and afterwards she was remission. But many swollen and tender joints appeared. MTX was administered simultaneously and she was remission again. Although she was treated with two DMARDs, the disease activity such as CRP was elevated. She was treated with infliximab and the disease activity was promptly improved. The infliximab was changed to etanercept for the reason of hoping pregnancy. Next, MTX was discontinued. Her pregnancy was confirmed and she gave birth in October, 2010. There have been several reports about a case of successful

pregnancy in Japanese RA patient treated with etanercept. This report might provide useful data about the treatment in pregnancy of the patients with RA.

P2-294

Cases of etanercept administration in hepatitis virus (HV)-positive RA patients

Takao Takeuchi¹, Masahiro Hayaishi², Norikazu Murata², Yasuhiko Hamada²

¹Clinical Immunology and Rheumatology Center, Hayaishi Hospital, Osaka, Japan, ²Department of Orthopaedic Surgery, Hayaishi Hospital, Osaka, Japan

Biologics may be contraindicated or given carefully in HV-positive RA patients (pts); especially in HBV-positive RA pts both MTX etanercept (ETN) are contraindicated. However we administered MTX followed by concomitant ETN, then ETN alone to a pt w/ low HBV load having strong request for both drugs under fully informed consent. With no concomitant antiviral drugs such as lamivudine, DAS28-4ESR-defined remission is maintained by MTX ETN. We will continue to carefully monitor liver function & hepatitis relapse based on quantitative HBV-DNA. There are 3 other HCV-positive RA pts also on ETN due to same reason, in whom RA disease activity is controlled and no worsening of liver function is noted. Conclusion We will discuss on how to treat HV-positive RA through presentation of such cases.

P2-295

RA cases with DM that required alteration of insulin dose during ETN therapy

Yukie Saio, Tadako Ohhashi, Koutaro Nagai

Department of Rheumatology, Hashima Municipal Hospital

Background: Patients with RA sometimes suffer from DM. how anti-TNF α preparation affect pathophysiology of DM is uncertain. We report cases of ETN treated RA patients with DM showed decreased requirement of insulin dose. Clinical course: From July 2005, Inoret® 12U/day was used for DM therapy. From September 2009, the patient was controlled by MTX 6mg/week. However, activity of RA worse and ETN treatment was begun from January 2010. On October 2010, RA was reached to remission phase, and insulin dose decreased to 4U/day at the remission phase. We experienced another 2 similar cases. Discussion: The possible reasons of decreased insulin dose during ETN therapy is inhibited TNF α due to inhibitory effect of ETN for TNF α resulted in improved uptake of glucose to the cells, and so on.

P2-296

Occurrence of RA after the GM-CSF treatment for pulmonary alveolar proteinosis

Akira Okamoto¹, Tetsuji Kawamura²

¹Institute of Rheumatology, National Hospital Organization Himeji Medical Center, Hyogo, Japan, ²Institute of Respiratory Medicine, National Hospital Organization Himeji Medical Center, Hyogo, Japan

She felt dyspnea on exercise on 61 years old. She consulted the hospital and chest X ray showed the bilateral ground glass opacity. Bronchial fiber examination and increasing of anti-GM-CSF antibody revealed that she had a autoimmune pulmonary alveolar proteinosis (PAP). Treatment of PAP by inhale of GM-CSF was done, and her condition was improved. After 5 years later from treatment

of inhale of GM-CSF, she had many joints pain and dyspnea on exercise. We recognized chest X-P showed interstitial pneumonia and increasing titer of rheumatoid factor, anti-CCP antibody, and anti-nuclear antibody, which were not detected before medication of PAP. We diagnosed she was rheumatoid arthritis which was related with inhale of GM-CSF. Arthritis and interstitial pneumonia were improved.

P2-297

Effect of irbesartan on IMT in the patients of RA with hypertension

Yasue Shimogaki¹, Atsushi Kohno², Kenji Kohriyama³, Takao Takeuchi⁴

¹Immunity Plaza, Department of Rheumatology, Osaka Kaisei Hospital, Osaka, Japan, ²Department of Rheumatology, Osaka Kaisei Hospital, Osaka, Japan, ³Department of Rheumatology, Shin-Suma Hospital, Kobe, Japan, ⁴Clinical Immunology and Rheumatology Center, Hayaishi Hospital

Oral steroids for patients of connective tissue disease or rheumatoid arthritis often cause secondary hypertension and progress atherosclerosis. We reported that 100mg-irbesartan in daily to the 102 patients for 24weeks was possible to be anti-atherogenic by suppressing the IMT increasing on the last conference. After we have continued this trial for 52weeks, we recognized irbesartan was either effective and safety. Therefore irbesartan is supposed to be useful for patients of connective tissue disease or rheumatoid arthritis with hypertension

P2-298

A case of hereditary spherocytosis with HPS due to human parvovirus B19

Kyoko Takano, Michita Suzuki, Eiji Nagasawa, Masao Katayama
Division of Rheumatology, Department of Internal Medicine, Nagoya Medical Center, National Hospital Organization, Nagoya, Japan

A 36-year-old female visited our hospital on August 21, 2010 because of fever for 4days. At admission, she had hepatosplenomegaly, laboratory test indicated pancytopenia, hyperferritinemia and positive IgM for human parvovirus B19 (HPV-B19). Bone marrow aspiration revealed hemophagocytosis. She was diagnosed as hemophagocytic syndrome (HPS) associated with HPV-B19. The diagnosis of hereditary spherocytosis was made on the basis of presence of spherocytes on peripheral smear, increased osmotic fragility and auto-hemolysis test results. Treatment with 60mg of prednisolone improved clinical and laboratory findings. We describe a rare case of hereditary spherocytosis associated with HPS induced by HPV-B19.

P2-299

A case of intravascular lymphoma (IVL) occurred in rheumatoid arthritis

Yasutaka Kimoto, Shigeru Yoshizawa

Department of Rheumatology, National Health Organization Fukuoka Hospital, Fukuoka, Japan

A 65 year-old woman with RA had admitted to our hospital suffered from fever lasting a week. She was diagnosed RA 20 years ago. CRP and LDH were marked elevated. CT revealed a cavity on the right upper lung, and the sputum was Gaffky 2. Antibiotic agents failed to lowering the fever. No swollen lymph node was observed. Because of her myelogram showed haemophagocytosis, high dose

corticosteroid was administered, but there was no effect to the clinical status. PET scan showed increased FDG uptake in the spleen. On random skin biopsy, the capillary vessel in subcutaneous tissue was obstructed by CD20 positive atypical cells. The diagnosis of IVL was made. After chemotherapy started, she became afebrile and laboratory data were normalized. We report a rare case of RA complicated with IVL.

P2-300

Treatment of Histiocytic Necrotizing lymphadenitis by steroid pulse therapy

Tomoko Miyashita¹, Katsunobu Yoshioka²

¹Osaka City General Hospital, Osaka, Japan, ²Osaka City Sumiyoshi Hospital, Osaka, Japan

A 19-year-old woman was hospitalized with a 2-weeks history of fever and swelling of cervical lymph node. A diagnose of histiocytic necrotizing lymphadenitis (HNL) was made by lymphonode biopsy. She seemed distressed and coexistence of hemophagocytic syndrome was suspected. She received methylprednisolone pulse therapy (MPT) (0.5 g/day for 3 days) without maintenance therapy and experienced dramatic improvement. We also used MPT for another 12 cases of HNL. All patients became afebrile without adverse events. There is no standard therapy for HNL and a tapered regimen of oral prednisolone therapy is generally used empirically. However, such a regimen takes long duration to complete. We reason that MPT is effective for HNL because it's free of adverse event and duration of therapy is short.

P2-301

Two cases of Hypopituitarism associated with flexion contracture

Yoshiko Shimamura¹, Makoto Tsugita¹, Koji Ogata¹, Kosuke Inoue¹, Yoshinori Taniguchi¹, Toru Kagawa¹, Yoshitaka Kumon³, Yoshio Terada¹

¹Department of Endocrinology, Metabolism, and Nephrology, Kochi Medical School, Kochi University, Kochi, Japan, ²Health Care Center, Kochi University, Kochi, Japan, ³Department of Laboratory Medicine, Kochi Medical School, Kochi University, Kochi, Japan, ⁴Hosogi Hospital, Kochi, Japan

We experienced two cases of hypoadrenocorticism associated with severe flexion contracture. One patient was a 54-year-old woman who was found to have panhypopituitarism due to Sheehan's syndrome. Another patient was an 81-year-old woman with isolated ACTH deficiency of unknown etiology. In both cases, the clinical features were different from those of Stiff-person syndrome and arthritis on collagen disease, and the symptoms were markedly ameliorated several months after the start of glucocorticoid replacement, suggesting that the contracture was caused by glucocorticoid deficiency. Although very infrequent, flexion contracture can be one of the physical manifestations of hypoadrenocorticism.

P2-302

New Compounds for Collapsed Health Care System in Japan.

Kimihiko Nakata

Nagao Clinic, Amagasaki, Japan

The recent collapse of the health care system has posed a big problem in Japan. This collapse more seriously affects the patients with rheumatic diseases than the patients with fatal diseases. As new compounds for collapsed health care system, 2 methods are reported

here. The first method is home care service. In places where rheumatic care is insufficient, rheumatologists must enroll in these home care services. The second method involves dispatching part-time rheumatologists to the rural districts, where there are few experts in rheumatic diseases. A rheumatologist who visits once a month is favorably received by the patients, full-time doctors, and hospital staff in the countryside. These 2 methods of ensuring access to rheumatic care help reconstruct the health care system in Japan.

P2-303

Prevalence and risk factor for CKD in RA patients

Yoshinori Matsumoto, Ken-ei Sada, Mariko Takano, Noriko Toyota, Ryutaro Yamanaka, Koichi Sugiyama, Hiroshi Wakabayashi, Tomoko Kawabata, Hirofumi Makino
Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences

Background: Several previous reports have demonstrated an increased mortality attributable to renal disease in rheumatoid arthritis (RA). Objective: To estimate the prevalence of chronic kidney disease (CKD) and association between impaired renal function and several risk factors in outpatients with RA in Okayama University Hospital Methods: The prevalence of CKD in RA was assessed in cross-sectional study. Furthermore, association between decreased estimated glomerular filtration rate (eGFR) and several risk factors in retrospective analysis. Results: Of 419 patients, 101 patients (24.1%) were classified as CKD. Age, hypertension, and use of methotrexate are associated with decreased eGFR. Conclusion: CKD in RA is quite common. DMARDS may be risk factor for impaired renal function.

P2-304

An attempt to establish a clinical pathway to diagnose the cause of fever

Akitake Suzuki¹, Ryuichi Yokohari¹, Eigo Kikuchi¹, Kazuaki Uekubo¹, Naoko Aoki¹, Yoshinobu Ishiyama¹, Taro Yoshioka², Takahiro Okai¹

¹Division of Rheumatology, Department of Internal Medicine, Kawakita General Hospital, ²Department of orthopedics, Kawakita General Hospital

Objective: To establish a clinical pathway to diagnose the cause of fever. Methods: Admitted 32 patients with fever were analyzed in terms of final diagnosis and how long it took to establish diagnosis. A questionnaire was designed to ask nurses to reporting physical findings to identify the cause. Based on these, a calendar-type pathway was made. Results: Definite diagnoses were made in 31 patients and median time was 13 days. Six out of 31 cases could have been diagnosed earlier and physical findings which nurses thought were important were ambiguous. Taking these into account, we made 7 day-pathway with listed specific histories and physical findings. An Important outcome was defined as "establishing diagnosis". Conclusion: Shorter time to diagnosis could result by using this pathway.

P2-305

Mortality rate of 6 CVD patients of our department during past 5 years

Shigeki Makino, Shuzo Yoshida, Kenichiro Hata, Takuya Kotani, Koji Nagai, Daisuke Wakura, Kentaro Isoda, Tohru Takeuchi, Toshiaki Hanafusa

Background: We aim to evaluate mortality rates of 6 collagen vascular disease (CVD) of our department. **Methods:** We reviewed clinical data of 6 CVD (RA, SLE, SSc, DM/PM, angiitis, primary Sjogren syndrome (pSS)) patients including cause of death, during past 5 years (from 2005.4 to 2010.3). **Results:** Deceased patients of RA are 25 patients per 1287 person-years (PY)(mortality rate 1.9%), SLE 10 patients per 1027 PY (1.0%), SSc 15 per 1138 PY (1.9%), DM/PM 11 per 241 PY (4.6%), angiitis 16 per 342 PY (4.7%), pSS 1 per 409 PY (0.2%). The mortality rate is high for DM/PM and angiitis. The causes of death of 14/20 RA patients are pulmonary disease. **Conclusions:** Among 6 CVD, DM/PM and angiitis had high mortality rates. Concerning with cause of death, pulmonary disease is prominent in RA patients.

P2-306

Rheumatoid arthritis patient who treated by leukocytapheresis repeatedly

Michiaki Kageyama¹, Makio Kusaoi¹, Kaoru Sugimoto¹, Go Murayama¹, Misa Yasui¹, Risa Yamada¹, Keisuke Oda¹, Katsura Hohtatsu¹, Toshio Kawamoto¹, Shin Onuma¹, Takayuki Kon¹, Fumio Sekiya¹, Michihiro Ogasawara¹, Kazuo Kempe¹, Ken Yamaji¹, Hiroshi Tsuda², Yoshinari Takasaki¹

¹Department of Rheumatology, Juntendo University School of Medicine, Tokyo, Japan, ²Department of Geriatric General Medicine, Juntendo Tokyo Koto Geriatric Medical Center, Juntendo University School of Medicine

We report a case of 58-year-old woman with rheumatoid arthritis (RA). She was diagnosed as RA in November 2005 because of the presence of serum rheumatoid factor, polyarthritis, hand arthritis, morning stiffness and radiographic erosions in hand X-ray. We administered sulfasalazine 1000mg/day and non steroidal anti-inflammatory drugs but the drug rash was appeared within one month. So we started Leukocytapheresis (LCAP) therapy from January 2007 and her DAS28-CRP was improved from 5.46 to 4.07. Now she is treated by LCAP therapy at intervals of three months and its efficacy is maintained. We report the successful case of LCAP therapy for RA.

P2-307

Leukocytapheresis may reduce antigen processing and T cell activation in RA.

Makio Kusaoi¹, Go Murayama¹, Misa Yasui¹, Risa Yamada¹, Ruka Hishinuma¹, Takuya Nemoto¹, Katsura Hohtatsu¹, Keisuke Oda¹, Michiaki Kageyama¹, Toshio Kawamoto¹, Shin Onuma¹, Takayuki Kon¹, Kaoru Sugimoto¹, Fumio Sekiya¹, Michihiro Ogasawara¹, Kazuo Kempe¹, Ken Yamaji¹, Hiroshi Tsuda², Yoshinari Takasaki¹

¹Department of Rheumatology and Internal Medicine, Juntendo University School of Medicine, Tokyo, Japan, ²Department of Geriatric General Medicine, Juntendo Tokyo Koto Geriatric Medical Center, Juntendo University School of Medicine, Tokyo, Japan

Leukocytapheresis (LCAP) is a safety, effective therapy even for rheumatoid arthritis (RA) patients whom disease modifying anti-rheumatic drugs (DMARDs) or biologic agents cannot be used because of their side effects, but mechanisms of LCAP efficacy are still unclear. We performed DNA microarray analysis using peripheral blood samples collected just before and after LCAP treatment, from RA patients (n=16). We found some genes mRNA expression

related with T cell activation or antigen presenting decreased after LCAP therapy by using gene ontology (GO); T cell activation (GO: 0042110), antigen processing and presentation (GO:0019882, GO: 0002504). LCAP may reduce T cell activation and antigen processing reaction, these lead in part to efficacy mechanisms in LCAP for RA patients.

P2-308

A case of cryoglobulinemia with synovitis

Sho Sendo, Goh Tsuji, Shunichi Kumagai

Department of Rheumatic disease, Shinko Hospital, Kobe, Japan

[Case] The patient is 51-year-old female. At the age of 35, she couldn't exclude hepatic virus C (HCV), although she was treated by Interferon for chronic hepatitis C. She had livedo reticularis on her bilateral legs at the age of 41. In July 2010, She had polyarthritis for the first time. Her HCV-RNA titer was high and cryoglobulinemia was pointed. The bone change was not detected in X ray and the synovial fluid obtained from her left knee was not infectious and not crystalline, while cryoglobulin was detected in it. The synovectomy was underwent from her left knee joint. The synovial tissue specimen revealed non-specific inflammation. After the combination therapy of IFN and ribavirin her arthropathy was partially reduced.

P2-309

Two cases of acrodermatitis continua with inflammatory arthritis

Hiroshi Okuno¹, Akira Sekiguchi¹, Keiki Miura¹, Ken Ogura¹, Eiji Itoi¹, Ryuhei Okuyama²

¹Department of Orthopaedic Surgery, Tohoku University School of Medicine, Sendai, Japan, ²Department of Dermatology, Shinshu University School of Medicine, Matsumoto, Japan

Acrodermatitis continua is a related psoriasis, an inflammatory, chronic skin disease. In acrodermatitis continua, the exanthema is chiefly distributed to limbs end. We experienced 2 cases of acrodermatitis continua with inflammatory arthritis. [Case 1] 37 y/o male. The distal regions of digits showed edematous erythema with arthralgia. The nail plates showed whitish to yellowish discoloration with onycholysis. Oral cyclosporine improved the condition of nail plates, not arthralgia. [Case 2] 57 y/o female. The nail plates of big toes were white-cloudy and atrophic. Periungual skin had brownish erythema with mild edema. Arthralgia was located in digits, knees and ankle joints. The ODT of tacrolimus improved the nail deformity. Arthritis was resolved by oral salazosulapyridine.

P2-310

Two cases of palmar fasciitis and polyarthritis syndrome (PFPAS)

Kentaro Noda, Kenichiro Hirai, Taro Ukichi, Ken Yoshida, Isamu Kingetsu, Daitaro Kurosaka, Akio Yamada

Department of Rheumatology, The Jikei University School of Medicine, Tokyo, Japan

Palmar fasciitis and polyarthritis syndrome (PFPAS) is a rare disorder characterised by progressive flexor contractions of both hands, fasciitis and arthritis. We report two cases of PFPAS. Case1: A 77-year-old man presented with a 2-month history of a progressive contractures of the fingers of hand and polyarthralgia. His past history revealed a gastric carcinoma with lymph node metastases, treated 4 month earlier with surgical resection and chemotherapy. His symptoms improved after steroid therapy. Case2: A 76-year-

old man presented with a 2-month history of a digital stiffness, followed by contractures of the fingers of hand. Upper endoscopy and CT scan revealed a esophageal carcinoma with para-aortic lymph node metastasis. His symptoms did not improve after steroid therapy and radiation therapy.

P2-311

Hypertrophic osteoarthropathy is an uncommon cause of fever of unknown origin.

Rei Araki, Mikiko Shinozaki, Yasuhiro Katsumata, Eiichi Tanaka, Yasushi Kawaguchi, Hisashi Yamanaka
Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

We present a case of secondary HOA accompanied with remittent fever. The case indicates that HOA is a rare cause of fever of unknown origin. <Case report> 24-year-old male with cyanotic heart disease was referred with prolonged remittent fever and polyarthritis. Examination revealed digital clubbing of the fingers/toes. His polyarthritis involved his knees/ankles with bony tenderness of distal tibia/fibula. CRP was 6.49 mg/dl. Infectious/malignant disorders were excluded. Radiographs of lower legs showed periostitis. A radionuclide bone scan demonstrated increased tracer uptake along the fibulae/tibiae. The diagnosis of HOA associated with congenital heart disease was confirmed. He was treated with low dose glucocorticoid with nearly complete resolution of arthritis and pyrexia.

P2-312

Anti-CCP antibody (+) paraneoplastic polyarthritis associated with lung cancer

Takao Yamanaka¹, Yusuke Ota²

¹Department of Internal Medicine, National Hospital Organization Minami-Okayama Medical Center, Okayama, Japan, ²Department of Orthopedic Surgery, National Hospital Organization Minami-Okayama Medical Center, Okayama, Japan

A 62-year-old gentleman with good previous health referred to our hospital because of the continuous general fatigue, weight loss, and abnormal shadow on chest X-Ray. CT revealed a hypodense mass and infiltrative shadow in the left lobe of the lung, lymphadenopathy of hilum of left lung and mediastinum, and metastasis of adrenal gland and brain. CEA3794, CYFRA21.3. We diagnosed pulmonary lymphangitis carcinomatosa caused by lung poorly differentiated adenocarcinoma (Stage IV). After a second course of induction chemotherapy (CDDP+Docetaxel), the abrupt onset of symmetrical polyarthritis occurred. RF1214, AntiCCP \geq 100. We diagnosed lung cancer-associated polyarthritis. He was treated successfully with sulfasalazine (1.0 g) and PSL (10mg).

P2-313

Efficacy of alendronate for early stage of multicentric reticulohistiocytosis

Hitoshi Goto, Shinsuke Yamada, Keiji Okamoto, Koichiro Yoda, Maki Nishimura, Yasuo Imanishi, Masaaki Inaba
Rheumatology, Osaka City University Graduate School of Medicine, Osaka, Japan

Intravenous alendronate administration (IVALD) was tried to treat 2 cases of early stage multicentric reticulohistiocytosis (MRH). Case 1: 37yo female with polyarthritis and eruption on hands diagnosed with MRH treated unsuccessfully with MTX, anti-TNF, PDL,

visited our office. As X-ray showed arthritis mutilans, IVALD started. Skin lesion started regression a month later, then arthralgia and instability of joints disappeared three months later. Case 2: 30yo female with polyarthritis and eruption on fingers diagnosed with MRH visited our office for IVALD. X-ray showed no bone manifestation. Skin lesion started regression a month later, then arthralgia disappeared three months later. IVALD might be most successful treatment of early stage MRH to prevent progression of joint destruction.

P2-314

Two cases of psoriatic arthritis successfully treated with adalimumab.

Mayuko Sakamoto, Akinori Yamamoto, Yasufumi Shindo, Hiroshi Kajiyama, Yuji Akiyama, Toshihide Mimura
Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University

(Case 1) A 52-year-old man, diagnosed with psoriatic arthritis (PsA), was treated with infliximab (IFX) for 4 years, followed by adalimumab (ADA) due to secondary failure of IFX. Skin lesion and arthritis subsided. PASI (Psoriasis area and severity index) decreased to 3.7 from 29.5.

(Case 2) A 34-year-old man, diagnosed with RA 13 years ago, was treated with DMARDs, which were not effective. PsA was diagnosed with findings of skin biopsy and pencil-in-cap sign in DIP. ADA improved skin lesion, arthritis and bone proliferative lesion.

(Conclusion) We treated two PsA cases with ADA, revealing that ADA was effective to IFX-resistant PsA, and that ADA improved bone proliferative lesion in PsA.

P2-315

The treatment of positive anti-CCP antibodies arthritis with Infliximab

Hiroko Morise¹

¹Fukui Red Cross Hospital. Orthopaedic Surgeon, Fukui, Japan, ²Fukui Red Cross Hospital. Dermatologist, Fukui, Japan

We present 2 cases of psoriasis, accompanied with positive anti-cyclic citrullinated peptide (CCP) antibodies and arthritis, treated with infliximab (IFX). Case 1, The patient is a 49 year-old man. During followed-up psoriasis, he had polyarthritis and positive anti-CCP antibodies. He was treated with IFX. The DAS28 was improved and exanthema was recovered. Case 2, The patient is a 43 year-old man and anti-CCP antibodies was positive. As psoriatic arthritis (PsA) he was treated with MTX by pre-doctor. But arthritis wasn't improved, and we chose the IFX. But it wasn't effective, so we increased IFX dosage. In these cases, it was difficult to distinguish RA and PsA, because they had positive anti-CCP antibodies and severe polyarthritis. We want to research treatment of psoriasis combined with RA

P2-316

Three cases with psoriatic arthritis treated with adalimumab in our institute.

Hirofumi Takei, Koji Nishimura, Takahiko Kurasawa, Ayumi Okuyama, Eiko Nishi, Hayato Nagasawa, Koichi Amano
Department of Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan

Case 1: A 51-year-old man developed psoriatic arthritis (PsA) in Sep 1996. He had been treated with salazosulfapyridine, then MTX, which wasn't ineffective and infliximab (IFX) was added in Nov

2004. Because of the lack of efficacy, IFX was switched to adalimumab (ADA) in Oct 2008. His symptoms disappeared. Case 2: A 51-year-old man developed arthritis in Feb 2008. Combination therapy of MTX and ADA was started for his PsA in Sep 2009 and led to dramatic improvement. Case 3: A 68-year-old woman had been treated with PSL, MTX and actarit for MCTD + RA. Tocilizumab was introduced in July 2008 for her persistent arthritis but wasn't effective. Re-evaluation revealed she had PsA, and ADA was started in Jun 2010 with successful outcome. Conclusion: ADA was effective in 3 patients with PsA in our institute.

P2-317

A case of psoriatic arthritis associated with interstitial pneumonia

Takuro Ozaki, Shuzo Yoshida, Yohei Fujiki, Daisuke Wakura, Kentaro Isoda, Tohru Takeuchi, Shigeki Makino, Toshiaki Hanafusa
First Department of Internal medicine, Osaka medical college

A 51-year-old man admitted to our hospital because of exertional dyspnea in 1997. Chest CT showed interstitial pneumonia, and video-assisted thoracic biopsy showed the histological picture of usual interstitial pneumonia. He had noticed eruption of his trunk from the same time. He was diagnosed with psoriasis and treated with steroid was started. In December 2009, he admitted to our hospital because of polyarthritis and progressive dyspnea. He was diagnosed with psoriatic arthritis associated with interstitial pneumonia, and treated with cyclosporine (200 mg/day) and adalimumab (40 mg, every 2 weeks) with favorable response.

P2-318

Case of Churg-Strauss syndrome presenting with pulmonary hemorrhage

Chisako Suzuki, Yui Shimizu, Tetsuya Tabeya, Hidetaka Yajima, Mikiko Obara, Motohisa Yamamoto, Yasuyoshi Naishiro, Hiroyuki Yamamoto, Toshiaki Sugaya, Hiroki Takahashi, Yasuhisa Shinomura

First Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan

Objective. We report three cases of Churg-Strauss syndrome (CSS) presenting with pulmonary hemorrhage (PH) and their clinical characteristics. **Result.** Case 1: A 51-year-old woman with 2-months history of CSS undertook steroid pulse therapy (IVMP) and plasma exchange (PE) for the treatment of PH. Finally she died of respiratory failure. Case 2: A 19-year-old woman was diagnosed as CSS with glomerulonephritis. Although she relapsed with PH, IVMP promptly improved her condition. Case 3: A 48-year-old woman suddenly developed PH, brain hemorrhage and myocardial failure due to CSS. IVMP and PE were effective for PH. **Conclusion.** PH in CSS was successfully treated with steroid therapy including IVMP except for the fetal case complicated with gastrointestinal tract involvement and cardiac disease.

P2-319

A case of CSS associated with 8th cranial neuritis treated by IVIG

Akihiro Tanaka¹, Yoshio Ozaki¹, Keiko Shimamoto¹, Hideki Amuro¹, Katsuyuki Kawakami¹, Yonsu Son¹, Tomoki Ito¹, Shosaku Nomura¹

¹First Department of Internal Medicine, Kansai Medical University, Moriguchi, Japan, ²Department of Otorhinolaryngology, Kansai Medical University, Moriguchi, Japan

A 52 years old woman who had been treated with prednisolone for Churg-Strauss syndrome (CSS) were admitted to our hospital because of her auditory disturbance and dizziness. She had lateral nystagmus, perceptive deafness of both ears, and eosinophilia (3844/ μ l). She was diagnosed as the eighth cranial neuritis according to the exacerbation of CSS, and a large amount of steroid were administered. However, her eosinophilia showed exacerbation with the steroid tapering. Intravenous immunoglobulin infusion therapy (IVIG) was used to treat her cranial. After IVIG, her auditory disturbance and dizziness have been remarkably improved. It has been reported that IVIG is effective in the peripheral neuropathy. This treatment may be expected to be effective in the cranial nerve disorder.

P2-320

Small-intestinal perforation in steroid-treated allergic granulomatous angitis

Ruka Hishinuma¹, Keigo Ikeda¹, Yoshinari Takasaki², Iwao Sekigawa¹

¹Department of Rheumatology and Internal Medicine, Juntendo University Urayasu Hospital, Chiba, Japan, ²Department of Rheumatology and Internal Medicine, School of Medicine, Juntendo University, Tokyo, Japan

Allergic granulomatous angitis (AGA) is a disorder characterized by extravascular granulomas, hypereosinophilia, and pulmonary and systemic small-vessel vasculitis. This case firstly showed short duration onset of bilateral severe peroneal neuropathy and gait disturbance. After admission, AGA was diagnosed and high-dose steroid therapy was initiated. Any symptoms were improved immediately. However, small-intestinal perforation was occurred without any warning sign after steroid therapy. Small-intestinal resection was performed and multiple small-intestinal ulcers by AGA were recognized in the pathological tissue. This case showed that patients with AGA are having possibility to involve small-intestinal perforation although steroid therapy was successful for improving any symptoms of AGA.

P2-321

A successful treatment of IVIG therapy for peripheral neuropathy with AGA

Hideyuki Shiba, Takuya Kotani, Kentaro Isoda, Koji Nagai, Daisuke Wakura, Kenichiro Hata, Shuzo Yoshida, Tohru Takeuchi, Shigeki Makino, Toshiaki Hanafusa

First Department of Internal Medicine, Osaka Medical College, Osaka, Japan

A 46 years old man with bronchial asthma in 2005, was diagnosed as allergic granulomatous angitis by eosinophilia, the elevation of CRP, asthma in the past, and peripheral neuropathy. Prednisolone (55mg/day) and azathioprine (25mg/day) therapy administered, the eosinophil count and CRP were improved and prednisolone was tapered to 10mg/day. But the weakness and sensory disorder of his bilateral lower legs were remained, 2 courses of high dose γ -globulin (25 g \times 5 days) were initiated in May 31, 2010. As a result, the weakness of his bilateral lower legs were improved (MMT; bilateral hamstring 4 \rightarrow 5, right tibialis posterior muscle 3 \rightarrow 4, left tibialis posterior muscle 3 \rightarrow 5), the modified barthel index(MBI) and the

visual analogue score(VAS) were also improved (MBI: 89→90,VAS72→40).

P2-322

Successful treatment with intravenous immunoglobulin in a patient with CSS

Akiko Idemoto, Tomoya Miyamura

National Hospital Organization Kyusyu Medical Center

A 75-year-old-man was diagnosed with Churg-Strauss syndrome (CSS) because of eosinophilia ,elevated of IgE,mononeuritis multiplex,interstitial pneumonia and renal dysfunction. He was treated with high dose of prednisolone (PSL) and intravenous cyclophosphamide pulse therapy. His symptoms and laboratory data markedly improved. The dose of PSL was decreased gradually in an outpatient setting. In April 2010,he had suffered worsening of numbness in his face and legs and serum CRP level elevated, suggesting an exacerbation of CSS.Administration of intravenous immunoglobulin (IVIg) (20g/body×5days) was started and good disease control was achieved.IVIg may be useful to an exacerbation of inflammation as well as peripheral neuropathy in steroid resistant CSS patients.

P2-323

A case of Wegener's granulomatosis complicated with diabetes insipidus

Kanae Masubuchi, Kentaro Noda, Kenichiro Hirai, Taro Ukichi, Ken Yoshida, Isamu Kingetsu, Daitaro Kurosaka, Akio Yamada

Department of Rheumatology, The Jikei University School of Medicine,Tokyo, Japan

A 22-year-old woman was diagnosed as crescentic glomerulonephritis in August 2009,and was treated by prednisolone. In April 2010, she complained polydipsia and polyuria. She also developed hearing loss, nasal stuffiness and headache in July 2010, and so was referred to our hospital. Nasal biopsy revealed Wegener's granulomatosis (WG). Brain MRI scanning revealed a enlarged pituitary gland, a thickened stalk, and a loss of posterior pituitary bright spot. A water deprivation test and DDAVP loading test showed central diabetes insipidus (DI). We started prednisone and cyclophosphamide treatment. Hearing loss recovered rapidly. But diabetes insipidus didn't recover. WG-related DI is rare and intractable. We report this case with a review of the literature.

P2-324

Two cases of MPO-ANCA positive Wegener's granulomatosis with hearing loss

Maiko Okumura, Koichiro Shinoda, Hiroyuki Hounoki, Reina Ogawa, Hirofumi Taki, Kazuyuki Tobe

First Department of Internal Medicine, University of Toyama, Toyama, Japan

We report two cases (Case 1: 80-year-old woman, Case 2: 66-year-old man) of Wegener's granulomatosis (WG) with hearing loss as an initial manifestation. They presented with a 2-months history of hearing loss and fever. Antibiotics treatments were ineffective and they admitted to our hospital. They were positive for MPO-ANCA. Head CT showed thickenings of mucosa in the nasal sinus and mastoid cavities. Chest CT revealed nodules and cavity formation. Case 1 also had tubulointerstitial nephritis, and Case 2 developed RPGN requiring hemodialysis. They were treated with steroid pulse therapy (followed by cyclophosphamide pulse therapy in a case of

Case 2). Since early diagnosis of WG is important, physicians should be aware that febrile hearing loss might be an initial manifestation of WG.

P2-325

A case of Wegener glaucomatosis complicated with intestinal involvement

Yohei Fujiki, Shuzo Yoshida, Ayaka Honjo, Takuro Ozaki, Tohru Takeuchi, Shigeki Makino, Toshiaki Hanafusa

First Department of Internal Medicine, Osaka Medical College, Osaka, Japan

30-year-old man admitted to our hospital because of fever, diarrhea, throat pain and oral ulcers. Laboratory findings showed elevated CRP (21.39 mg/dl) and positive PR3-ANCA with normal renal function. Head CT showed sinusitis. Colonoscopy showed mild edema of the mucosa and spontaneous bleeding. A biopsy specimen of the oral ulcer showed necrotizing granuloma. He was diagnosed with Wegener granulomatosis (WG) and treated with prednisolone (65mg/day) and azathioprine (75 mg/day) with improvement of his symptoms and laboratory findings. We report a rare complication of intestinal involvement in WG.

P2-326

A case of Wegener's granulomatosis beginning with cerebral bleeding

Hirokazu Takaoka¹, Atsushi Hashimoto¹, Shinichi Nogi¹, Kanako Iwata¹, Hidekazu Futami¹, Yoshiyuki Arinuma¹, Akiko Komiya¹, Hisanori Nakayama¹, Hiroshi Furukawa², Toshihiro Matsui¹, Shigeto Tohma²

¹Department of Rheumatology, Sagamihara National Hospital, National Hospital Organization, Sagamihara, Japan, ²Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, National Hospital Organization, Sagamihara, Japan

A 46-year-old man had bilateral omalgia accompanied by inability to elevate the upper extremities. He was diagnosed for right thalamic bleeding by CT scan and hospitalized for one month. Four months later, petechiae appeared on his lower extremities and omalgia and gonalgia gradually deteriorated. Two months later, he developed vertigo and tinnitus with vomiting. Since CT showed abnormalities in the lung, physician suspected pneumonia and started antibiotics, but his symptoms did not improve. Therefore, he was hospitalized in our hospital. He developed right deafness, sinusitis, hemoptysis, hematuria, proteinuria, and showed seropositivity of PR3-ANCA, and was diagnosed for Wegener's granulomatosis (WG). This is a rare case of WG beginning with cerebral bleeding.

P2-327

A case of aortitis syndrome diagnosed with PET-CT and MRI in the initial stage

Yoshimasa Hamano, Masayuki Nishide, U Rin, Takashi Hosokawa, Hideko Nakahara, Shinji Higa, Taro Kuritani, Tsuyoshi Igarashi, Keiji Maeda

NTT West Osaka Hospital, Osaka, Japan

A 45-year-old female was referred with fever of unknown origin. She presented with exertional dyspnea, cough, headache and arthralgia, and elevated inflammatory markers. 18F-fluoro-deoxy-glucose positron emission tomography (FDG-PET)/CT showed increased FDG uptake in the pulmonary trunk and ascending part of

aorta, and magnetic resonance imaging (MRI) demonstrated thickened arterial wall and inflammatory changes, which suggested aortitis syndrome and 30mg/day of prednisolone (PSL) was introduced. Within two weeks symptoms had improved and laboratory data was normalized. Some patients with aortitis syndrome have non-specific symptoms at an initial stage and proper diagnosis with FDG-PET/CT and MRI allow early treatment.

P2-328

A case of aortitis syndrome which occurred on 81 years old

Shinsuke Yamada, Hitoshi Goto, Keiji Okamoto, Koichiro Yoda, Maki Nishimura, Yasuo Imanishi, Masaaki Inaba
Department of Rheumatology, Osaka City University School of medicine, Osaka, Japan

A-81-years-old female suffered from headache, neck pain, general fatigue, and high grade fever in 9 months. She was diagnosed aortitis syndrome by FDG-PET which showed up takes around aorta. Steroid therapy led to improvement in all symptoms.

P2-329

A case of Takayasu's arteritis complicated with uveitis as an initial sign

Kensuke Irino¹, Taiichiro Miyashita¹, Yasumori Izumi¹, Atsushi Kawakami⁴, Katsumi Eguchi⁵, Kiyoshi Migita³

¹Rheumatology and General Internal Medicine, NHO Nagasaki Medical Center, Omura, Japan, ²Radiology, NHO Nagasaki Medical Center, Omura, Japan, ³Clinical Research Center, NHO Nagasaki Medical Center, Omura, Japan, ⁴The First Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan, ⁵Rheumatology, Sasebo Municipal Hospital, Sasebo, Japan

A 33 year-old male was admitted to our hospital because of further examination of uveitis. He noticed arthralgia and low-grade fever 3 months ago, accompanying with easy fatigability of left upper arm. Furthermore, blurred vision and floaters of the left eye appeared one month before admission, which was diagnosed with uveitis in the eye. FDG-PET/CT revealed FDG accumulation in the left subclavian artery, and its occlusion were observed in contrast enhanced CT. Because clinical findings suggesting Behcet's disease was not found, diagnosis of Takayasu's arteritis was made. Clinical symptoms were quickly subsided after oral prednisolone 40mg/day was started. Male cases of non-Behcet's aortitis, especially complicated with uveitis as an initial manifestation, seem to be extremely rare.

P2-330

Comprehensive analyses of serum peptides in microscopic polyangiitis

Yukiko Takakuwa^{1,2}, Manae S. Kurokawa^{2,3}, Seido Ooka¹, Kouhei Nagai², Mitsumi Arito², Kazuki Okamoto², Hiroko Nagafuchi^{1,3}, Wako Yumura³, Kunihiro Yamagata³, Shunichi Kumagai³, Akihiro Ishizu³, Machi Suka³, Hidehiro Yanada^{1,3}, Shoichi Ozaki^{1,3}, Tomohiro Kato^{2,3}

¹Division of Rheumatology and Allergy, Department of Internal Medicine, St. Marianna University School of Medicine, ²Clinical Proteomics and Molecular Medicine, St. Marianna University Graduate School of Medicine, ³Japanese study group for MPO-ANCA-associated vasculitis, JMAAV

[Objective] To identify biomarkers of microscopic polyangiitis (MPA), we explored serum peptidome. [Methods] Serum peptides

from 33 patients with MPA, 20 with the other systemic vasculitis (oSV) and 25 with SLE were comprehensively analyzed by mass spectrometry. Peptide function was examined by ELISA and real-time PCR. [Results] One of the peptides, p1523, showed significantly higher ion intensity in MPA than that in oSV and SLE. p1523 was identified as C-terminal 13 amino acid residues of apolipoprotein A-I (AC13). Stimulation of human microvascular endothelial cells with AC13 significantly upregulated IL-6 and IL-8 secretion. [Conclusion] AC13 is a candidate biomarker for MPA, and may exacerbate the local vascular inflammation through upregulation of the proinflammatory cytokines.

P2-331

The effect of remission maintenance by CDAI in RA patients with Tocilizumab

Hiroshi Sawano
Shimizu Welfare Hospital

Objective: To evaluate the effect of remission maintenance by CDAI in RA patients with Tocilizumab (TCZ) under the real world. Methods: In two sites, we investigated 52 of 101 patients that had become remission with TCZ treatment. Results: 52 patients became the remission on 12 weeks (mean), and continued during 20 weeks (mean). 29 of 52 patients had been maintaining the remission, but others were not so. The main reason why the remission is not continued is an increase of TJC. 6 of 23 patients became the remission again, but others were maintained by the low disease activity. Conclusion: We were suggested that remission rate by TCZ treatment was high, and is able to maintain it.

P2-332

Achievement and maintenance of clinical remission in RA treatment with TCZ.

Sumito Kawamura¹, Michio Minami², Koji Suzuki², Yasuhiko Nishio²

¹Department of Orthopaedic Surgery and Center for Rheumatology and Arthroplasty, Kobayashi Hospital, Kitami, Hokkaido, Japan,

²Department of Rheumatology, Hokkaido Orthopaedic Memorial Hospital, Sapporo, Hokkaido, Japan

For 47 RA patients with 5.35 in av. DAS and 7.6 years in av. disease duration, the clinical remissions of TCZ treatment were analyzed by DAS 28-ESR and EULAR criteria improvements. At 24 weeks, good response was in 61.5% and moderate in 30.8%. TCZ treatment could be continued in 95%. There was no discontinuation due to side effects. TCZ was highly effective in response, continuation-rate and safety.

P2-333

Predictive factors for efficacy in tocilizumab therapy in rheumatoid arthritis

Hajime Miyazato, Mamoru Kanazawa, Toshifumi Kawakami, Kenji Kido, Makoto Kubo, Hiroshi Tanaka, Yasuhiro Tamimoto, Takeshi Tokito, Atsunori Tokushige, Kimio Nibu, Noriyuki Miyazaki, Kenji Yamamoto, Manabu Yamamoto, Toshiko Watada, Shinji Fukuta, Toshihiko Taguchi
Yamaguchi IL-6 Meeting

Objective: To study factors contributing to the achievement of remission at 48 weeks in rheumatoid arthritis (RA) patients receiving tocilizumab (TCZ). Subjects and methods: The subjects were 46 patients who could be observed for at least 48 weeks. The mean

age was 61.0 years, and the mean duration of illness was 10.1 years; 69.5% of the patients were concomitantly receiving MTX and 82.6% were concomitantly receiving PSL. **Results:** The number of tender joints ($p = 0.0302$) and the presence or absence of PSL therapy ($p = 0.0473$) at baseline were identified as factors contributing to remission at 48 weeks. **Conclusions:** TCZ treatment for RA results in a higher rate of remission in patients with fewer tender joints at baseline and in patients not using PSL at baseline.

P2-334

A case of congenital sideroblastic anemia exacerbated during TCZ therapy for RA

Sho Ueda^{1,2}, Kentaro To¹, Hiroshi Tsukamoto¹, Hiroaki Niino¹, Yojiro Arinobu^{1,2}, Yasushi Inoue¹, Masahiro Ayano¹, Ayako Takagi¹, Satomi Hisamoto¹, Takahiko Horiuchi¹, Koichi Akashi^{1,2}

¹Department of Clinical Immunology, Rheumatology, and Infectious diseases, Kyushu University Hospital, Fukuoka, Japan, ²Center for Cellular and Molecular Medicine, Kyushu University Hospital, Fukuoka, Japan

A 31-year old female with congenital sideroblastic anemia (CSA), treated with Vit.B6, folic acid, and Vit. B12, developed RA which was resistant to MTX, tacrolimus, TNF inhibitor. The arthritis was significantly improved with TCZ therapy, however, the anemia progressed at the time of 5th administration of TCZ. Laboratory findings showed increased levels of serum ferritin, Fe, and decreased number of reticulocyte, suggesting the exacerbation of ineffective erythropoiesis. Bone marrow examination revealed a decreased number of erythroblast that was mostly (96%) consisted of sideroblast. TCZ therapy discontinued, followed by red blood cell transfusions and iron chelate. CSA was improved after 3 months from last administration of TCZ. TCZ might be associated with the exacerbation of CSA.

P2-335

Lymphoma in a patient with RA treated with infliximab followed by tocilizumab

Yumi Sasae, Hiroyasu Hirano, Akiko Yoshida, Takeo Sakuta, Yoshitaka Morita

Department of Rheumatology, Kawasaki Medical School Hospital, Okayama, Japan

We report the case of a 68-year-old female with rheumatoid arthritis who developed lymphoma. She had received infliximab (IFX) and MTX for 4 years, and presented with general fatigue with severe liver dysfunction in March 2008. Enhanced CT scans of the liver showed no abnormality. Since discontinuation of IFX and MTX improved her liver dysfunction, treatment with tocilizumab (TCZ) was initiated in July 2008. However, she developed high fever with recurrence of liver dysfunction in September 2009. The CT scans showed multiple low density areas in liver and spleen, and biopsy revealed a diagnosis of EBV-associated Hodgkin lymphoma. Administration of IFX and MTX possibly contributed to re-activation of EBV and progression of lymphoma in our case, and TCZ may have masked the systemic symptom.

P2-336

A case of diverticular perforation during tocilizumab therapy

Mariko Sato, Mayuko Moriyama, Yoshiko Sumita, Masahiro Kondo, Yohko Murakawa

Department of Rheumatology, Faculty of Medicine, Shimane University

A 64-year-old man was diagnosed with rheumatoid arthritis and treated with methotrexate (MTX) 8mg/wk in September 2009. Because of resistance to MTX, tocilizumab (TCZ) therapy was started in February 2010. He started feeling left lower abdominal pain 24 days after the initiation of TCZ therapy. He also had fever and diarrhea the next day. Physical examination showed abdominal rebound tenderness in the lower and upper left quadrants. Laboratory data showed that CRP was 36.8 mg/dl. Computed tomography revealed free air in abdomen, suggesting gastrointestinal (GI) perforation. Exploratory laparotomy showed diverticular perforation in the descending colon, and diverticulectomy was performed. There are a few reports of GI perforation due to TCZ treatment, which all physicians should be aware of.

P2-337

A case of RA who got bleeding from colon after primary no effect with Tocilizumab

Shintaro Tsuge¹, Arata Nakajima¹, Koichi Nakagawa¹, Masato Sonobe¹, Yoshifumi Shibata¹, Yasuchika Aoki¹, Yu Sasaki¹, Manabu Fujino¹, Teruo Furufu¹, Toru Suguro²

¹Department of Orthopedic Surgery, Toho University Sakura Medical Center, ²Department of Orthopedic Surgery, Toho University Omori Medical Center

[Introduction] Perforation of intestine is one of serious side effects caused by TCZ, however, its incidence rate is not known. We report an RA patient who got bleeding from diverticula of colon soon after primary no effect with TCZ. [Case: 53yrs, male] He has a history of DM but has not been treated continuously. He was diagnosed as RA three years ago and has been treated with 8mg of MTX per week. As he showed moderate disease activity with 4.4 of DAS28, TCZ was introduced him. Following the 2nd administration, however, he was determined as primary no effect with TCZ. Eleven days after the 2nd administration, he suddenly got in a shock state due to melaena. Colonfiberscopy revealed bleeding from diverticula of colon. Currently, we are treating him with 10mg of MTX and no biologics.

P2-338

A case of high KL-6 level after treatment with tocilizumab.

Chisa Okura, Koichi Okamura, Yukio Yonemoto, Tsutomu Kobayashi, Tsuyoshi Ichinose, Tetsuya Kaneko, Kenji Takagishi
Department of Orthopaedic Surgery, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan

We report a 65-year-old woman treated with Tocilizumab (TCZ), who got high KL-6 levels, but interstitial pneumonia did not happen. She was diagnosed as RA in 2001. She visited our hospital in 2002. Nevertheless MTX was started from 2004, high disease activity was continued. So, IFX (3mg/Kg) was added from October 2008 to April 2009. Treatment with IFX gave no effect on this patient, we administered TCZ (8mg/Kg) May 2009. After treatment with TCZ, KL-6 rose temporarily, but no changes in chest plain x-ray and CT. We also identified no malignant lesion in FDG-PET/CT. The value of KL-6 was below; before treatment 482, 8 weeks later 1512, 12 weeks later 1406, 15 months later 439U/ml. She achieved clinical remission 6 months after treatment with TCZ and the remission has been maintained.

P2-339

A case report of thrombopenia with tocilizumab therapy

Tomoaki Yoshikawa¹, Mamoru Matsumoto¹, Toru Yamakawa¹, Satoshi Hosoi²

¹Department of Orthopedic Surgery, Yamada Red Cross Hospital, Mie, Japan, ²Suzuka University of Medical Science

It has been reported that Tocilizumab (TCZ) improved curative effects on RA which any TNF blockers were not effective on. This paper is a case report that TCZ achieved full curative effect on a secondary failure case with Infliximab (IFX), but induced thrombopenia (TP). A 59 years old RA woman for 16 years (stage III, class II), began to be treated with IFX 2 years ago, and achieved moderate response. But, secondary failure was appeared and DAS28-ESR were not improved despite IFX dose was increased. Although DAS28 was improved by exchange into TCZ, the platelet count was seriously decreased. The TP was not completely improved despite withdrawal of TCZ. These results suggested that the TP induced by TCZ was not easily improved, and that TCZ must be carefully readministered.

P2-340

Necrotizing fasciitis developing during anti-IL6 therapy of rheumatoid arthritis

Akiko Yoshida, Yumi Sasae, Hiroyasu Hirano, Takeo Sakuta, Yoshitaka Morita

Department of Rheumatology, Kawasaki Medical School Hospital, Okayama, Japan

Skin infections are some of the most common complications in patients with rheumatoid arthritis, but necrotizing fasciitis is rarely seen. We report the case of a 65-year-old woman with this infection during treatment with tocilizumab (TCZ). Blood tests showed neutrophil cell counts of 2,680/ μ l before the initiation of TCZ, and 1,050/ μ l at the 12th administration. Two weeks after the 12th infusion, she presented with swelling of her left forearm with purpura. Laboratory tests showed neutrophils 4,982/ μ l and CRP<0.03 mg/dl. Shortly after admission, she developed septic shock. She was diagnosed as having a necrotizing fasciitis and emergency debridement of the left forearm was performed. Neutropenia should be considered as a risk factor of severe bacterial infection during treatment with TCZ.

P2-341

TCZ is efficacious in RA patients regardless of the number of previous TNFi

Keisuke Izumi, Yuko Kaneko, Hidekata Yasuoka, Noriyuki Seta, Hideto Kameda, Masataka Kuwana, Tsutomu Takeuchi

Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

AIM: To elucidate efficacy and safety of tocilizumab (TCZ) in patients with RA stratified according to the number of previous TNF inhibitors (TNFi). **METHODS:** We examined clinical backgrounds of RA patients treated with TCZ and prospectively evaluated its efficacy 24 weeks after its initiation. **RESULTS:** Of 38 patients, 13 were previously treated without TNFi, 16 with one TNFi (infliximab (IFX):2, etanercept (ETN):5, adalimumab (ADA):1), and 9 with two TNFi (IFX+ETN:4, IFX+ADA:2, ETN+ADA:3). The proportion of patients achieving remission at week 24 with no, one and two previous TNFi were 63%, 57% and 63%, respectively. Three ceased TCZ due to adverse events (one TNFi: 2 cases, two TNFi: 1 case). **CON-**

CLUSION: TCZ is an efficacious and safe treatment for RA regardless of the number of previous TNFi.

P2-342

The working status of RA patients with or without biologics use in IORRA cohort

Daisuke Hoshi¹, Eiichi Tanaka¹, Ataru Igarashi², Eisuke Inoue¹, Kentaro Kikuta², Ayako Nakajima¹, Shigeki Momohara¹, Atsuo Taniguchi¹, Kiichiro Tsutani², Hisashi Yamanaka¹

¹Institute of Rheumatology Tokyo Women's Medical University,

²Graduate School of Pharmaceutical Sciences, The University of Tokyo

[Purpose and Methods] To examine the working status of RA patients who were treated with biologics (Bio) for at least 6 months (user group: n=211) or without Bio (non-user group: n=4,243) in IORRA. **[Results]** In the user/non-user group: mean age 53.5/60.5 y.o., Female 89/84%, RA disease duration 13.0/13.6 years, DAS28 3.31/3.21, J-HAQ 1.03/0.69, EQ-5D 0.72/0.78 at baseline. The percentages of maintaining working status at RA onset, reduced working hours due to RA, quitted job due to RA in the past and full-time employees at present in the user and non-user group were 23.0% and 34.4%, 19.5% and 8.9%, 15.5% and 8.0% and 54.1% and 46.5%, respectively. **[Conclusion]** Although Bio users tend to reduce working hours and quit job in the past, they might be able to work at present as non-Bio users.

P2-343

Analysis of RA therapy and disease activity classified by the disease duration

Toshihiro Matsui^{1,3}, Shigeto Tohma^{2,3}

¹Department of Rheumatology, Sagami National Hospital, National Hospital Organization, Kanagawa, Japan, ²Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami National Hospital, National Hospital Organization, Kanagawa, Japan, ³iR-net

[Aim] To compare the medication and disease activity of RA patients between the groups classified by disease duration. **[Patients]** 7085 RA patients (5817 females, 82.1%) registered in NinJa 2009 were analysed. **[Results]** In all patients, mean DAS28-ESR was 3.58 and remission rate was 24.2%. DAS28 (3.24) and remission (35.5%) were best in the group of "disease duration 2-4 yrs" and they became worse as disease duration increased. However, in the group of "<2 yrs", disease control was not well (DAS28:3.84, remission: 22.5%) and the frequency taking DMARD (80.0%), MTX (55.4%), and Biologics (8.5%) were less than averages of total patients (87.5%, 55.4%, 17.5%, respectively). **[Conclusion]** Our study indicates that disease control of recent-onset RA patients is not enough under the present state.

P2-344

With Tocilizumab, 123 RA patients validity study in multicenter research group

Yuichiro Yabe¹, Atsushi Kaneko², Tomone Shioura³, Kiwamu Saito², Nobuyuki Asai⁴, Tomonori Kobayakawa⁵, Hisato Ishikawa⁶, Toshihisa Kojima⁷, Naoki Ishiguro⁷

¹Department of Rheumatology, Tokyo Kosei Nenkin Hospital, Shinjuku, Tokyo, Japan, ²Department of Orthopedics and Rheumatology, Nagoya Medical Center, Nagoya, Aichi, Japan, ³Department of Rheumatology, Shizuoka Kousei Hospital, Shizuoka, Japan, ⁴Department of Orthopedics, Nakatsugawa Municipal General Hospital,

Nakatsugawa, Gifu, Japan, ⁵Department of Orthopedics, Toyohashi Municipal General Hospital, Toyohashi, Aichi, Japan, ⁶Department of Orthopedics and Rheumatology, Nagano red cross Hospital, Nagano, Japan, ⁷Department of Orthopedics and Rheumatology, Nagoya University, Nagaya, Aichi, Japan

Purpose: multicenter study on continuity and effectiveness for Tocilizumab (TCZ). Target: 123 RA patients with TCZ among biological drug treatment group (Tsurumi Biologics Communication). Method: after 12 months, continuation rate and effectiveness were studied between bio naive and not, also between combination with MTX and without. Result: for all example, continuation rate, 85.4%, DAS28ESR (4), 3.01(←5.80), rate of low disease activity (LDA) and remission was 66.9%. For continuation rate, DAS28, LDA and remission rate, there was no difference between bio naive and not. Although no difference about continuation rate, but MTX combined group DAS28, 2.50, is low ($p=0.0048$), LDA and remission rate, 85.1%, was high ($p=0.0004$). Study: TCZ treated with MTX could achieve higher treatment goals.

P2-345

Analysis of indirect cost for RA patients using large cohort database, IORRA

Ataru Igarashi¹, Kentaro Kikuta¹, Eiichi Tanaka², Daisuke Hoshi², Shigeki Momohara², Atsuo Taniguchi², Ayako Nakajima², Hisashi Yamanaka², Kiichiro Tsutani¹

¹Dept. of Drug Policy & Management, Graduate School of Pharmaceutical Sciences, The University of Tokyo, ²Institute of Rheumatology Tokyo Women's Medical University

Objective: To examine annual indirect cost in an IORRA cohort of RA patients in Japan.

Methods: We calculated indirect of RA patients, participants of the 17th IORRA Studies in Oct. 2008. We also assessed correlations between these costs and QOL.

Results: Data from 5284 RA patients were extracted. Due to RA, 18.7% of those cut down their work and 15.8% of those are retired. Annual indirect costs, including occasional absence from work due to exacerbation and burden for house work were JPY760,000. These costs increased progressively with worsening QOL, from JPY480,000 to 1,910,000.

Conclusions: QOL score has strong influences on indirect cost of RA patients. The results also suggest that the increase in non-medical cost may be suppressed by proactively controlling RA.

P2-346

Quality of Life assessment in the patients with rheumatic diseases

Kei Ikeda, Hironori Kawashima, Kentaro Takahashi, Yukiko Hiramatsu, Masaya Yokota, Arifumi Iwata, Daisuke Kashiwakuma, Hidefumi Wakashin, Hiroaki Takatori, Akira Suto, Shin-Ichiro Kagami, Kotaro Suzuki, Koichi Hirose, Norihiko Watanabe, Hiroshi Nakajima

Department of Allergy and Clinical Immunology, Chiba University Hospital, Chiba, Japan

[Purpose] Quality of Life (QoL) is an important outcome in the management of rheumatic diseases. The purpose of this study is to elucidate the correlation between disease pathophysiology and components of QoL index. [Methods] QoL was evaluated with SF-36 in 1019 outpatients and the correlations with patient characteristics, diagnoses, and laboratory results were assessed. [Results] Physical

summary score was decreased in patients with polymyositis, microscopic polyangitis, scleroderma, and rheumatoid arthritis (NBS (Norm-Based Score): 27.0, 34.3, 37.6, and 36.8, respectively) and mental summary score was decreased in Takayasu arteritis (NBS: 42.4). [Conclusion] Disease specific factors need to be taken into account in the assessment of QoL in rheumatic diseases.

P2-347

Patient-Physician discordance in assessment of global disease severity in RA

Yuko Kaneko, Masataka Kuwana, Hidekata Yasuoka, Noriyuki Seta, Hideto Kameda, Tsutomu Takeuchi

Keio University School of Medicine, Department of Internal Medicine, Division of Rheumatology

To explore the degree and causal factors of discordance between patient and physician assessment of disease severity in rheumatoid arthritis using database of SAKURA study. One hundred fifteen patients with RA and their rheumatologists assessed a visual analog scale (VAS) for global disease severity independently before treatment. Positive discordance, defined as a patient minus physician rating of 20mm on a 100mm, was found in 24%, and negative discordance, defined in an opposite manner, was found in 14%. More tender joint count of hands, pain VAS of patients and Dressing and Grooming score in HAQ were associated with positive discordance, and higher erythrocyte sedimentation rate with negative discordance.

P2-348

Regional Pathway for Treatment of RA and Electrical Information System.

Tomotaro Sato, Daihei Kida, Nobunori Takahashi, Atsushi Kaneko
Department of Orthopaedic Surgery and Rheumatology, National Hospital Organization, Nagoya Medical Center, Nagoya, Japan

Since September 2007, we have used the RACRC-Path: Rheumatoid Arthritis Circulatory Regional Collaboration-Pathway, for 42 hospitals and 67 patients as a tool of biologic and non-biologic DMARDs in convenience for patients and physicians. Collaborating hospitals are situated close to RA patients, after induction phase of biologics, they can take care of patients. We have used electronic system which can browse record from collaboration hospitals. Critical pathway and electrical connection can be useful for rheumatoid arthritis characteristics.

P2-349

Risk factors for coronary heart disease in Japanese RA patients using IORRA

Eiichi Tanaka, Toru Yamada, Eisuke Inoue, Naoki Sugimoto, Daisuke Hoshi, Kumi Shidara, Eri Sato, Mariko Kitahama, Yohei Seto, Ayako Nakajima, Shigeki Momohara, Atsuo Taniguchi, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Purpose: To investigate the risk factors of CHD in Japanese patients with RA.

Methods: The occurrence of first-ever CHD events were collected from 2000 to 2008 by IORRA. The adjusted hazard ratios (HR) for CHD events were calculated using time-dependent cox proportional hazards model.

Results: Among 8,387 RA patients (38,297 person-years), 88 first-

ever CHD events occurred. Hypertension (HR: 2.9), hypercholesterolemia (HR: 2.7), current smoking (HR: 2.2) and DAS28 (HR: 1.2) were significant factors associated with CHD events.

Conclusion: Both traditional risk factors and higher DAS28 are independent significant risks for CHD, suggesting that not only controlling RA disease activity but also managing the co-morbid diseases is important for the improvement of long-term prognosis of RA patients.

P2-350

Excess coronary heart disease incidence in Japanese RA patients using IORRA

Eiichi Tanaka, Toru Yamada, Eisuke Inoue, Naoki Sugimoto, Daisuke Hoshi, Kumi Shidara, Eri Sato, Mariko Kitahama, Yohei Seto, Ayako Nakajima, Atsuo Taniguchi, Shigeki Momohara, Hisashi Yamanaka

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Purpose: To clarify an incidence of coronary heart disease (CHD) in Japanese RA patients.

Methods: The occurrence of first-ever CHD events were collected from 2000 to 2008 by IORRA. The age-adjusted incidence rate of CHD was calculated.

Results: Among 8,387 RA patients (38,297 person-years, mean 55.3 y.o., RA duration 7.5 y., female 82.5%), 34 and 54 first-ever CHD events occurred in men and women, respectively. The age-adjusted incidence rates (per 100,000 person-years) of all CHD/acute myocardial infarction/angina pectoris were 298.7/169.3/129.4 and 108.8/42.3/66.5 in men and women, respectively. These incidences were higher compared to those in the Japanese population-based studies.

Conclusion: These findings suggest that RA itself is an important risk for CHD in Japanese RA patients.

P2-351

A case of T cell type malignant lymphoma as MTX-LPD in RA patient under MTX and Etanercept therapy

Kazuhide Aiki^{1,2}, Takashi Kato²

¹Aiki Orthopedic Clinic, ²Department of Nephrology and Rheumatology, Ishikawa Prefectural Central Hospital

A 52 year old woman with RA, treated with MTX (8mg/w) and etanercept (ETN, 25mg/w), was suffered from high-fever in October, 2009. At first, chest X-ray abnormality and elevation of CRP suggested pneumonia. On admission, MTX and ETN ceased. A diagnosis of malignant lymphoma (ML) was proposed on the basis of lymphadenopathy and nodular shadows in the lung on CT scans. Biopsy findings of neck lymph-node and bone marrow (BM) revealed T cell ML concomitant with BM invasion. Although her manifestations such as thrombocytopenia were progressive, high-fever and thrombocytopenia began to improve spontaneously a week after ceasing MTX and ETN. This finding may be consistent with MTX related ML. In this case, six course of treatment with CHOP was performed and complete remission achieved.

P2-352

The effect of increased Methotrexate for Rheumatoid Arthritis

Nobuyuki Takahashi¹, Taio Naniwa², Kaneshige Sasaki²

¹Department of Rheumatology, East medical center Higashi Municipal Hospital City of Nagoya, Aichi, Japan, ²Department of Rheumatology, Nagoya City University Hospital, Aichi, Japan

Method: Twenty eight patients with active rheumatoid arthritis (DAS28 \geq 3.2) despite at least 3 months of methotrexate (MTX) therapy at a stable dose of 6 to 8 mg per week received MTX at a dose 12-13mg/week. After 2 months at the time of increase, disease activity was assessed according to the criteria of the ACR and DAS28. Results: The mean age; 63 years, mean disease duration 4.1 years, MTX final average dose 12.4mg/week. A moderate response according to EULAR response criteria was achieved 79%. ACR20%, 50%, 70% were 57%, 29%, 7%. At the time of the previous increase of MTX, 16 cases out of 17 cases had been found effective, were more effective. Average 1.4 years later, in patients received MTX alone, remission was 10 cases. Seven cases showed side effects.

P2-353

Questionnaire study of MTX usage for patients under treatment with MTX

Midori Suzaki¹, Yumi Kobayashi¹, Tomomi Tsuru¹, Misato Nakagawa¹, Hitoshi Nakashima²

¹Medical Co. LTA, PS Clinic, Fukuoka, Japan, ²Fukuoka University hospital, Fukuoka, Japan

There are many issues when MTX used by patients with RA, because the prescription time schedule is complex compared to daily taking medicine. We require patient compliance instruction at the start of the therapy. We investigated 91 patients under MTX treatment about compliance and disease control of the patients. 55 patients experienced arranged administration, however 36 patients administered as prescription. There is no difference in sex. In the 6mg/week group and 20s, 30s group have tendency for arranged administration. (6mg/8mg forgetting rate 87.5%/60.9%; 20s 80.3%, 30s 80%). In male cases of arranged administration, they administered MTX on the next day, however in female cases, they administered after 12 hours. There were not the patients who performed overdosage.

P2-354

Experience of treatment of tacrolimus for rheumatoid arthritis

Atsushi Nakamura, Katsuaki Kanbe, Junji Chiba, Koichiro Hayata, Yasuo Inoue, Kaori Hobo

Department of Orthopaedic Surgery, Tokyo Women's Medical University, Medical Center East

Tacrolimus, an immunosuppressive drug, was approved for the treatment of RA, however the efficacy is not clear especially in combination with infliximab or etanercept or tocilizumab. We analyzed CRP and MMP-3 improvement after treatment of tacrolimus in 114 patients with mean age of 62.8. We used infliximab for 26 patients and etanercept for 21 patients and tocilizumab for 4 patients with tacrolimus. After 3 months, CRP was improved to 1.69 mg/dl from 2.55mg/dl. MMP-3 was improved to 199.2mg/dl from 211.4mg/dl after 6 months. One patient got remission by tacrolimus with etanercept. The efficacy was recognized 0.5 mg/day of tacrolimus for early RA showing low CRP.

P2-355

Clinical efficacy and steroid-reduction capability of tacrolimus in RA patient

Misato Kawakami¹, Junko Maruyama¹, Yasunobu Takizawa¹, Atsuko Murota¹, Kazuyoshi Ishigaki², Noboru Hagino², Takeyuki Kanzaki², Kenji Takagi¹, Keigo Setoguchi¹

¹Department of Immunological diseases, Tokyo metropolitan hospital, Tokyo, Japan, ²Department of Allergy and Rheumatology, Graduate School of Medicine, the University of Tokyo Hospital

Objectives: To evaluate the clinical efficacy and the steroid-reducing capability of tacrolimus in patients with rheumatoid arthritis (RA). **Patients and Methods:** We conducted a retrospective review of medical records of patients with RA who initiated tacrolimus treatment for over 24 weeks. **Results:** 26 patients (22 female, 4 male) were included in this study. Tacrolimus was added to ongoing methotrexate (MTX) in 7 patients and steroid in 20 patients. The mean DAS28 (CRP) score decreased from 4.46 at treatment initiation to 2.7 at 1 year follow up. The mean dose of prednisolone decreased from 4.5mg to 4.1mg at 1 year follow up. **Conclusion:** Tacrolimus treatment, as employed in actual clinical practice, was resulted in improvement of DAS28 score and success in steroid-reduction in therapy.

P2-356

Tacrolimus might be effective for RA patients with much more swollen joints.

Kenji Mamoto¹, Yuko Sugioka¹, Tadashi Okano¹, Masahiro Tada¹, Shigeyuki Wakitani¹, Tatsuya Koike²

¹Departments of Orthopaedic Surgery Osaka City University Medical School, ²Departments of Rheumatology Osaka City University Medical School

The objective of this study was to assess the usefulness of tacrolimus for rheumatoid arthritis patients. Eighty RA patients treated with tacrolimus for more than 6 months were enrolled in this study. At baseline mean age was 65.9 years old; disease duration was 17.6 years; dosage of MTX was 4.2mg/w. 52.5% and 57.5% patients were received biologic agents and MTX, respectively. The continuation rate at month 6 was 82.5%. According to EULAR response criteria, 47.6% of the patients who continued TAC achieved moderate response. Multivariate analysis indicated that only the count of swollen joints was independent predictor for attainment of moderate response (Relative risk 0.864, 95% CI: 0.764-0.977, $P=0.019$). Efficiency of TAC was associated with the higher counts of swollen joints in RA patients.

P2-357

Adequate administration of tacrolimus for RA patients, and clinical results.

Fumio Shinomiya¹, Noriaki Mima¹, Keiichirou Nannba¹, Kenji Tani², Mitsuhiro Kohn², Akifumi Honjo²

¹Centre for Rheumatic Disease, Mima Hospital in Yoshinogawa City, Yoshinogawa, Japan, ²Department of General Medicine, Tokushima University Graduated School, Tokushima, Japan

Action mechanism of tacrolimus (TAC) is different from methotrexate (MTX) and biological agents (BIO). In the treatment of rheumatoid arthritis (RA), TAC administration has adapted as MTX cases of cessation, and addition of MTX and BIO to the effect for insufficient cases. The clinical course of 101 cases for adverse reactions and invalidity except for cases of cessation was investigated.

Though the score of DAS28 was 6.16 in average at starting time, the significant improvement in 6 months to 3.86 was shown. The inflammatory reactions also showed the significant lowering. In 3 groups which administered TAC, the improvement was still continued after the MTX cessation, and addition or switching of BIO were seen only in small numbers.

P2-358

Comparison of Azathioprine and Tacrolimus efficacy in RA with IP

Keisuke Kobayashi, Jiro Yamana, Rie Sasaki, Motoaki Kin, Mitsuhiro Iwahashi, Seizo Yamana
Higashihiroshima Kinen Hospital

Interstitial pneumonitis (IP) is seen in 20% of RA patients. RA with IP (RA-IP) patients are difficult to achieve remission because impossible to use MTX. DAS28-ESR of RA-IP and RA-non IP is 3.3, 3.0 respectively. Azathioprine (AZP) and Tacrolimus (TAC) are sometimes used instead of MTX but there is no evidence of comparison of efficacy. We examined the efficacy compared with 8 AZP and 22 TAC cases that continuous administration was possible for more than 1 year. There is no difference in DAS28-CRP and age at 0 week. The rate of DAS28-CRP ≤ 2.3 achievement after 1 year, AZP is 50%, TAC is 45%. RF increased 2.3 times in TAC, although it is stable in AZP. IP was not deteriorated in both groups. AZP is slightly more effective than TAC. We suggest that it should be use AZP for high RF level RA-IP.

P2-359

Slowly progressive renal dysfunction with tacrolimus in rheumatoid arthritis

Harutsugu Okada, Ryosuke Hanaoka
Department of Rheumatology, Kamitsuga General Hospital, Tochigi, Japan

OBJECTIVE: To study the incidence and clinical features of renal dysfunction in patients with rheumatoid arthritis (RA) treated with low-dose tacrolimus.

METHOD: We reviewed estimated glomerular filtration rate (GFR), disease activity score 28 (DAS28) and trough levels of tacrolimus from the medical records of RA patients during the treatment with low-dose tacrolimus retrospectively. All data were analysed at the point of baseline, 4, 8, 12, and 24 weeks.

RESULTS: DAS28 showed significant improvement at 8 weeks. Though serious deterioration of renal function was not recognized, there were modest but significant decreases in GFR at 24 weeks.

CONCLUSION: In RA patients treated with low-dose tacrolimus, renal dysfunction of tacrolimus could develop gradually in contrast to its efficacy.

P2-360

Clinical efficacy of Tacrolimus for rheumatoid arthritis

Kenji Takenouchi¹, Kenji Takahashi¹, Toshikazu Kamada², Masahito Koikiwa³, Hiroshi Nakamura¹

¹Department of rheumatology, ²Department Orthopaedics, Hara Orthopaedic Hospital, Tokyo, Japan, ³Department Rheumatology and Orthopaedics, Syuwa General Hospital, Saitama, Japan

(Purpose) To evaluate the clinical efficacy of Tacrolimus (TAC) in RA. (Patients) 256 RA patients who were treated with TAC were investigated. (Results) The average TAC dosage was 1.9 mg/day. The continuation rate was 67% through 1 to 3 years and

54% at 4 years. In 54 patients who were followed-up for 2 years, 15 were estimated as remission, 8 were low disease activity and 26 were moderate disease activity, respectively, by EULAR criteria. 58 out of 256 patients discontinued TAC due to side effects. (Conclusion) TAC was used mainly for patients who had difficulty in biologics use and about a half of them obtained remission or low disease activity.

P2-361

Adding tacrolimus (TAC) in RA patients with inadequate response to MTX therapy

Shigeru Matsuda, Natsuko Nakagawa, Koji Tateishi, Kiminobu Yokoyama, Yasuhiro Terashima, Kohzoh Kohyama, Chihiro Tanaka, Miki Murata, Takashi Yamane, Ryosuke Yoshihara, Yasushi Tanaka, Kazuko Shiozawa, Shigeaki Imura
Rheumatic disease center, Konan Kakogawa Hospital, Hyogo, Japan

We evaluated the efficacy of TAC as add-on therapy in RA patients with inadequate response to MTX administration 8mg/w or more. In this study, 24 RA patients using MTX (average 9.0mg/w) treated with TAC (average 1.6mg/d). Clinical efficacy was assessed retrospectively. At 6 months, 22 patients continued TAC add-on therapy, and their clinical results were improved significantly. At the latest investigation, among 21 patients with low or moderate activity at first, 16 patients were classified in low activity, 1 in moderate, and 4 in dropout. Otherwise among 3 patients with high activity, one was in moderate activity and two were in dropout. TAC add-on treatment was effective to RA patients with inadequate response to MTX therapy, especially to the patients with low or moderate disease activity.

P2-362

Efficacy of tacrolimus for MTX-refractory rheumatoid arthritis

Ko Katayama

Katayama Orhopedic Rheumatology Clinic

(Objective) Tacrolimus (TAC) was administered to 68 patients with MTX-refractory RA to evaluate the clinical improvement and inhibition of joint destruction. (Methods) DAS28-ESR, annual percent change (Δ TSS) of the modified total Sharp score (mTSS) were compared before and after addition of TAC. (Results) Mean age; 63.5 years, mean duration of diseases; 81.9 months, and mean follow-up period; 17.3 months. DAS28-ESR decreased from 5.38 at baseline to 3.90 at the time of final observation. Thirty-three patients were evaluated radiologically, and the majority showed inhibition of joint destruction. Fifteen patients discontinued TAC treatment because of transfer to another hospital (3), lack of efficacy (3), and adverse events (9). (Conclusion) TAC was effective for MTX-refractory RA patients.

P2-363

Clinical features of polymyositis in the elderly patients

Shuzo Sato, Rie Saito, Haruyo Iwadate, Hiroko Kobayashi, Hiroshi Watanabe, Hiromasa Ohira

Department of Rheumatology and Gastroenterology, Fukushima Medical University School of Medicine, Fukushima, Japan

Objective: To evaluate the clinical features of polymyositis (PM) in the elderly patients. Methods: We retrospectively investigated clinical features of 21 PM patients treated in our clinic from 1988 to 2010. They were divided into 2 groups; young group (younger than 70-year-old) and elderly group (over 70-year-old). Results:

We observed that serum CK levels in elderly group were significantly lower than those in young group ($P < 0.05$). However, there were no significant differences in hospitalization period, serum aldolase levels, anti-Jo-1 antibody prevalence, and complicated interstitial pneumonia. Conclusion: Elderly PM patients showed lower serum CK levels at the onset of disease.

P2-364

Two patients in the same family with anti-ARS antibody-associated myositis

Takashi Ozaki, Hiroyuki Yamashita, Yuji Yoshida, Yuko Takahashi, Arisa Shimizu, Kenji Itoh, Hiroshi Kaneko, Akio Mimori

Division of Rheumatic Diseases, National Center for Global Health and Medicine

We describe two familial cases of myositis and interstitial pneumonia (IP) with positive serum anti-aminoacyl tRNA synthetase antibodies (Ab) (assayed at Kyoto University). Mother: A 72-year-old female developed progressive IP and Raynaud's phenomenon. Increased levels of serum CK and anti-EJ Ab together with an abnormal electromyogram led to a diagnosis of polymyositis. She required home oxygen therapy despite treatment with steroids and cyclosporine. Daughter: A 38-year-old female manifested fever, polyarthritis, muscle weakness, Raynaud's phenomenon, and chronic IP. Dermatomyositis, diagnosed based on the presence of Gottron's sign and serum anti-PL-12 Ab, remitted following steroid and tacrolimus therapy. Anti-ARS Ab production may be associated with certain genetic susceptibilities.

P2-365

Improvement of pneumatosis intestinalis in overlap syndrome by corticosteroids

Hiroyasu Hirano, Akiko Yoshida, Yumi Sasae, Takeo Sakuta, Yoshitaka Morita

Kawasaki Medical School Hospital

Pneumatosis intestinalis (PI) refers to the presence of gas within the wall of the small or large intestine. Management options for patients with symptomatic PI generally include conservative therapy, high-flow oxygen administration and surgery. We show a case of 43-year-old female with PI who was successfully treated by corticosteroids. She was diagnosed as having overlap syndrome (dermatomyositis and systemic sclerosis) in 2003. In November 2008, she was suffered from abdominal fullness and pain. Ultrasound imaging revealed PI. Conservative therapy did not change her PI. In March 2009, the dose of methylprednisolone was increased to 60 mg/day from 14 mg/day, which resulted in the dramatic improvement of PI. Abdominal vasculitis may have contributed to the progression of PI in our case.

P2-366

A case of dermatomyositis developed shortly after initiation of etanercept

Michita Suzuki, Kyoko Takano, Eiji Nagasawa, Masao Katayama, Atsushi Kaneko

National Hospital Organization Nagoya Medical Center

A 58-year-old female, who had a long history of RA without any adequate therapies, was referred to our hospital in February 2010 presenting with fever and polyarthralgia. She was diagnosed as an exacerbation of RA (stage III, class II) with inactive interstitial

lung disease. Etanercept (ETN) 25mg/week was initiated in March and was effective in first two weeks, yet she began to experience pain in her shoulders and knees and the serum CK level increased. The physical examination revealed Gottron's papules, periungual erythema and proximal muscle tenderness and weakness. An electromyogram showed myogenic conversion and anti-Jo-1 antibody was negative. She was diagnosed as dermatomyositis (DM) in June and was successfully treated with oral PSL 40mg/day. This case indicates that ETN could induce DM.

P2-367

Ameliorative effect of tocilizumab on two patients with refractory polymyositis

Masashi Narazaki, Yoshihiro Hishitani, Atsuyoshi Morishima, Mari Kawai, Toru Hirano, Keisuke Hagihara, Yoshihito Shima, Atsushi Ogata, Toshio Tanaka

Dept. of Respiratory Medicine, Allergy and Rheumatic Diseases, Osaka University Graduate School of Medicine

We report two cases of refractory polymyositis (PM) that responded well to anti-interleukin-6 receptor antibody, tocilizumab.

Case 1. 40-year-old male with PM and interstitial lung disease. Azathioprine, or cyclosporine A did not show a steroid-sparing effect. The two injections of tocilizumab decreased CPK value from 871 U/L to normal. After 6 months, the chest CT revealed a decrease of ground glass opacity. **Case 2.** 31-year-old male with PM. Azathioprine, cyclosporine A or methotrexate did not show a steroid-sparing effect. The injections of tocilizumab made CPK value decreased gradually from 1572 U/L and normalized after 9 months. Although further clinical trials are required, it may be possible that tocilizumab is an optional treatment for refractory PM.

P2-368

Complications and prognosis of hypomyopathic and classical dermatomyositis

Kenji Fujii^{1,2,3}, Yasuhiro Osugi^{2,3}, Yoshinobu Koyama², Toshiyuki Ota^{1,2}

¹Department of Laboratory and Transfusion Medicine, University of Occupational and Environmental Health, Fukuoka Japan, ²Division of Rheumatology, Iizuka Hospital, Fukuoka, Japan, ³Kaita Hospital, Fukuoka, Japan

Aims & Methods We evaluated interstitial pneumonia (IP), malignancy and 3-year survival rate of hypomyopathic dermatomyositis (HDM:7 cases) and classical DM (CDM:6 cases).

Results 6 HDM cases had IP, 2 cases died of severe treatment-resistant IP within three months. 5 remainder of HDM cases were successfully treated without malignancy. In CDM, 5 cases had dysphagia, 4 of them had malignancy at the onset, and three died. Another one case without malignancy died of military tuberculosis. Also, only one case without dysphagia was associated with IP, but developed malignancy after two years.

Discussion Many cases of HDM had IP, but the prognosis of successfully treated cases were good. In CDM, malignancy were high rate, 3-year survival rate was low, and dysphagia was a poor prognostic factor.

P2-369

Fasciitis is a common lesion detectable early after the onset of dermatomyositis

Ken Yoshida, Daitaro Kurosaka, Eigo Takahashi, Kenichiro Hirai, Kentaro Noda, Taro Ukichi, Kazuhiro Furuya, Maimi Yanagimachi, Isamu Kingetsu, Akio Yamada

Division of Rheumatology, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan

Purpose: To investigate fasciitis in dermatomyositis (DM).

Methods: En bloc biopsy combined with STIR MRI was performed on 15 patients with DM and 7 patients with other rheumatic diseases including polymyositis (PM).

Results: In all patients with DM, MRI revealed abnormal hyperintense areas in the fascia. The hyperintense areas had progressed from the fascias into the muscles. En bloc biopsy revealed fasciitis in most of the patients with DM. Fasciitis was not detected in any of the 7 patients with other rheumatic diseases.

Conclusions: Fasciitis was recognized as a common lesion that appears early after the disease onset in DM. The results of MRI suggest that inflammation in myopathy of DM progresses from the fascia into the muscle. Fasciitis may be a lesion specific to DM rather than to PM.

P2-370

Analysis of steroid-resistant patients with polymyositis/dermatomyositis (PM/DM)

Kyoichi Nakajima, Yuji Akiyama, Takuma Wada, Muneo Ota, Mayuko Sakamoto, Yuki Shimada, Akinori Yamamoto, Yasufumi Shindo, Yoshihiro Yoshida, Kazuhiro Yokota, Yasuto Araki, Haruhiko Akiba, Hiroshi Kajiyama, Kojiro Sato, Yu Asanuma, Toshihide Mimura

Department of clinical rheumatology and applied immunology, Saitama Medical University, Saitama, Japan

(Objective) Oral corticosteroid (CS) is effective in PM/DM, but CS-resistant patients (CSR) need additional steroid-pulse therapy or immunosuppressants. In this study, we analyzed the characteristics of CSR. (Methods) Five PM and ten DM were enrolled. CSR were given additional therapy after the initial CS. We compared CSR and non-CSR clinically. The area under the curve (AUC) was calculated as the sum of the areas beneath the line connecting adjacent CK level at each time point. (Results) The max CK were higher in CSR ($p=0.0127$). Weekly AUC increased more in CSR at two, three, and four weeks ($p<0.05$), despite the same CS dose ($p=0.1341$). It took longer in CSR till CK became normal ($p=0.0007$). (Conclusion) Patients with high max CK and larger AUC at two weeks might need additional therapy.

P2-371

Characterization of HRCT findings of interstitial pneumonia in dermatomyositis

Takaaki Ishida, Takuya Kotani, Koji Nagai, Kenichiro Hata, Shuzo Yoshida, Tohru Takeuchi, Shigeki Makino, Toshiaki Hanafusa

First Department of Internal Medicine, Osaka Medical College, Osaka, Japan

We investigated the chest high-resolution computed tomography (HRCT) findings of dermatomyositis with interstitial pneumonia (DM-IP) patients. The subjects were 34 patients with DM-IP who was initially diagnosed in our department between January, 2004 and August, 2010. We assessed the chest HRCT findings at the first

visit in our department. The distribution of the IP was predominantly shown in subpleural and dorsal lower lung fields bilaterally. Ground glass opacity (GGO), reticular shadow, linear shadow, traction bronchiectasis (TBE), consolidation, honey-combing like cyst, and subpleural band (SPB) were shown in 97%, 85%, 82%, 74%, 71%, and 41% of DM-IP patients, respectively.

P2-372

A case report, RA patient with infected and dislocated hip prosthesis

Toshiyuki Kawanishi, Yukio Yoshida, Gen Kuroyanagi
East medical center Higashi municipal Hospital city of Nagoya

Treatment for infected and dislocated hip prosthesis:
The case is 66 y.o., female. occurred a deep periprosthetic infection after a total hip arthroplasty at 30 y.o. and had two revision operation. Then, she was treated with systemic antibiotic therapy. After 22 years the last revision surgery, she had fistulae in the hip region attributable to MRSA. Acetabular and femoral components were removed and treated with bacteria-specific local and systemic antibiotic therapies. Afterwards, there is no infection sign.

P2-373

Rheumatoid synovial cyst of the hip, a case report

Makoto Kawasaki, Hisayoshi Inoue, Ken Sabanai, Katsumi Sato
Department of Orthopaedics, Tohoku Rosai Hospital

The case is a woman, 67 years old (stage IV, class IV). Her onset of RA was in 34 years old. Anterior thigh pain and lower abdominal pain were appeared without trauma, and then the pain was increased gradually. In her physical examination, the limit of motion in her hip joint was shown multidirectionally. The hip joint was shown as a destructive change of Larsen grade IV in the X ray view. The MRI and contrast X ray views of the hip indicated the cystic lesion communicated with the hip joint. It was undergone the THA and removal of the cystic lesion. The pathological finding of the cystic lesion indicated synovial. We experienced one case of Rheumatoid synovial cyst which occurred in the hip. The symptom was relieved by THA and synovial extraction, and the mass was reduced.

P2-374

The number of CD64 on neutrophil is useful marker for detect the local infection

Katsumitsu Arai¹, Junya Ajiro², Toshihiro Matsui³, Akiko Komiya⁴, Shigeto Tohma⁴

¹Niigata Prefectural Central Hospital, Department of Orthopedic Surgery, ²Niigata Prefectural Central Hospital, Department of Internal Medicine, ³Department of Rheumatology, Sagami National Hospital, National Hospital Organization, ⁴Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami National Hospital, National Hospital

Case1. 73-year-old woman who had loose hip prosthesis in 2 years after primary operation with pain and local heat. Infection was suspected but her CRP, ESR and WBC were normal. The number of CD64 on neutrophil was high. Removal of prosthesis was made and tissue culture around the prosthesis showed MRSA infection. After treatment of MRSA infection, the number of CD64 on neutrophil was normal and her condition was good, revision surgery was performed. No infectious sign showed in her hip joint in 4 month after surgery. Case2. 54-year-old woman with RA, who had swelling and

damaged left knee joint and increasing CRP. Because the frequent intraarticular injection, infection was suspected. Joint fluid culture was negative and the number of CD64 on neutrophil was normal. TKA was performed.

P2-375

Accuracy of ultrasonography and D-dimer for DVT screening after arthroplasty.

Shigeo Hagiwara, Koh Shimizu
Department of Orthopaedics Surgery, Chiba Rosai Hospital

Ultrasonography and D-dimer is popular for DVT screening after arthroplasty but, accuracy is controversial. We research the accuracy of ultrasonography and D-dimer by comparing venography. A total of 266 patients who underwent arthroplasty (TKA158, THA109) were investigated the existence of DVT by venography, ultrasonography and D-dimer 10 days after operation. DVT was confirmed 47 patients in TKA, and 2 patients in THA. The sensitivity of ultrasonography is 24% and, the specificity is 75%. The sensitivity of D-dimer is 92% and, the specificity is 47%. Both test has limitation for screening of DVT.

P2-376

Acute pseudogout following total knee arthroplasty: A case report

Hiroyuki Kojin, Shin Sasaki
Kosei Chuo General Hospital

We report a case of acute pseudogout involving the replaced knee joint on the 9th day after total arthroplasty. The patient was on 85-year-old female with advanced left gonarthrosis. Total joint arthroplasty was performed in July 2010 and the post-operative course was uneventful. However, she complained of worsening knee joint pain on the 9th post-operative day and signs of inflammation were noted. Although the culture was negative, calcium pyrophosphate dihydrate was recognized in the joint effusion. Calcification had been seen on pre-operative X-ray films of her knee joint. Furthermore, NSAID alone relieved her symptoms well. We considered that the event was pseudogout, which should be included in the differential diagnosis of knee pain after total arthroplasty.

P2-377

3 cases of postoperative infection in RA with biological treatment.

Hideko Torihata¹, Ayako Kubota², Takashi Nakamura², Yoshiyasu Miyazaki², Toyomitsu Tsuchida³, Toru Suguro², Kazuaki Tsuchiya²
¹Department of Orthopaedic Surgery, ISUZU Hospital, Tokyo, Japan, ²Department of Orthopaedic Surgery, Toho University School of Medicine, Tokyo, Japan, ³Tsuchida clinic

We were examined three cases of late infection surgery for RA. Case 1: A 65-year-old woman performed TAA. She was treated ETN, developed TAA infection, we removed the prostheses. Culture results were enterobacter cloacae. We performed ankle arthrodesis after that remained free of infection. Case 2: A 58-year-old woman performed Swanson flexible hinge toe implant insertion surgery. She was treated IFX. She developed prostheses infection, we removed the prostheses. Culture results were CNS. Case 3: A 54-year-old woman performed Swanson flexible hinge toe implant insertion surgery. She is treated IFX, developed prostheses infection, we removed the prostheses. Culture results were pseudomonas aeru-

ginosa. After the infection was considered to have subsided, we started treatment with ETN.

P2-378

Early failure of total ankle arthroplasty in RA patient treated with tocilizumab

Akihide Nampei¹, Makoto Hirao², Hideki Tsuboi³, Kenrin Shi², Hideki Yoshikawa², Jun Hashimoto²

¹Department of Orthopaedic Surgery, Osaka Rosai Hospital, ²Department of Orthopaedics, Osaka University Graduate School of Medicine, ³Department of Orthopaedic Surgery, National Hospital Organization Osaka Minami Medical Center

A 48-year-old male RA patient treated with tocilizumab was received left total ankle arthroplasty. After 6 months, radiolucent area around tibial component and subsidence of talar component were appeared. After 2 year, the patient became to feel strong pain occasionally. From laboratory examinations, inflammatory response was none, but the possibility that tocilizumab mask the septic inflammation was considered, implant was removed at first. From the intraoperative specimen, culture was negative and neutrophil infiltration was not observed. Then revision ankle arthroplasty was done. This case resulted in aseptic loosening, it is important to take notice of infection under the tocilizumab therapy because inflammatory response, such as CRP was not elevated until the infection became severe.

P2-379

Scarf osteotomy for forefoot deformity in patients with rheumatoid arthritis

Hiraku Motomura, Isao Matsushita, Eiko Seki, Tomoatsu Kimura
Department of Orthopaedic Surgery, Faculty of Medicine, University of Toyama

Objective: To evaluate joint-preserving procedures for forefoot deformity in patients with rheumatoid arthritis (RA). Methods: We selected 3 patients with rheumatoid forefoot deformities, low disease activity and absence of power doppler signals of metatarsophalangeal (MTP) joints by ultrasonography. We performed Scarf osteotomy for Hallux valgus (HV) and oblique shortening osteotomies for lesser toe deformities. Results: The mean JSSA score improved from 56.3 to 85.0. The mean HV angle, M1M2 angle and M1M5 angle decreased from 34.9 to 5.8, from 11.2 to 4.7, and from 25.6 to 14.3, respectively. There was no recurrence of painful callosity or HV deformity. Conclusion: Scarf osteotomy can be a useful procedure for forefoot deformities in patients with low disease activity.

P2-380

Reduction of a claw toe by DuVries arthroplasty in rheumatoid forefoot

Ken Ogura, Masahito Hatori, Hiroshi Okuno, Keiki Miura, Eiji Itoi, Akira Sekiguchi
Tohoku University Hospital

Reduction of claw toe in RA forefoot by DuVries arthroplasty was performed for 8 feet of 5 patients. Dorsal foot were soft enough to reposition the MP joint. Swanson implant was used to 6 hallux valgus. CRP, DAS28, and JSSF score were collected. HV angle and M1M2 angle were measured by standing radiograph. Mean follow up was 38 months. Biological DMARD was used for patients who have high disease activity. CRP and DAS28 decreased from 1.5 to 0.1 and from 4.4 to 2.9 respectively. JSSF score was improved from

41 to 73. HV angle and M1M2 angle were reduced from 40.6 to 21.6 and from 19.9 to 10.7 respectively. Redislocation of the 2nd MP joint was observed and painful callosity recurred in one foot. Although spontaneous arthrodesis was observed in one MP joint, plantar callosity did not recur.

P2-381

Radiological issues after joint-preserving surgery against RA forefoot deformity

Makoto Hirao¹, Kenrin Shi¹, Hideki Tsuboi², Akihide Nampei³, Hideki Yoshikawa¹, Jun Hashimoto¹

¹Department of Orthopaedics, Osaka University Graduate School of Medicine, ²Dept. of Orthopaedics, National Hospital Organization Osaka Minami Medical Center, ³Dept. of Orthopaedics, Osaka Rosai Hospital

With progression of RA drug therapy, the importance of joint-preserving surgery against forefoot deformity has been recognized in recent years. We also preserve MP joints since 2000, however some issues occur including ankylosis of MP joint, non/mal-union in bone cutting site, and recurrence of the dorsal displacement. In this study, the frequency of such failures was surveyed. Thirty one cases of joint-preserving surgeries (shortening osteotomy in II-V metatarsal bone) were evaluated (21: proximal shortening osteotomy in 1st metatarsal bone, 10: distal one). In these cases, non union was occurred in 4 cases, recurrence of the displacement was in 1 case, and ankylosis of MP joint was in 3 cases. To avoid ankylosis, now we are shortening the duration of joint fixation after surgery.

P2-382

Ankle arthrodesis with vascularized sliding bone graft in limited scleroderma

Noriaki Okumura, Taku Kawasaki, Naruhito Kodama, Katsuhisa Kikuchi, Yoshigata Matsusue
Shiga University of Medical Science, Department of Orthopaedic Surgery, Shiga, Japan

An ankle arthrodesis with rheumatic disease is occasionally complicated by pathological fracture or non-union. In this report, we present a case of treatment of avascular necrosis of the talus with vascularized sliding tibial bone graft. A 76-year-old woman with several years' history of limited scleroderma without oral corticosteroids complained of an ankle pain. Since the conservative therapy was not successful for an ankle pain, we operated on using vascularized bone graft sliding to the talus by anterior approach. With vascularized bone graft, we found an improvement on X-ray with osteosynthesis and prevented a pathological fracture and a progression of the collapse. The vascularized tibial bone graft is a useful technique for a patient with rheumatic disease.

P2-383

Cytomegalovirus infection during immunosuppressive therapy

Yo Ueda, Yuko Takahashi, Hiroyuki Yamashita, Hiroshi Kaneko, Akio Mimori

Division of Rheumatic Diseases, National Center for Global Health and Medicine

A chart review over 5 years for the frequency and clinical features of CMV infections during immunosuppressive therapy for rheumatic diseases. Patients: 236 cases (79 SLE, 42 vasculitides, 37 myositis, and 78 other diseases) had received steroid therapy of ≥ 30 mg prednisolone equivalent/day. CMV infection was diagnosed

based on CMV antigenemia $\geq 5/150000$ neutrophils and clinical abnormalities that responded to anti-viral therapy, or biopsy-proven CMV. Results: 31 (13%) of the 242 cases developed CMV infection, and 19 of the 31 cases had received adjunctive immunosuppressive agents. All the infected patients survived. The most common initial manifestation of CMV infection was thrombocytopenia. Monitoring for CMV antigenemia and platelet count may improve the prognosis of CMV infection.

P2-384

Five cases of cytomegalovirus gastroenteritis in patients with immunosuppression

Takamichi Kanbayashi, Isamu Yokoe, Shinji Tsuruta, Hitomi Haraoka

Itabashi Chuo Medical Center, Tokyo, Japan

The gastrointestinal tract is one of the common sites of CMV infection. We examined five cases of CMV gastroenteritis occurring during steroid therapy. Three patients with rheumatic disease, one patient with drug-induced pneumonia, and one patient with COP were being treated with prednisolone. Its average dose was 34 mg at the onset of CMV gastroenteritis. They had CMV infection an average of 26 days after steroid therapy, and the infection caused gastroduodenal ulcers, esophagitis, and rectal ulcer. Only two patients were definitely diagnosed by histological examination, and the other three patients had positive PCR results for CMV antigens and CMV DNA in addition to the clinical course. Comprehensive judgment including clinical findings and various laboratory findings is necessary.

P2-385

Efficacy of folic acid for anti-cytomegalovirus-drug-related cytopenia

Hidekazu Futami¹, Shinichi Nogi¹, Kanako Iwata¹, Hirokazu Takaoka¹, Yoshiyuki Arinuma¹, Atsushi Hashimoto¹, Hisanori Nakayama¹, Toshihiro Matsui¹, Tatsuo Ikenaka³, Akiko Komiya², Hiroshi Furukawa², Shigeto Tohma²

¹Department of Rheumatology, Sagami Hospital, National Hospital Organization, ²Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami Hospital, National Hospital Organization, ³Department of Rehabilitation, Sagami Hospital, National Hospital Organization

A 72-year-old woman with RA taking infliximab and MTX developed pericarditis related to RA. High-dose of corticosteroid was administered, but she infected with cytomegalovirus (CMV). Ganciclovir (GCV) injection was started from 150mg/day considering her impaired renal function; however, severe cytopenia was observed. After discontinuation of GCV and recovery of cytopenia, we re-challenged the injection of GCV (125mg/day) or Valganciclovir (450mg every other day) in combination with folic acid (20mg/day) and CMV infection improved without cytopenia or other adverse events. Under the condition of latent insufficiency in folic acid such as in patients treated with MTX, co-administration of folic acid with the drugs which could affect hematopoiesis may avoid drug-induced cytopenia.

P2-386

Analysis of cut-off level of CD64 on neutrophils of RA patients using biologics

Yuki Shimada, Kyoichi Nakajima, Fumihiko Miyoshi, Takuma Wada, Muneo Ota, Mayuko Sakamoto, Akinori Yamamoto, Yasufumi Shindo, Yoshihiro Yoshida, Kazuhiro Yokota, Yasuto Araki, Haruhiko Akiba, Hiroshi Kajiyama, Kojiro Sato, Yu Asanuma, Yuji Akiyama, Toshihide Mimura

Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University, Saitama, Japan

(Objective) It is usually used that 2000 molecules per neutrophil (mpn) as the cut-off level of CD64 expression on neutrophils, but some reports used the higher levels. We analyzed the cut-off level of RA patients using biologics. (Methods) The expression levels of CD64 were measured by flow cytometry on the days of tocilizumab (TOC) or infliximab (IFX) infusion. Analyzed were 133 samples of 69 RA patients infection was ruled out. (Results) CD64 expression was 1550 ± 1006 mpn (average \pm SD) of all patients. There were 24.5/32.5% (TOC/IFX) of samples over 2000 mpn, and its CD64 values were $2797 \pm 1056/2873 \pm 677$ mpn ($p=0.3635$), respectively. (Conclusion) Of importance is the careful judgement of CD64 expression levels in the RA patients receiving biologics.

P2-387

A case of RA patient with multiple pyogenic arthritis during etanercept therapy

Kazuhiro Sugimori, Isao Matsushita, Hiraku Motomura, Eiko Seki, Tomoatsu Kimura

Department of Orthopaedic Surgery, University of Toyama

62-years old woman developed RA in 1976. She was treated with etanercept (ETN) since November, 2008. She was suffered from pyogenic arthritis of right ankle and bilateral shoulder joints due to MSSA in April, 2009. Because of septic shock, she was stopped to administration of ETN. We performed arthroscopic and open debridement of shoulder and ankle joint, respectively. In May, 2009, phlegmone of right calf was developed. She had bilateral TKA infection and was received prosthetic removal. Vancomycin, Meropenem, and Cefazolin were administrated. Because the infection of the whole body was calmed, we performed bilateral TKA revision in June, 2010. ETN induced an immunosuppression state of RA patient. Therefore, we should examine whole body of the patient treated with ETN carefully.

P2-388

A case of chronic active EB virus infection complicating SLE and AIH

Arisa Shimizu, Haruka Tsuchiya, Hiroyuki Yamashita, Akio Mimori

National Center for Global Health and Medicine, Tokyo, Japan

We report a rare case of chronic active EBvirus infection (CAEBV) complicating systemic lupus erythematosus (SLE) and autoimmune hepatitis (AIH). A 45 year old female was admitted with fever, splenomegaly and liver dysfunction. She had been treated with 5mg of prednisolone (PSL) for remitted SLE since age 4. AIH was diagnosed on labo data and we administered 30mg of PSL, which lead to improvement of the symptoms, but they kept on relapsing as steroid was tapered. Within 5 years, high grade fever, further liver dysfunction, intractable gastric ulcer developed and her peripheral blood sample revealed elevated titer of EBV-DNA, liver and gastric mucosal biopsy showed infiltration of EBER-ISH posi-

tive lymphocytes and EBV infection was established in CD8+ T cells and she was diagnosed as CAEBV.

P2-389

Risk Factor for Adverse Effects by Trimethoprim-Sulphamethoxazole.

Reika Maezawa, Kazuhiro Kurasawa, Junya Nagasawa, Ryutaro Yamazaki, Satoko Arai, Takayoshi Owada, Takeshi Fukuda
Pulmonary Medicine and Clinical Immunology, Dokkyo Medical University, Tochigi, Japan

Risk factors for AEs by TMP-STX in CVD patients are unknown and also clinical features of AEs remain to be clarified. To identify risk factors for AEs of TMP-STX. To clarify clinical features of the AEs in CVD patients with immunosuppressive therapy. Subjects were consecutive 541 patients, 312 patients with CVD and 229 patients with pulmonary diseases, who received TMP-STX for prophylaxis of PCP from 2003 to 2009 in department of pulmonary medicine and clinical immunology in Dokkyo Medical University. Positivity for anti-RNP antibody is a risk factor for adverse effects of trimethoprim-sulphamethoxazole in collagen-vascular disease patients. Patients with anti-RNP antibody showed fever as an adverse effect of trimethoprim-sulphamethoxazole.

P3-390

Two cases of semi-constrained TEA for distal humerus fracture in RA

Takahito Yamasaki, Yasushi Oshima, Kensuke Kido, Torao Kusakabe
Department of Orthopaedics, Japanese Red Cross Kyoto Daini Hospital, Kyoto, Japan

Primary total elbow arthroplasty (TEA, Discovery elbow system, Biomet) in the management of acute distal humerus fracture was performed for 2 patients with RA. The patients were a 79 years old female with Steinbrocker stage III and class III in case 1, and a 66 years old male with Steinbrocker stage III and class II in case 2. The fracture types according to the AO classification were C3 and C1, respectively. Three months after surgery, flexion arc was 20 to 145 degrees in case 1 and was 20 to 130 in Case 2, and both cases had excellent results. The treatments of distal humerus fractures for osteoporotic patients were difficult. The cases without severe load on the surgery sites post operation could be recommended to performed TEA, especially severe commuted fracture and bone destruction cases.

P3-391

Treatment of Intraosseous Cystic Lesion in Distal Radius in Rheumatoid Arthritis

Jun Hashimoto¹, Makoto Hirao², Kenrin Shi², Akihide Nampei³, Tsuyoshi Murase², Hideki Yoshikawa²
¹NHO Osaka Minami Medical Center, ²Department of Orthopaedic Surgery, Osaka University Graduate School of Medicine, ³Department of Orthopaedic Surgery, Osaka Rousai Hospital

We investigated the radiological outcomes of our new surgical treatment for juxta-articular intra-osseous cystic lesions in distal radius, curettage and packing with interconnected porous calcium hydroxyapatite (IP-CHA) which is an artificial bone substitute with excellent bone inductivity. Six female patients with RA were studied with minimal follow-up of 1 year after the surgery. Based on the final radiographs obtained an average of 1.9 year postoperatively, all

patients exhibited sufficient incorporation of IP-CHA into surrounding bone. In one case with connectivity between cystic lesion and radio-carpal joint, we failed to pack the IP-CHA sufficiently. This procedure is a feasible method, by which the prevention of pathological fracture and joint destruction could be highly expected.

P3-392

Two cases of RA who were able to avoid biologics after arthroplasty of the wrist

Yoshifumi Shibata¹, Arata Nakajima¹, Koichi Nakagawa¹, Masato Sonobe¹, Yasuchika Aoki¹, Shintaro Tsuge¹, Yu Sasaki¹, Manabu Fujino¹, Teruo Furufu¹, Toru Suguro²

¹Department of Orthopedic Surgery, Toho University Sakura Medical Center, ²Department of Orthopedic Surgery, Toho University Omori Medical Center

[Introduction] We report two RA patients who were supposed to receive biologics but were able to avoid them after arthroplasties of the wrist. [Case 1: 59yrs, female] She has been treated with 8 mg of MTX per week but showed high disease activity with 1.23 of CRP and 318 of MMP3. Three months after surgery, she got low disease activity. [Case 2: 57yrs, female] She has been treated with 6 mg of MTX per week but showed high disease activity with 2.4 of CRP and 200- of MMP3. Three months after surgery, she got low disease activity. [Discussion] It has not been determined which should be chosen next biologics or surgery when DMARDs cannot improve symptoms. In patients whose CRP levels are relatively low and arthritis is localized, arthroplasties have potential to avoid biologics.

P3-393

A case of RA elbows complicated with olecranon fractures

Reou Ohguchi, Kiichirou Andou, Hidenori Muro, Hironari Sakurai
Tosei General Hospital

The patient was a 61 years old female who had been treated as rheumatoid arthritis (RA) for more than twenty years. She had left olecranon fracture and one year after she had right olecranon fracture. The elbows are severe damaged by RA, and we gave up the treatment of osteosynthesis of the olecranon. We had an operation of removal of olecranons and of replacement of total elbows. Now range of motion of her elbows, especially supination and pronation was improved. The complaint of her elbows and her activities of daily living were also improved, too. We have experienced a case of severe RA elbows with olecranon fractures. We have difficulty in the treatment of such case, but the way of this operation is often useful.

P3-394

Role of leptin in the B cell function

Rong Hou¹, Qingshun Lin¹, Aya Sato¹, Katsuko Sudo², Sachiko Hirose¹

¹Department of Pathology, Juntendo University School of Medicine, Tokyo, Japan, ²Animal Research Center, Tokyo Medical University, Tokyo, Japan

[Background] Leptin is a cytokine-like hormone and involved in the control of not only food intake but also immune responses. Recently it has been shown that leptin suppresses Treg function; however, the role for B cell function is not known. In this study, we investigated the role of B cell function using leptin-deficient mice. [Methods] We generated leptin-deficient *B6.ob/ob.Yaa* congenic mice and compared the serum levels of IgG and IgM between *B6.Yaa* and *B6.ob/ob.Yaa* mice. [Results] The class switch from IgM

to IgG was suppressed in *B6.ob/ob.Yaa* mice. [Conclusion] Leptin may accelerate B cell function in the stage of class switch recombination.

P3-395

Type I interferon derived from macrophage can suppress regulatory T cells.

Takeshi Nakatsue

Section of Molecular Biology, Division of Biological Sciences, University of California, San Diego, La Jolla, California, USA, Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Ja

Objective: Infection is one of the most important complications in autoimmune disease. It was reported that interleukin-6 derived from dendritic cells stimulated by lipopolysaccharide (LPS) suppress regulatory T cells (Treg) (*Science*, 2003). I hypothesized that type I interferon (IFN) derived from antigen presenting cells also suppress Treg. **Methods:** Bone marrow-derived macrophage (Mφ) were incubated with LPS. CFSE stained CD4 cells were incubated with Treg, conditioned media (CM) from Mφ, and anti-CD3 antibody and were analyzed by flow cytometry. **Result:** Treg suppressed CD4 cells. CM from Mφ suppressed Treg. Anti-IFN α receptor antibody suppressed the CM. CM from IFN regulatory factor 3 deficient Mφ did not suppress Treg. **Conclusion:** Type I IFN derived from Mφ can suppress Treg.

P3-396

NKT cell is required for the generation of autoantibody-inducing CD4⁺ T cell

Yuko Fujita¹, Ken Tsumiyama¹, Shunichi Shiozawa^{1,2,3}

¹Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan., ²Department of Medicine, Kobe University Graduate School of Medicine, Kobe, Japan., ³The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan.

Objective: The autoantibody-inducing CD4⁺ T (*ai*CD4⁺ T) cell is the key for the cause of systemic autoimmunity. Here we studied the role of NKT cell in the break of anergy and the generation of *ai*CD4⁺ T cell.

Methods: Spleen cells of mice were stimulated with α -galactosylceramide (α -GC), and this supernatant herein termed NKT-sup. This NKT-sup was repeatedly immunized in CD1d KO mice, following immunization 2x with SEB to induce T cell anergy. Spleen cells were stimulated *in vitro* with SEB, and IL-2 and mitotic events were measured.

RESULTS: The once-anergized T cells of CD1d KO mice were re-activated from anergy to resume IL-2 production and proliferation after repeated immunization of NKT-sup.

Conclusion: NKT cell and its effector molecule are required for the generation of *ai*CD4⁺ T cell.

P3-397

IL-33 contributes to joint inflammation via mast cell immune function

Shinjiro Kaieda

Division of Respiratory, Neurology and Rheumatology, Kurume University School of Medicine

Mast cells (MCs) have been recognized as potential participants in inflammatory arthritis. Recent studies have highlighted potent effects of the synovial fibroblast-derived IL-33 on the phenotype of

MCs. We explored the importance of this axis in the K/BxN serum transfer model of arthritis. Compared with littermate controls, ST-2 KO mice exhibited a reduced intensity of arthritis. Since activation of MCs in this model proceeds via Fc γ receptors, we examined the implications of IL-33 exposure to IgG-mediated activation of MCs. Pre-incubation with IL-33 markedly enhanced production of pro-inflammatory cytokines such as IL-1 β and MIP-2. These findings define a novel role of IL-33 in the priming of MCs for immune complex-mediated inflammation and demonstrate a key role for IL-33 in arthritis.

P3-398

Beyond Inflammasome: Role of dipeptidyl peptidase I in IL-1b maturation In Vivo

Hajime Kono¹, Tamiko Yanagida¹, Maki Takayama¹, Kurumi Asako¹, Hiroto Kikuchi²

¹Department of Internal Medicine, Teikyo University School of Medicine, ²Department of Microbiology and Immunology, Teikyo University School of Medicine

(background) Although we and others showed that the acute neutrophilic inflammation to crystals almost entirely depends on IL-1b In Vivo, mice deficient in inflammasome components showed only a modest reduction in these responses. (Materials and Methods) The neutrophil and monocyte response to the silica crystals or dead cell i.p. injection were quantified after 4 or 14 hours. (Results) Fourteen hours after injection of silica crystal, the mean total number of neutrophil ($\times 10^6$) in the peritoneal cavity were 1.9 (WT), 2.1 (Caspase-1 KO), 1.3 (DPPI KO), 1.0 (DPPI/Caspase-1 DKO), 0.4 (IL-1b KO), 0.3 (IL-1R KO) and 0.0 (PBS injected WT control). (Conclusion) The data indicate that DPPI plays a role in the crystal- or dead cell- induced acute inflammatory responses in addition to Caspase-1.

P3-399

Comprehensive gene expression profiling of the joint of gp130F759 mice

Katsuhiko Ishihara, Ayano Yahagi, Taro Saika, Hideya Igarashi
Immunology and Molecular Genetics, Kawasaki Medical School, Kurashiki, Japan

To understand the earliest pathophysiology of arthritis in the knock-in mouse gp130F759 having Y759F mutation in gp130, microarray analysis of the joints between female gp130F759 and control B6 at 5 months' old was performed. Among 34,383 genes, 2,425 genes exhibited more than 2-fold increase, whereas 3,027 genes did the decrease. The numbers of genes showing more than 4-fold increase or decrease are 334 or 278, respectively. Pathway analysis revealed 3 pathways for blood clotting cascade, heme biosynthesis, and matrix metalloproteinases exclusively consist of up-regulated genes. Among genes in immune system, the expression of *ZAP70* mediating TCR signal was increased. The data indicate that expression of the genes capable destroying the joint starts in gp130F759 as early as 5 months' old.

P3-400

Chemokines expressed by the regenerating muscle cells in murine myositis model

Shinya Hirata, Naoki Kimura, Nobuyuki Miyasaka, Hitoshi Kohsaka

We have established mouse C protein-induced myositis (CIM) as a model of polymyositis. Adoptive transfer of CIM demonstrated that both activated antigen-specific T cells and CFA-induced activation of innate immunity at the muscles were essential for induction of the autoimmune myositis. We planned to investigate whether chemokines are produced by muscle fibers affected by autoimmune myositis. Three chemokines were expressed by *in vitro* differentiation of murine myofibroblast cells, and in CIM muscle tissues. These implied that inflammatory chemokines were expressed in regenerating muscle cells and myositis tissues. Although we need to investigate these chemokines associate with onset of myositis. They might contribute to activation of innate immunity in the muscles.

P3-401

The effect of E-selectin on the progression of CD8+cell infiltration in MRL mice

Shuhei Yoshimoto¹, Kimihiko Nakatani¹, Osamu Asai¹, Ken-ichi Samejima¹, Hirokazu Sakan¹, Masayuki Iwano¹, Masato Nose²

¹First Department of Internal Medicine, Nara Medical University, Kashihara, Nara, Japan, ²Division of Pathogenomics, Department of Pathology, Ehime University Graduate School of Medicine, Toon, Ehime, Japan

MRL/lpr mice spontaneously develop lupus nephritis and vasculitis. Previously, we showed the progression of glomerular lesions was restrained in MRL/lpr mice overexpressed of serum soluble E-selectin protein (sE (+) MRL/lpr mice). In this study, we examined the effect of soluble E-selectin on the progression of vasculitis and perivascular inflammatory cells infiltration. In sE (+) MRL/lpr mice at age of 12, 16, and 20 weeks, the severity of vascular lesions and perivascular CD8+T cells infiltration levels were decreased, compared with MRL/lpr mice. However, the degrees of perivascular CD4+T cells infiltration in sE (+) MRL mice were similar with those in MRL/lpr mice. In conclusion, soluble E-selectin may protect the progression of vasculitis and suppress perivascular CD8+T cells infiltrations.

P3-402

Proteome analysis of serum peptide related to the onset of arthritis of CIA rat

Hiroyuki Mitsui^{1,3}, Kazuki Okamoto¹, Manae S. Kurokawa¹, Mitsumi Arito¹, Kouhei Nagai¹, Kazuo Yudo², Moroe Beppu³, Tomohiro Kato¹

¹Dept. of Clin. Proteomics & Mol. Med., St. Marianna Univ. Schl. Med., Kawasaki, Japan, ²Dept. of Front. Med., Inst. of Med. Sci., St. Marianna Univ. Schl. Med., Kawasaki, Japan, ³Dept. of Orthop. Surg., St. Marianna Univ. Schl. Med., Kawasaki, Japan

Objective: To investigate pathological and diagnostic peptides on the onset of rheumatoid arthritis (RA), we analyzed serum peptides increased or decreased around the onset of arthritis in the collagen-induced arthritis (CIA) model rats. Methods: Serum samples were obtained at early, middle and late stages of CIA. Then serum peptides which changed between the CIA rats and the control group were detected by mass spectrometry. Results: We successfully detected 55 peptides which showed different intensity between the two groups. Of these, 19 peptides were increased in the CIA group compared to the control group. These peptides, now we are trying to

identify their sequences, may have pathological and/or diagnostic peptides in CIA and further in RA.

P3-403

The possible involvement of Cas-L/Nedd9 in collagen-induced arthritis

Tomoki Katayose, Satoshi Iwata, Yoshiko Kichikawa, Osamu Hosono, Hiroshi Kawasaki, Yoshiyuki Kanai, Hirotoshi Tanaka, Chikao Morimoto

Division of Clinical Immunology, Advanced Clinical Research Center, the Institute of Medical Science, the University of Tokyo, Japan

(Background) Cas-L/Nedd9 is a cytoplasmic docking protein downstream of b1 integrins, which is essential for cell invasion and migration. (Methods & Results) To examine the pathophysiological role of Cas-L in RA, collagen-induced arthritis was employed using Cas-L ^{-/-} (homo), Cas-L ^{+/-} (hetero), and wild-type (wt) mice. Although the incidence of arthritis was unaltered, wt and hetero mice showed higher severity of arthritis compared to homo mice, which was evaluated by scoring and histology. The serum levels of inflammatory cytokines, TNF- α , IL-17, and IL-6 were higher in wt and hetero mice, whereas that of anti-inflammatory cytokine, IL-10 was higher in homo mice. (Conclusion) Cas-L may play an essential role in pathophysiology of RA partially through the regulation of cytokine production.

P3-404

The role of S1P3 receptor signaling in the bleomycine-induced pulmonary fibrosis

Ken Murakami¹, Masataka Kohno¹, Masatoshi Kadoya², Amane Nakabayashi¹, Takashi Kida¹, Hidetake Nagahara¹, Wataru Fujii¹, Kaoru Nakamura¹, Takahiro Seno¹, Aihiro Yamamoto¹, Hidetaka Ishino¹, Yutaka Kawahito¹

¹Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, ²Matsumita Memorial Hospital, Osaka, Japan

Sphingosine-1-phosphate (S1P) is a bioactive sphingolipid metabolite involved in many critical cellular processes including proliferation, migration, and angiogenesis. To clarify the role of S1P3 receptor signaling in the pathogenesis of pulmonary inflammation and fibrosis, we injected bleomycine intratracheally into S1P3-deficient (KO) and wild type (WT) mice. In acute phase, S1P3 KO mice exhibited significantly attenuation of body weight loss and less inflammation histologically. In chronic phase the pulmonary fibrosis in KO mice was also less than WT. Total cell count of bronchoalveolar lavage fluid on the 7th day was less in KO mice than WT controls. These results indicate that S1P3 receptor signaling plays an important role in the pulmonary inflammation and fibrosis.

P3-405

The influence of joint destruction on the improvement of body function and ADL

Shinichiro Fujita¹, Masamitsu Natsumeda², Ryutaro Yamanaka², Misuzu Yamashita², Koji Takasugi², Kayo Ezawa², Kazuhiko Ezawa², Yoshihisa Nasu³, Keiichi Nishida⁴

¹Department of Rehabilitation, Kurashiki Kosai Hospital, Kurashiki, Japan, ²Department of Internal Medicine, Kurashiki Kosai Hospital, Kurashiki, Japan, ³Department of Orthopaedic Surgery, Kurashiki Kosai Hospital, Kurashiki, Japan, ⁴Department of Human Morphology

gy, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Objective: To consider intervention of rehabilitation therapy for RA patients who start anti-TNF therapy. **Methods:** We examined body function (grip, DASH) and ADL (m-FIM, m-HAQ) of 80 patients at starting of therapy and after one year. We compared their variables between patients of Stainblocker Stage 1/2 and patients of Stage 3/4. **Results:** After one year follow-up, body function and ADL were significantly improved in the former group. The latter group showed less improvement in function of fingers, hands and upper extremities than the former group. **Conclusion:** Patients with mild joint destruction are adaptable to constructive and recuperative intervention of rehabilitation. Patients with severe joint destruction need environmental intervention such as welfare equipment and splint bandage.

P3-406

A survey on the effects of music therapy for patients with rheumatoid arthritis

Yasushi Miura^{1,2}, Kinue Matsuo¹, Koji Fukuda², Masayasu Takahashi², Masahiro Kurosaka², Ikuko Yamasaki³

¹Department of Rehabilitation Science, Kobe University Graduate School of Health Sciences, Kobe, Japan, ²Department of Orthopaedic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan, ³Department of Occupational Therapy, School of Health Sciences, Tokyo Univ. of Technology, Tokyo, Japan

OBJECTIVE: Recently music therapy is widely innovated in various fields including rehabilitation, however, few reports have been made in rheumatology. Since 2003, our department has held monthly patient education classes for patients with RA. We surveyed the effects of music therapy for patients with RA in the class. **METHODS:** Music therapy was conducted by a music therapist. Eight songs were sung with a piano accompaniment. General condition was surveyed with 10cm VAS and pain was with face pain rating scale.

RESULTS: Twelve patients were participated the survey. VAS was improved from 3.3 ± 2.4 to 2.5 ± 2.8 ($P < 0.05$), and face scale was also improved from 5.6 ± 2.6 to 3.1 ± 2.4 ($P < 0.01$) after music therapy.

CONCLUSION: Music therapy is effective to improve physical condition for patients with RA.

P3-407

A Case of RA: Cerebral Infarction During Etanercept Therapy and Home Discharge

Nagachika Sugisaki^{1,2}, Takashi Aikawa¹, Yoshihiro Ishihara¹, Yoshinari Takasaki², Masahiko Yasuda^{1,2}

¹Nakaizu Spa Hospital, Izu city, Japan, ²Division of Rheumatology Department of Internal Medicine, Juntendo University School of Medicine, Tokyo, Japan

A 69-year-old woman had rheumatoid arthritis (RA). Etanercept (ETN) improved inflammation but upper-limb function decreased. She was referred and admitted to our hospital for RA rehabilitation. She had hypertension and hyperlipidemia controlled by oral drugs, but developed hemorrhagic cerebral infarction (HCI) at our hospital. After acute treatment at another hospital, we readmitted her for post-infarction rehabilitation, continued etanercept, and reinitiated rehabilitation. Left hemiplegia remained after ~6 months but ADL improved, and she was discharged to home. This patient had RA with HCI and decreased ADL. This case was thought to be valuable be-

cause her home discharge was possible with totally managed care, focusing on rehabilitation with nurses, medical social workers, and therapists.

P3-408

Anti-ribosomal P protein antibodies with macrophage activating syndrome in SLE

Satoko Tejima, Toshihiro Tono, Noriko Tono, Tatsuo Nagai, Sumiaki Tanaka, Shunsei Hirohata

Department of Rheumatology and Infectious Disease, Kitasato University School of Medicine, Sagami-hara, Japan

We have recently disclosed that anti-P enhance the production of proinflammatory cytokines of activated monocytes. The current study was undertaken to explore the association of anti-P with MAS in SLE. Autoantibodies and cytokines were analysed in sera from 8 SLE patients with MAS who had been hospitalized between 2006 and 2010. Of the 8 patients anti-DNA, anti-Sm, anti-P were positive in 4 patients, 1 patient and 4 patients, respectively. Serum IL-6 and IL-17 levels were elevated in 7 patients, serum IL-18 levels were elevated in all patients. Serum IFN- α levels were elevated in one patient, and serum IFN- γ levels were elevated in 3 patients. The results indicate that pathogenesis of MAS in SLE is heterogenous. Moreover, the data also suggest that anti-P might be involved in MAS in SLE.

P3-409

Three cases of SLE complicated with AIHA treated with immunoadsorption

Koji Shimaya¹, Shogo Kawaguchi¹, Yoh Ishiguro²

¹Department of Gastroenterology and Hematology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan, ²Division of Endoscopy, Hirosaki University School of Medicine and Hospital, Hirosaki, Japan, ³Public Noheji Hospital, Aomori, Japan

Autoantibodies and complement contribute to pathogenesis of SLE and AIHA. Rapid removal of autoantibodies is beneficial for SLE and AIHA. We presented three cases of SLE complicated with AIHA, who were treated with immunoadsorption. Case 1: A 27-year old female developed high-grade fever, purpura and hemolytic anemia. She had positive ANA, anti-ds-DNA antibody, direct coombs test. Case 2: A 49-year old female has SLE since 1997. Hemolytic anemia has flared up again. She had positive ANA, anti-ds-DNA antibody, immune complex and direct coombs test. Case 3: A 67-year old female developed fever, pancytopenia, hemolytic anemia, pleuritis and lymphadenitis. She had positive ANA, anti-ds-DNA antibody, immune complex and direct coombs test.

P3-410

Assessment of Combined Calcineurin Inhibitor and Mizoribine Therapy for SLE

Hideyuki Horikoshi, Mitsuyo Matsumoto, Kunio Takada, Masahiro Nakashima, Takashi Nakanishi, Tomoaki Higuchi, Takahiro Yoshikawa, Kimihiro Suzuki

Department of Internal Medicine, Division of Rheumatology, National Defence Medical College, Tokorozawa, Japan

[Objective] The efficacy and safety of combined calcineurin inhibitor (CNI) and mizoribine (MZR) therapy for systemic lupus erythematosus (SLE) were retrospectively assessed. [Methods] SLE patients on maintenance CNI therapy in whom it was difficult to reduce their corticosteroid dose ($n=19$) were administered MZR at 150

mg/day. [Results] The CNIs used were ciclosporin in 14 patients and tacrolimus in 5 patients. The average corticosteroid dose was reduced from 11.7 mg/day to 4.7 with improvement of immunological parameters following the additional use of MZR. [Conclusion] These results suggest that additional use of MZR is effective for improving symptoms without any serious adverse effects in SLE patients on CNI therapy in whom it is difficult to reduce their corticosteroid doses.

P3-411

CVD-pulmonary arterial hypertension (CVD-PAH) south-boso area, Chiba

Tamao Nakashita, Akira Inoue, Natsuki Fujio, Shinji Motojima
Rheumatology and Allergy, Kameda Medical Center, Chiba, Japan

The prevalence of CVD-PAH has been reported to be around 10 %. However, we have an impression that the prevalence of CVD-PAH in south-boso area is low. We had a screening of PAH in patients with SSc, MCTD and SLE by using UCG. A total of 89 patients, 46 SSc, 13 MCTD and 30 SLE, were screened by UCG and estimated RV systolic pressure (e-RVSP) of more than 35 mmHg was diagnosed as suspected PAH. The mean age was 56 years (range: 24 – 89), and the mean disease duration was 9.8 years (range: 0.5 – 35). There were only 2 patients who meet the criteria (2.2 %). e-RVSP did not have a significant correlation with disease duration, but had significant correlations with BNP and NT-proBNP. It was suggested that the prevalence of CVD-PAH is low in this area but the reason has not been known.

P3-412

The treatment against CNS-Lupus with association of high DNA

Masaki Akamine, Kazunori Uehara, Takashi Oura
Hemodialysis Unit, Oura's Lupus Clinic, Nahacity Okinawa Japan

A 33 year-old female patient was diagnosed with SLE in 2003. In 2009, she visited our clinic as she had recurrence. Laboratory findings showed high anti-DNA antibody as 300 IU/ml, as well as markedly high anti-RNP antibody, anti-SM antibody, and anti-SS-A antibody. Since various antibodies were abnormally high with complications of psychological symptom, the patient was diagnosed as CNS-lupus. We performed pulse therapy and prescribed prednisolone. Simultaneously, we performed double filtration plasmapheresis (DFPP) to remove abnormally high antibodies. After 8 sessions, anti-DNA antibody decreased below 100 IU/ml. The psychological symptom and rashes were cured.

P3-413

Efficacy of tacrolimus for SLE with or without low dose corticosteroid

Toyohiko Sugimoto, Yukiko Hiramatsu, Masaaki Furukawa, Takao Sugiyama, Makoto Sueishi
Simosizu National Hospital

To evaluate the efficacy of tacrolimus in systemic lupus erythematosus patients without organ involvement.
Methods; Twelve patients were administered tacrolimus and low dose corticosteroids for the deterioration of their disease without organ

P3-414

Spontaneous repair of steroid-associated osteonecrosis in SLE patients

Junichi Nakamura¹, Tomonori Shigemura¹, Yoshitada Harada², Koh Shimizu³, Satoshi Iida⁵, Koya Kamikawa⁷, Munenori Takeshita¹, Masahiko Suzuki⁸

¹Department of Orthopaedic Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan, ²Chibaken Saiseikai Narashino Hospital, Narashino, Japan, ³Chiba Rosai Hospital, Ichihara, Japan, ⁴Chiba Kaihin Municipal Hospital, Chiba, Japan, ⁵Matsudo City Hospital, Matsudo, Japan, ⁶Funabashi Orthopaedic Hospital, Funabashi, Japan, ⁷Teikyo University Chiba Medical Center, Ichihara, Japan, ⁸Chiba University Research Center for Frontier Medical Engineering

Objective: To clarify spontaneous repair of osteonecrosis in SLE.

Methods: 537 joints (251 hips and 286 knees) in 144 SLE patients were included with follow-up period of 14 years. Osteonecrosis developed in 537 joints (44%). After initial therapy, SLE was well maintained in 159 joints but recurred in 79 joints. Spontaneous repair was evaluated with MRI.

Results and Conclusion: Spontaneous repair was observed in 117 joints (49%); for osteonecrosis of the femoral head, 48% of type C2 hips, 50% of C1 hips, 71% of B hips, and 100% of A hips. Spontaneous repair was observed in 57% without SLE recurrence and 34% with recurrence. Cox regression analysis indicated that type A hips had a 2.5 times and non-recurrence group had a 2.3 times higher likelihood of repair.

P3-415

Tacrolimus therapy for SLE with sustained mild to moderate disease activities

Yoko Wada¹, Daisuke Kobayashi¹, Shuichi Murakami¹, Takeshi Kuroda², Masaaki Nakano³, Ichiei Narita¹

¹Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, ²Health administration center of Niigata University, Niigata, Japan, ³Department of Medical Technology, School of Health Sciences, Faculty of Medicine, Niigata University, Niigata, Japan

Purpose; To examine the effect of tacrolimus (Tac) in patients with systemic lupus erythematosus (SLE) with sustained mild to moderate disease activities. Methods; In 26 of 238 SLE patients who visited our hospital between April to June 2010, the clinical and laboratory findings were compared before and after Tac administration. Results; Twenty-five patients continued Tac therapy, and the titer of anti-dsDNA antibody and SLEDAI were significantly improved after Tac administration. One patient discontinued Tac because of the elevation of anti-dsDNA antibody and pleuritis. Her serum trough level of Tac was 2.2 ng/ml, and pleuritis was improved after changing Tac to cyclosporine 300mg daily. Discussion; The insufficient dosage of Tac might be one of the causes of relapse in a dropout case.

P3-416

Mycophenolate mofetil (MMF) in lupus and lupus nephritis patient

Yasuhiro Suyama, Mitsumasa Kishimoto, Yuri Ohhara, Atsushi Nomura, Hisanori Shimizu, Eishi Uechi, Ken-ichi Yamaguchi, Yukio Matsui, Masato Okada

[RATIONALE] In this study we report 9 SLE patients with MMF in our hospital.

[Method] A retrospective review of medical records in our hospital was performed.

[RESULTS] Analysis of the data revealed 9 SLE patients (8 is female, 1 is male) with MMF during the period. The ethnic group was Japanese (6), American (2), and Canadian (1). Lupus nephritis (6), CNS lupus with chronic inflammatory demyelinating polyneuropathy (1), and generalized morphea with SLE (1) were recorded. Observation period was from 1 month to 5 years and 6 months. Maintenance dose of MMF was from 0.75 g/day to 2.5 g/day. Infection (Tuberculosis in 1 patient and Varicella-zoster virus in 1 patient) was observed, but any other severe adverse effects were not noted.

[CONCLUSIONS] MMF is relatively safe and effective in SLE.

P3-417

Effectiveness of PSL and Tac combination therapy in SLE with thrombocytopenia

Nobuhisa Hirase, Hideyuki Watanabe, Hiroshi Nishikawa, Hideaki Goda, Shoichiro Ikuyama

Division of Rheumatology, Hematology, and Metabolic Diseases, Kyushu University Hospital at Beppu, Beppu, Japan

Case1: A 64-years-old woman was diagnosed as SLE in 1993. She received maintenance treatment with prednisolone (PSL) 5 mg/day. Her platelet count fell to less than 100,000/ μ l since May 2010. She was diagnosed as hemophagocytic syndrome (HS). She was administered tacrolimus (Tac), and her platelet count increased. Case2: A 65-years-old woman was diagnosed as SLE in 2003. Her platelet count was 7000/ μ l. She was administered PSL and underwent a sanitization treatment, and her platelet count increased. The PSL was gradually decreased. After reducing the PSL dosage to 7 mg/day, her platelet count was observed to range from 40,000/ μ l to 50,000/ μ l. She was diagnosed as HS. She was administered Tac. Combination therapy with PSL and Tac is considered to be an effective treatment of thrombocytopenia in SLE.

P3-418

Association between decreased serum L-ficolin level and thrombocytopenia in SLE

Rie Saito, Hiroshi Watanabe, Shuzo Sato, Haruyo Iwadata, Hiroko Kobayashi, Hiromasa Ohira

Department of Gastroenterology and Rheumatology, Fukushima Medical University School of Medicine, Fukushima, Japan

To investigate the relationship between L-ficolin and systemic lupus erythematosus (SLE), serum L-ficolin levels were measured by ELISA in patients with SLE as well as healthy controls. We observed that serum levels of L-ficolin in patients with SLE were significantly lower when compared with those in healthy controls. Investigations about the differential expression of L-ficolin in SLE patients and their clinical subset revealed that thrombocytopenia was associated with decreased levels of serum L-ficolin. There were no correlations between serum L-ficolin levels and SLE Disease Activity Index, serum C3 levels or serum C4 levels. Our results suggest that L-ficolin may have a pathogenic role in patients with SLE.

P3-419

Combination therapy with AZP and TAC in SLE refractory to steroids

Shuzo Yoshida, Tohru Takeuchi, Kentaro Isoda, Koji Nagai, Kenichiro Hata, Shigeki Makino, Toshiaki Hanafusa

First Department of Internal Medicine, Osaka Medical College, Takatsuki, JAPAN

Objective: To evaluate the efficacy and safety of combination therapy with azathioprine (AZP) and tacrolimus (TAC) in SLE refractory to steroids. **Methods:** Eight SLE patients (2 men and 6 women) were treated with combination with AZP and TAC. AZP dose ranged from 50 mg to 125 mg/day, and Tac dose ranged from 2 mg to 4 mg/day. **Results:** Prednisone dose before the combination therapy was 19.8 ± 15.4 mg/day. The serum C3 level, and SLEDAI were 66.6 ± 29.1 mg/day and 6.25 ± 7.4 , respectively. Serum C3 level and SLEDAI at 3 months after the combination therapy were 79.1 ± 22.9 mg/dl, and 1.14 ± 1.6 mg/dl, respectively. SLE had improved in 7 patients, and had failed to respond to treatment in one. **Conclusion:** Combination therapy with AZP and TAC is efficient and well tolerated in SLE refractory to steroids.

P3-420

An autopsy case of systemic lupus erythematosus with cryptococcal meningitis

Amane Nakabayashi, Hidetaka Ishino, Takashi Kida, Hidetake Nagahara, Wataru Fujii, Ken Murakami, Kaoru Nakamura, Takahiro Seno, Aihiro Yamamoto, Masataka Kohno, Yutaka Kawahito

Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

A 72-year-old woman with systemic lupus erythematosus, who was treated with tacrolimus (1.5 mg/day), mizoribine (150 mg/day), and prednisolone (17.5 mg/day), showed rapid progression of dementia and unconsciousness. Examination of the cerebrospinal fluid with India ink and cryptococcal antigen testing were positive, so she was diagnosed as cryptococcal meningitis. Although she was treated with Amphotericin B and flucytosine or fluconazole, she was getting worse and finally died with multiple organ failure. Cryptococcal antigen collected at autopsy was remarkably elevated. Cryptococcal meningitis is an important opportunistic infection and often fatal. We should pay attention to progress of dementia of an immunosuppressed patient, which may be the first symptom of cryptococcal meningitis.

P3-421

A case of *Helicobacter cinaedi* bacteremia in SLE

Kurumi Asako, Hirotoshi Kikuchi, Maki Takayama, Akiteru Takeuchi, Hajime Kono

Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan.

31-year-old woman developed SLE and RA. She was admitted to the hospital for suspected cellulitis. Although the administration of cefazolin and clindamycin was initiated after admission, pazu-floxacin was eventually administered instead of these drugs for drug eruption. Since no symptomatic improvement was observed, treatment was replaced with aztreonam (AZT). In blood culture, *H. cinaedi* was detected, and AZT was administered continuously, since the drug was considered to be effective. Decline of fever was confirmed on the 3rd day of AZT administration, and CRP became negative on the 18th day of treatment. *H. cinaedi*, which causes an

emerging infection, requires long period of time to grow, and thus it is important to extend the duration of culture when this bacterium is suspected.

P3-422

Validity of 2010 ACR/EULAR RA Criteria for undifferentiated arthritis.

Satoshi Shinohara

Tochigi Rheumatology Clinic, Utsunomiya, Japan

An evaluation of the validity of 2010 ACR/EULAR RA Classification Criteria was performed. Out of 500 outpatients, 72 undifferentiated arthritis pts with swollen joint(s) were classified using both the old 1987 and the new 2010 criteria into 4 groups (old/new: +/+, +/-, -/+, -/-) and were compared to current diagnosis. +/+, +/-, -/+, and -/- groups consisted of 18 pts (RA:18, PsA:1, HES:1), 3 pts (RA:2, PsA:1), 13 pts (RA:12, OA+CKD:1), 38 pts (non-RA:38), respectively. The sensitivities of the new and old criteria were 93.3%, and 60.0%, while their specificities were 92.9%. In my Rheumatology Clinic Practice, a new criteria has been beneficial for early diagnosis. In view of these results, differential diagnosis including PsA, HES, and OA is necessary during diagnostic procedure.

P3-423

Comparison of the 1987ACR, 2010, 2010ACR/EULAR and 1988 Japanese criteria for RA

Masaomi Yamasaki¹, Naoki Katsuyama¹, Takahito Kimata¹, Shoichi Ozaki²

¹Division of Rheumatology, Yokohama City Seibu Hospital, St.Marianna University School of Medicine, ²Division of Rheumatology and allergy, St.Marianna University School of Medicine

Objective: To evaluate differences in classification between the 1987 ACR-criteria, 2009, 2010 ACR/EULAR criteria and 1988 early RA criteria by Japanese Ministry of Health and Welfare. Methods: 104 patients newly arrived were retrospectively analyzed. Results: At the first presentation, 34 patients fulfilled the 1987-criteria, 46 patients the 2009-criteria, 34 patients the 2010-criteria and 46 the 1988-criteria. 12 of 46 patients fulfilling the 2009-criteria did not fulfill the 2010-criteria. There is a statistical difference only in the score of serology between 2009 and 2010-criteria ($p < 0.001$). The sensitivity was 93.8% in 2009-criteria and 69.3% in 2010-criteria. Conclusion: Radiographic approach, excluded from 2010-criteria, is essential for classification of RA.

P3-424

Validity of a 2010 ACR/EULAR rheumatoid-arthritis (RA) classification criteria

Hirotohi Matsumoto¹, Mari Ushikubo¹, Kumiko Akiya¹, Ikuko Tanaka², Shigenori Tamaki³, Hisaji Ohshima¹

¹Department of Connective Tissue Disease, Tokyo Medical Center, Tokyo Japan, ²Fujita Health University School of Medicine, Department of Clinical Laboratory, ³Department of Rheumatology, Mie Chuo Medical Center

Purpose) Validity of the novel classification criteria in our country was studied. Methods) Seventy four cases with joint swellings before publication of the criteria were enrolled. "RA" was defined by the definition of the criteria of RA, i.e. DMARD was started. Results) 1; "RA" was 37, where a sensitivity and specificity of the criteria were 97% and 100%, respectively. Osteoarthritis (OA), MCTD, DM, and SLE were ruled out. 2; The 1987 ACR criteria showed

lower sensitivity. 3; Although a case of ACPA+ did not fill the new criteria, DMARD was used as "RA". Conclusion) The new criteria for RA was suggested to be a useful tool in our country. Differential diagnosis was important. ACPA seemed to be useful for clinical diagnosis for RA.

P3-425

Proposing a Method of Regional Assessment in Rheumatoid Arthritis (RA)

Susumu Nishiyama¹, Tetsushi Aita¹, Yasuhiko Yoshinaga¹, Shoji Miyawaki¹, Hiroki Kishimoto², Michio Toda², Yoshiki Yoshihara², Shinya Miyoshi², Akira Manki³

¹Rheumatic Disease Center, Kurashiki Medical Center, ²Department of Orthopedics, Kurashiki Medical Center, ³Department of Pediatrics, Kurashiki Medical Center

We showed a method of regional assessment in 37 patients with RA, who received IFX or TCZ. Joints were divided into 4 regions: upper/large, upper/small, lower/large and lower/small. Joint index was calculated as follows: affected joint counts divided by the number of joints in each region. At the baseline, there was no difference of joint indices between the groups except for swollen joint index in upper/small. In lower/large region, TCZ group showed significantly less swollen joint index than IFX group at 15 and 30w. As a whole, the TCZ group showed significantly lower persistence rate of swollen joints than the IFX group. Comparison in each group revealed that there was a difference only in lower/large region. This method can show us the difference of drug efficacy on a specific region.

P3-426

Are doctors evaluating the disease activity using DAS28?

Hideshi Yamazaki¹, Tetsuo Takanashi¹, Toshihisa Kanamono², Fusazo Urano³, Sadahiro Suzuki³, Hiroyuki Kato⁴, Masayuki Matsuda⁵

¹Center for Rheumatic Disease, Marunouchi Hospital, Matsumoto, Japan, ²Dept. of Rheumatology, Nagano Red Cross Hospital, Nagano, Japan, ³Arthritis and Lupus Center, JA Shinonoi General Hospital, Nagano, Japan, ⁴Dept. of Orthop. Surg., Shinshu University, Matsumoto, Japan, ⁵Dept. of Neurology and Rheumatology, Shinshu University, Matsumoto, Japan

Objective: To investigate whether doctors perform DAS28 in Nagano prefecture. Methods: 95 doctors who had been treating RA patients answered the questionnaire about DAS28. The contents of questionnaire were about understanding of DAS28 and performing DAS28. Results: Most of doctors have known about DAS28 (92%). However only 15 doctors (17%) always perform DAS28. 27 doctors (31%) often perform DAS 28. 45 doctors (51.7%) don't perform DAS28. Conclusions: Most of doctors who treat RA patients know DAS28, but half of them perform DAS28.

P3-427

Efficacy of temporal artery biopsies for the diagnosis of giant cell arteritis

Natsuko Miura, Takashi Nakazawa, Shunichi Fujita, Keisuke Nishimura, Toshihiko Yokota
Department of Endocrinology and Rheumatology, Kurashiki Central Hospital, Kurashiki, Japan

Temporal artery biopsy is the gold standard test for making a diagnosis of GCA. Abnormal temporal artery findings are a part of diagnostic criteria for GCA. We performed a retrospective study to

determine the utility of temporal artery biopsy in patients suspected of having GCA. The biopsy results in patients who underwent a temporal artery biopsy are reviewed. Positive histology, confirming the diagnosis of GCA, was reported in seven cases, five of which were considered to have active arteritis in the temporal artery with inflammatory cell infiltration, whereas, the other two cases were interpreted as non-active phase of GCA, showing either surrounding fibrillation. We concluded there are active and non-active phases of inflammation at the time of temporal artery biopsy.

P3-428

Temporal arteritis presenting with abducens nerve palsy

Miwa Nishida, Yoshinobu Matsuura, Isao Murakami, Saori Hatachi, Masato Yagita
Kitano Hospital, Tazuke Kofukai Medical Research Institute, Osaka, Japan

A 64-year-old man had fever, headache and neck pain since February 2010. Treatment with 30mg of prednisolone (PSL) improved these symptoms. However, they recurred after the interruption of PSL. In addition, the left abducens nerve palsy also developed. Laboratory examination revealed elevated C-reactive protein level and high erythrocyte sedimentation rate. Although there was no evidence of vasculitis in biopsied sample of right temporal artery, his clinical symptoms and laboratory data met 1990 ACR Criteria for the Classification of Temporal Arteritis (TA). Treatment with 60mg of PSL resulted in prompt disappearance of the headache and left ocular movement fully improved three months later. We herein report the rare case with TA having abducens nerve palsy.

P3-429

Polyarteritis nodosa with perirenal hematoma due to the ruptured renal aneurysms

Taro Miyagawa, Yasuyuki Shinozaki, Tadashi Toyama, Akinori Hara, Kiyoki Kitagawa, Kengo Furuichi, Takashi Wada
Department of Nephrology, Kanazawa University Hospital, Ishikawa, Japan

A 60s'-year-old man developed numbness of his lower legs in July 2010. He was admitted the hospital due to worsening of the symptom and hypertension. Laboratory findings indicated anemia, increased levels of C-reactive protein, and renal dysfunction. On the 8th hospital day, severe right flank pain occurred suddenly, he was transferred to our hospital. Computed tomography and angiography showed right perirenal hematoma with small aneurysmatic dilations in the intrarenal branches of the right renal arteries. Selective embolization was performed to the bleeding. Based on his clinical and radiographic findings, he was diagnosed polyarteritis nodosa. He was received steroid and intravenous cyclophosphamide therapy. Clinical and laboratory findings improved and he went into remission.

P3-430

A case of Henoch-Schoenlein purpura complicated with serositis

Yuri Ohara¹, Masato Okada¹, Yasuhiro Suyama¹, Hisanori Shimizu¹, Atsushi Nomura², Eishi Uechi¹, Ken-ichi Yamaguchi¹, Mitsumasa Kishimoto¹

¹St. Luke's International Hospital, Tokyo, Japan, ²Chubu Rosai Hospital, Aichi, Japan

A 22-year-old man was admitted to our hospital because of 17 week-history of palpable purpura on the lower extremities and three

day-history of intermittent colicky abdominal pain with watery diarrhea, arthralgia and fever. Biopsy of the purpura demonstrated the leukocytoclastic vasculitis with IgA deposition, by which we diagnosed Henoch-Schoenlein purpura (HSP). Colicky pain improved after starting mPSL 60mg/day. Thereafter, he reported pleural chest pain with dispnea and examinations revealed pericardial and bilateral pleural effusion. Therefore we started mPSL 1g/day for 3 days then effusion disappeared. Serositis is a rare complication in HSP and most of them associated with tuberculous pleuritis under treatment or rheumatic fever. It is important to note this complication in HSP.

P3-431

Henoch-Schonlein Purpura in Adults: Outcome and Prognostic Factors

Rika Kawamura, Satoshi Hara, Yasushi Kakuchi, Hiroshi Fujii, Kazunori Yamada, Masami Matsumura, Mitsuhiro Kawano
Division of Rheumatology, Department of Internal Medicine, Kanazawa University Graduate School of Medicine, Kanazawa, Japan

Henoch-shonlein Purpura nephritis (HSPN) has been extensively studied in children, but in adult, prognosis and strategy for treatment are much less known. We analyzed retrospectively the clinicopathological features and outcome of 44 patients with HSPN during 1990-2009. 18 males and 26 females were analyzed. Age at diagnosis of HSPN was 52.8±16.2 (year; mean ± SD). Mean follow up was 61.8±57.3 (month; mean ± SD). Creatinine clearance dropped under 50 ml/min in 10 patients. 2 patients underwent dialysis therapy. Pathological findings and initial treatment did not correlate with the risk of the deterioration of renal function. The age and Ccr at the onset of HSPN and proteinuria were associated with poor renal prognosis. No significant improvement of renal outcome was related with steroid.

P3-432

Risk factors extending hospitalization for vasculitis in the elderly patients

Mariko Takano¹, Ken-ei Sada¹, Noriko Toyota¹, Yoshinori Matsumoto¹, Ryutaro Yamanaka¹, Koichi Sugiyama¹, Hiroshi Wakabayashi¹, Tomoko Kawabata¹, Fumio Otsuka², Hirofumi Makino¹

¹Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, ²Okayama University Hospital, Okayama, Japan

Objective: Elderly patients with vasculitis occasionally fail to leave hospitals after hospitalization despite the disease remission. We studied the factors that are relevant to determination for leaving hospitals. **Methods:** 32 patients aged ≥ 65 years with vasculitis were recruited. The main outcome is a discharge disposition, which was examined in relation to patients' characteristics, disease activities and therapies. **Results:** 26 patients returned home and 6 patients continued another hospitalization. Among the factors examined, the performance status (PS) and hemodialysis were most relevant to the determination of continuation or discontinuation of the hospitalization. **Conclusion:** Intervention improving the patients' PS would be important for the elderly patients with vasculitis.

P3-433

Vasculitis with eosinophilia/cryoglobulinemia is a paraneoplastic syndrome

Yusuke Yamada¹, Kazuhisa Nozawa¹, Yoshinari Takasaki¹, Iwao Sekigawa²

¹Department of Rheumatology, School of Medicine, Juntendo University, ²Department of Rheumatology, Juntendo University Urayasu Hospital

We report a case associated with paraneoplastic cutaneous vasculitis caused by hyper eosinophilic syndrome (HES) with mixed cryoglobulinemia (MC). Recently, neoplasms have been suggested to possibly produce antigens consequently thus causing paraneoplastic vasculitis. In the case, severe eosinophilia and cryoglobulinemia were observed in laboratory test. A biopsy specimen from a skin lesion revealed leukocytoclastic vasculitis with severe perivascular infiltrate of eosinophils. The cutaneous vasculitis was considered to be a manifestation of HES with MC and there were no etiological factors of HES and MC. The finding of our case suggested that the potential presence of malignancies should be kept in mind as a possible underlying disorder especially in the presence of HES with MC.

P3-434

Six cases of autoimmune disease treated with intravenous immunoglobulin

Junichi Hosokawa, Kotaro Kumano, Masaki Hiraguri, Takao Yanagisawa

Department of Internal Medicine, Narita Red Cross Hospital

Intravenous immunoglobulin (IVIG) is recommended as a therapeutic option in intractable autoimmune disease. We report six cases of autoimmune disease treated with IVIG. 64 years old female of Henoch-Schönlein purpura (HSP) complicated deep leg ulcer, 70 years old female of MPA with mononeuritis multiplex, and 54 years old female of CNS lupus, who were refractory to glucocorticoid and immunosuppressant, were dramatically improved by IVIG therapy. In 80 years old female of Churg-Strauss syndrome (CSS) case, IVIG was not effective for peripheral numbness, but improved cardiac damage. In two cases of 51 years old female of CSS with mononeuritis multiplex, and 46 years old female of CNS lupus, IVIG therapy was not effective. Adverse events were not observed in any case.

P3-435

Refractory hypertrophic pachymeningitis favorably treated with tacrolimus

Noriko Takahashi, Hideyuki Okada, Takahide Ikeda, Hiroyuki Morita, Tatsuo Ishizuka

Department of General Internal Medicine, Gifu University School of Medicine, Gifu, Japan

A 61-year-old woman who had been treated with PSL for a year against a high titer of MPO-ANCA at regional central hospital, had severe lumbago during tapering of PSL. Contrast-enhanced MRI showed meningeal thickness extending to thoracic and lumbar vertebrae, suggesting a diagnosis of hypertrophic pachymeningitis. Wegener's granulomatosis was suggested by patient's history of otitis media, a positive finding of MPO-ANCA and exclusion of other diseases. Treatment with glucocorticoid, cyclophosphamide, a large amount of intravenous immunoglobulin, rituximab and methotrexate were not effective. Administration of tacrolimus successfully improved her symptoms, laboratory data and MRI finding. Tacrolimus

should be considered for patients with refractory hypertrophic pachymeningitis.

P3-436

Constrictive vasculopathy-associated autoantibodies to ACE2 : the 2nd report

Yuko Takahashi¹, Shiori Haga², Yukihito Ishizaka², Akio Mimori¹

¹Division of Rheumatic Diseases, National Center for Global Health and Medicine, ²Department of Intractable Diseases, Research Institute, National Center for Global Health and Medicine

We found vasculopathy-associated autoantibodies to angiotensin converting enzyme 2 (anti-ACE2 Ab) in collagen diseases accompanied by pulmonary artery hypertension (PAH) or digital necrosis, on examining serum from 18 vasculopathy patients, 24 control patients, and 28 healthy subjects (Arthritis Res Ther, 2010). **Patients:** The disease specificity of the antibody was studied in an additional 38 (including two vasculopathy) patients with collagen diseases. **Results:** 9 patients (7 SLE, 1 SSc, and 1 possible SjS) with high serum anti-ACE2 Ab titers were newly identified in this study. Of these, reduced serum ACE2 activity was found in 2/2 of PAH and 1/7 patients without vasculopathy ($p=0.08$). The data suggest that only anti-ACE2 Ab with ACE2-inhibitory activity is associated with vasculopathy.

P3-437

Successful early treatment in a case of Cogan's syndrome

Hirota Tsuno, Yuko Takahashi, Yuji Yoshida, Hiroshi Kaneko, Akio Mimori

Division of Rheumatic Diseases, National Center for Global Health and Medicine

A 53-year-old man was admitted to our hospital because of fever of 2 weeks duration, blurred vision for 10 days, hypacusis, and numbness of the left hand for 3 days. In addition to uveitis, hypacusis, and aseptic meningitis, a nerve conduction study indicated multiple mononeuropathy, and positron emission tomography (PET)/CT revealed diffuse aortitis. Accordingly, the patient was diagnosed with Cogan's syndrome. Steroid-pulse therapy was started, followed by 1 mg oral prednisolone/kg/day. His uveitis and hypacusis improved immediately, but the peripheral neuropathy persisted, for which intravenous gamma globulin therapy was added, although its efficacy was unclear. In patients with the PET/CT-confirmed disease, prompt steroid-pulse therapy can prevent progressive hypacusis.

P3-438

Ischemic colitis associated with rheumatic diseases – review of twenty cases.

Ikuko Masuda¹, Masako Hara¹, Hisae Ichida², Kae Takagi², Takahisa Gono², Yasuhiro Katsumata², Yasushi Kawaguchi², Hisashi Yamanaka²

¹International University of Health and Welfare, Sanno Hospital, Tokyo, Japan, ²Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Ischemic colitis is not common condition associated with rheumatic diseases. We have studied twenty cases of ischemic colitis (7 systemic lupus erythematosus (SLE), 5 rheumatoid arthritis, 4 scleroderma, 3 myositis, and 1 vasculitis syndrome) out of 600 patients who were examined by colonoscopy during 2004-2008. Eight of twenty cases had ischemic episodes such as abdominal pain or mele-

na. Ischemic colitis had been reported to be an uncommon gastrointestinal complication in patients with SLE. However, seven out of 85 SLE patients examined were diagnosed as ischemic colitis, and one of the patients developed perforation of the colon in later year. Colonoscopic screening may be useful to discern ischemic colitis associated with hidden intestinal vasculitis in patients with rheumatic diseases.

P3-439

Decrease of DLco, relative to VC, in patients of PAH associated with CTD

Yoshimi Matsuo, Naoyuki Kuse, Shigeko Inokuma, Hiromitsu Asashima, Shinichiro Nakachi, Ryo Rokutanda, Kiyofumi Hagiwara, Shoko Kobayashi
Department of Allergy and Rheumatology Japanese Red Cross Medical Center, Tokyo, Japan

Objective: To examine the relative decrease of diffusing capacity for carbon monoxide (DLco) to vital capacity (VC) in female patients of pulmonary arterial hypertension associated with connective tissue diseases (CTD-PAH). **Methods:** Pulmonary functions in three groups were retrospectively analyzed; 11 female patients with CTD-PAH, 105 female with CTD without PAH, and 172 female with others treated at our center. Their %VC, %DLco, and %DLco/%VC were compared among the groups. **Results:** Their mean±SD were %VC: 78.9±19.0, 91.0±19.6, 99.4±20.6%, %DLco: 51.4±19.9, 73.4±19.7, 86.2±25.3%, and %DLco/%VC: 0.65±0.21, 0.79±0.18, 0.88±0.27, respectively. They were significantly lower in CTD-PAH female patients ($p < 0.05$). **Conclusion:** Decrease of DLco relative to VC is significant in CTD-PAH.

P3-440

Evaluation of lumbar DEXA by tocilizumab in patients with rheumatoid arthritis

Kensuke Kume, Kanzo Amano, Susumu Yamada
Department of Rheumatology, Hiroshima Clinic, Hiroshima, Japan

Background) IL-6 is related bone regulation. There is no evidence that IL-6 receptor antigen, tocilizumab effect bone density in patients with rheumatoid arthritis.

Methods) 12 patients be treated by tocilizumab in RA were evaluated lumbar DEXA from baseline to weeks 54.

Results) Baseline DEXA (YAM 84.3% ± 12.2), and weeks 54 (YAM 85.2% ± 8.8) had no significant difference. But two YAM low cases (<80%) had very improvement (>5%).

Discussion) Tocilizumab may be prevented lumbar spine bone density loss in patients with RA.

P3-441

Effect of corticosteroid on serum BAP and urinary NTx in rheumatoid arthritis

Taketoshi Kushida, Yusuke Ueda, Norihiro Ichikawa, Takahiko Wada, Hirokazu Iida
Department of Orthopaedic Surgery, Kansai Medical University, Osaka, Japan

Objective: The aim of this study was to evaluate the effect of a corticosteroid on the YAM, serum BAP, and urinary NTx levels of female rheumatoid arthritis (RA) patients.

Methods: We measured the YAM, serum BAP, and urinary NTx levels of 40 patients treated with corticosteroid and 32 patients not treated with corticosteroid.

Results: The YAM levels were almost same levels between the both groups. The BAP levels of the corticosteroid group were lower than the group not treated with a corticosteroid. Otherwise, The NTx levels of the corticosteroid group were higher than the group not treated with a corticosteroid.

Conclusion: We have to notice that the BAP levels of the corticosteroid group may decrease compared with non-corticosteroid group because corticosteroid suppresses the BAP levels.

P3-442

Osteopontin as a marker for bone destruction in RA patients

Haruyo Iwadata, Hiroko Kobayashi, Rie Saito, Shuzo Sato, Kiori Yano, Hiroshi Watanabe, Hiromasa Ohira
Department of Gastroenterology and Rheumatology, Fukushima Medical University School of Medicine, Fukushima, Japan

Objective: We measured osteopontin (OPN) levels in plasma and urine to investigate whether OPN levels associated with biochemical markers in rheumatoid arthritis (RA) patients. **Methods:** Plasma and urinary levels of OPN were measured by ELISA in 80 patients. Spearman's correlation coefficient were used to evaluate whether the OPN levels correlated with RF titers, anti-CCP antibody titers, DAS 28 scores, MMP-3 levels, tartrate-resistant acid phosphatase (TRACP)-5b levels, and C-terminal telopeptide of type I collagen levels. **Result:** Plasma OPN levels significantly correlated with levels of TRACP-5b ($r=0.33$, $P=0.004$). **Conclusion:** Plasma OPN level may be a useful predictive marker for bone destruction in RA patients.

P3-443

Inhibitory effect of human mesenchymal stem cells on osteoclast differentiation

Koichi Oshita¹, Kunihiro Yamaoka¹, Nobuyuki Udagawa², Shunsuke Fukuyo¹, Koshiro Sonomoto¹, Yosuke Okada¹, Kazuyoshi Saito¹, Yoshiya Tanaka¹

¹The First Department of Internal Medicine, School of Medicine, University of Occupational & Environmental Health, Japan, Kitakyushu, Japan, ²Department of Biochemistry, Matsumoto Dental University, Nagano, Japan

Ever since the use of biologics, the treatment goal for RA has become remission. However, treatment aiming repair of destructed joints has not yet been developed. Mesenchymal stem cells (MSCs) are multipotent cells with known immunosuppressive effect. Herein we have evaluated the effect of MSCs on osteoclastogenesis. When MSCs was cocultured with CD14⁺ cells in osteoclastogenic media under cell-cell contact free condition, the number of osteoclast and bone resorbing activity was significantly inhibited by least constitutive production of osteoprotegerin by MSCs. Our result indicates that MSCs possess the potential to suppress progressive bone destruction by inhibiting osteoclastogenesis in RA patients. Moreover, our notion supports MSCs as a novel treatment tool for RA aiming joint repair.

P3-444

Differentiation of subchondral insufficiency fracture with osteonecrosis

Takuaki Yamamoto, Goro Motomura, Takashi Itokawa, Taro Mawatari, Yasuharu Nakashima, Yukihide Iwamoto

PURPOSE: Subchondral insufficiency fracture of the femoral head (SIF) often undergoes subchondral collapse and needs to be differentiated from osteonecrosis. **METHOD/MATERIALS:** Images in 32 SIF hips were compared with those in osteonecrosis. **RESULTS:** The shape of the low intensity band in SIF was irregular and serpiginous paralleling the articular cartilage, which seems to be useful for the differentiation with osteonecrosis. In addition, gadolinium enhancement showed high signal intensity in SIF. Histopathologically, the low intensity band on MRI in SIF corresponded to both the fractured bone and the associated repair tissue. **CONCLUSIONS:** In the majority of SIF cases, the irregular shaped low intensity band on T1 weighted image was the characteristic finding.

P3-445

Osteonecrosis of the knee with alcohol-related osteonecrosis of the femoral head

Tomonori Shigemura¹, Junichi Nakamura¹, Yoshitada Harada², Koh Shimizu³, Satoshi Iida⁵, Koya Kamikawa⁷, Munenori Takeshita¹, Masahiko Suzuki⁸

¹Department of Orthopaedic Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan, ²Chibaken Saiseikai Narashino Hospital, Narashino, Japan, ³Chiba Rosai Hospital, Ichihara, Japan, ⁴Chiba kaihin Municipal Hospital, Chiba, Japan, ⁵Matsudo City Hospital, Matsudo, Japan, ⁶Funabashi Orthopaedic Hospital, Funabashi, Japan, ⁷Teikyo University Chiba Medical Center, Ichihara, Japan, ⁸Chiba University Research Center for Frontier Medical Engineering

Objective: To clarify the incidence of osteonecrosis of the knee in patients with alcohol-related osteonecrosis of the femoral head.

Methods: From 1986 to 2010, we performed MRI screening of bilateral hip and knee in 51 patients (47 male and 4 female) with alcohol-related osteonecrosis of the femoral head. Osteonecrosis of the femoral head was bilateral in 25 patients and one side in 26 patients. Mean age at presentation was 44 years. We evaluated the incidence of osteonecrosis of the knee and the risk factors.

Results: Osteonecrosis of the knee was observed in 8 patients (16%) 11 knees (11%). There were no significant differences between the groups with osteonecrosis of the knee and without in gender, rate of osteonecrosis of the femoral head, and weekly alcohol consumption.

P3-446

Case report of the both femoral neck fracture of the ION

Shinji Kobayashi

Shiseido General Hospital

Femoral neck fracture rarely occurs in the course of ION. We describe one such rarely case. A 65-year-old man visited our clinic because of developing pain in the both hips. He had been taking steroids due to myelodysplastic syndrome. Low-signal intensity bands extended to the neck were detected on T1 weighted MRI images. He visited our clinic again 6 months later after the first visit because of suddenly increased left hip pain. On radiographs, we found out left femoral neck fracture and performed bipolar hemiarthroplasty. Two month later, the same arthroplasty was performed for another side because of severe pain. The pathological specimen demonstrated that the fracture site was the junction between the necrosis and the repairing zone.

P3-447

Bilateral incomplete fracture on the femur and the tibia ushing Humira

Toru Yamagami, Kazuo Shimizu, Kiyoshi Sakai, Takashi Kawane, Yasunori Suzuki

Toyama red cross hospital rheumatic center

71old female has been treating rheumatoid arthritis from 1998, and was introduced to our hospital in June 2008 to control the rheumatoid arthritis. Humira started in January 2010. The joint arthritis trend to light. In March, both knees were in pain without accident. There is no swelling and edema on the joints. The radiographs, there is no traumatic change. However, MRI examination of both the femur and tibia showed fractures.

Rheumatoid arthritis is worsening osteoporosis. Stimulation of everyday life caused the fractures on both the femur and the tibia. It was necessary that to be careful to distinguish from worsening of rheumatoid arthritis.

P3-448

Foraminal stenosis following late collapse of a vertebral body of lumbar spine

Yu Sasaki¹, Yasuchika Aoki¹, Koichi Nakagawa¹, Arata Nakajima¹, Yoshifumi Shibata¹, Manabu Fujino¹, Masato Sonobe¹, Toru Suguro², Teruo Furufu¹

¹Toho University Sakura Medical Center, ²Toho University Omori Medical Center, ³Chiba University Hospital

A 85 years-old woman fell, resulting L3 compression fracture. She was treated conservatively for 3 months, but, back pain worsened, and severe pain and muscle weakness appeared on her bilateral lower extremities (MMT3-4). MRI showed a late collapse of L3 body and bilateral foraminal stenosis on L3-L4. Surgery was conducted to decompress the L3-L4 foramen, and to fuse the unstable segment. L3 pedicle was subtracted and the cranial part of L3 vertebral body and L2-L3 disc were resected. Posterior spinal fusion was performed using fusion cage and pedicle screws. Her symptoms improved completely at 4-months post-operatively. Our procedure that can decompress the foramen and fuse the unstable segment is an effective treatment for foraminal stenosis due to late collapse of the vertebral body.

P3-449

A case of RS3PE syndrome showing bone marrow edema and bone erosion on MRI

Hiroaki Taguchi, Takayuki Hoshiyama, Kazuo Nishi, Takahiro Suzuki, Yutaka Okano, Satoshi Akizuki

Internal Medicine, Kawasaki Municipal Kawasaki Hospital, Kanagawa, Japan

A 68-year-old woman visited our clinic in May 2009. In addition to marked edema of the distal extremities, synovitis of both hands and fingers was noted. Serum examination revealed that CRP was high, but rheumatoid factor were absent. Plain radiography of the joints showed normal findings. MRI showed bone marrow edema and bone erosion in both wrist joints. Except for the MRI findings, the clinical picture was the most typical of RS3PE syndrome. Therefore, treatment was initiated with prednisolone (15 mg). Consequently, the clinical symptoms subsided rapidly, and no relapse has been observed to date. Although usefulness of MRI in the early

diagnosis of RA has attracted attention, our present case suggests that RS3PE syndrome may show RA-like features on MRI.

P3-450

A case of RS3PE syndrome with bilateral pleural effusion.

Katsuhisa Kikuchi¹, Taku Kawasaki¹, Noriaki Okumura¹, Kenichirou Miyahara², Toshiro Sugimoto³, Shinji Imai¹, Yoshitaka Matsusue¹

¹Department of Orthopaedic Surgery, Shiga University of Medical Science, ²Wakakusa Clinic, ³Department of Internal Medicine, Shiga University of Medical Science

The pleurisy of SLE or RA is often reported, however that of remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome is rare. We report a case of RS3PE syndrome with bilateral pleural effusions in a 83-year-old woman. The pleural effusions were exudative, negative for rheumatoid factors, negative for malignant cells and had no bacteria. With daily 20mg of oral steroid, remission of polyarthritis and pitting edema occurred, with a coincidental decrease of pleural effusions.

P3-451

A case of RS3PE syndrome following IgA nephropathy

Koji Harada¹, Mikiko Yoshikawa¹, Yasuhiro Akai²

¹Department of Nephrology, Rakuwakai-Otowa Hospital, ²Center for Postgraduate Training, Nara Medical University

70 year-old man was admitted for proteinuria and anasarca after flu-like symptom. He was found to have apical hypertrophic cardiomyopathy 2 year prior to admission. He had no family history of rheumatic diseases. Renal biopsy demonstrated minor glomerular abnormalities on light microscopy. Because mesangial deposit of IgA was shown on immunofluorescence, he was diagnosed as IgA nephropathy. The day after renal biopsy, he developed remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome. Glucocorticoid was started with disappearance of proteinuria and anasarca, followed by the resolution of joint symptoms. We report this case because the association between IgA nephropathy and RS3PE has not been described.

P3-452

Case of RS3PE syndrome without arthralgia

Yoshiki Morita

Department of Nephrology, Nagoya Central Hospital, Nagoya, Japan

An 85-years old man was admitted with progressive edema in the bilateral pedals and legs and a fever of over 38 degrees. The symptoms were anorexia and general malaise but not arthralgia. Examination revealed bilateral pitting edema of dorsum of hands and feet but not articular swelling. Blood test showed anemia and raised inflammatory markers. For a close inspection of unknown fever, PET-CT was performed. FDG was accumulated in the multiple joint parts. So that the RS3PE syndrome was possible, MRI was performed. It showed soft tissue edema of dorsum of hand and flexor tenosynovitis. We diagnosed by the MRI findings and raised serum VEGF. He was treated with oral PSL15mg/day and after a month edema was improved. It was the rare case without joint symptoms as RS3PE syndrome.

P3-453

A case of eosinophilic fasciitis with high elevation of C-reactive protein.

Norikuni Kawanaka

National Hospital Organization Zentsuji National Hospital

Here, I report the case of eosinophilic fasciitis with high elevation of C-reactive protein. A 58-year-old man presented with a 5-month history of bilateral myalgia of the lower limbs, which subsequently spread to the upper limbs and a reduced general condition. Laboratory examination showed high elevation of C-reactive protein and hypergammaglobulinemia. Magnetic resonance imaging (MRI) showed thickening of the muscular fascias of the thigh in high signal intensity on T2-weighted images. Examination of a full-thickness skin biopsy revealed an inflammatory process and fascial changes consistent with eosinophilic fasciitis and vasculitis. Histological finding showed vasculitis associated with high elevation of C-reactive protein. This case was successfully treated with corticosteroids.

P3-454

Use of MRI in diagnosing eosinophilic fasciitis (EF): Report of three cases.

Ayako Hirata¹, Hideki Ito¹, Ryuta Endo¹, Reiko Miura¹, Norihide Hayashi¹, Yuichi Izumi¹, Takehisa Ogura¹, Toshiaki Oharazaki², Takehiko Ogawa¹

¹Division of Rheumatology, Toho University Ohashi Medical Center, ²Division of Pathology, Toho University Ohashi Medical Center

We investigated MRI findings and correlation between the pathological findings and the MRI findings in 3 EF patients. Those patients presented bilateral myalgia of the lower limbs, irreducible flexion of the fingers and scleroderma. Laboratory examination showed peripheral eosinophilia associated with moderate elevation CRP. In all 3 EF patients, MRI examinations revealed thickening and hyperintensity of the superficial muscle fasciae of distal legs, or arms on STIR sequences, with strong enhancement after administration of contrast agent. MRI-guided muscle biopsy demonstrated fascia infiltration characterized by polynuclear eosinophils. Those patients were successfully treated with 30mg/day prednisolone. MRI is useful for establishing the diagnosis, guiding the choice of biopsy site.

P3-455

Six cases of eosinophilic fasciitis (EF): A case-series study

Yasuhiro Kazuma, Ryuichi Sada, Yukio Tsugihashi, Teruhisa Azuma, Hiroyasu Ishimaru, Kazuhiro Hatta

Tenri Yorodu Hospital, Tenri, Japan

【Background】The clinical features of EF are unclear. **【Purpose】**We reported a case series study of EF treated with systemic corticosteroid. **【Result】**We enrolled 6 cases, who were treated in Tenri Hospital from 1995 to 2010. Age range was between 15-70 years. Cases include 5 men and 1 woman, with eosinophilic pneumonia in 2 cases. We found residual symptoms in 3 cases ("Residual" group) and improved symptoms in 3 cases ("Remission" group). Two patients among Residual group spent more than 6 months before steroid administration and no patient among Remission group. Trunk involvement was found in 2 patients among Residual group, and in none among Remission group, respectively. **【Conclusion】**We found residual lesion more in cases with delay of steroid administration or trunk involvement.

P3-456

The occurrence of eosinophilia with organ involvement in three siblings

Mineto Ohta, Kenchi Takenaka, Kenji Nagasaka
Ome Municipal General Hospital, Tokyo, Japan

Case 1: A 51-year-old woman (sixth sibling) with a history of asthma was admitted to our hospital in 2002 because of wheal, lymphadenopathy and mononeuropathy multiplex. Blood tests revealed eosinophilia (5834 cells/ μ L). Case 2: A 58-year-old man (fourth sibling) with asthma was hospitalized in 2004 because of fever, wheal, and arthritis. Blood tests revealed peripheral eosinophilia (2496 cells/ μ L). Case 3: A 61-year-old man (third sibling) who suffered from prurigo since 2005 was hospitalized in 2010 because of exacerbation of the rash and right pleural effusion. Blood tests revealed peripheral eosinophilia (811 cells/ μ L). Many eosinophils were observed in the pleural effusion. Glucocorticoid treatment relieved their symptoms. Genetic factors may contribute to this pathogenesis.

P3-457

Secondary hemophagocytic syndrome in adults: Analysis of 10 patients

Hiroyuki Hounoki¹, Koichiro Shinoda², Reina Ogawa¹, Maiko Okumura¹, Hirofumi Taki¹, Kazuyuki Tobe²

¹First Department of Internal Medicine, University Hospital, University of Toyama, Toyama, Japan, ²First Department of Internal Medicine, School of Medicine, University of Toyama, Toyama, Japan

We present 10 cases of secondary hemophagocytic syndrome (HPS) diagnosed between 2008 and 2010. All patients presented fever. Thirty percent of the patients presented with evidence of hemophagocytosis. All of the patients had at least a bi- or tri-cytopenia. Elevated liver enzymes, hyperferritinemia and elevated soluble IL-2R were seen in 90, 100 and 60% of the patients, respectively. Presumed causes were haematological malignancies (n=2), infection (n=1), rheumatologic illness (n=3) and idiopathic (n=4). The mortality rate was 20%, all of which were associated with hematological malignancies. Fever with hyperferritinemia and bi- or tri-cytopenia is a clue to early diagnosis of HPS. We conclude early recognition, diagnosis and treatment including immunosuppressant are crucial point.

P3-458

Weber-Christian disease associated with granulomatous mastitis

Shuichi Nakayama¹, Yoshinori Taniguchi¹, Toru Kagawa¹, Ayako Ishibashi¹, Yoshiko Shimamura¹, Koji Ogata¹, Kosuke Inoue¹, Yoshitaka Kumon², Yoshio Terada¹

¹Department of Endocrinology Metabolism and Nephrology, Kochi Medical School, Nankoku, Japan, ²Department of Laboratory Medicine, Kochi Medical School, Nankoku, Japan

35-year-old woman presented with a 4-week history of fever, polyarthralgia and painful nodules in the right breast, trunk and extremities. PET/CT revealed significantly elevated uptake in right breast, lower back and extremities. The needle biopsy specimen of right breast nodule demonstrated granulomatous mastitis (GM) with panniculitis. The skin biopsy specimen of the cutaneous nodule showed lobular panniculitis with fat degeneration and infiltration of foamy histiocytes and multinucleated giant cells. We diagnosed as Weber-Christian disease (WCD) associated with GM, and started steroid therapy. One month after, nearly all laboratory data and

imaging tests were normalized. This case, to our knowledge the rare report of WCD associated with GM, might represent a variant type of WCD.

P3-459

Study of Gastroesophageal Reflux Disease and QOL in Rheumatic Disease Patients

Jo Nishino, Miyuki Nozaki, Daisuke Hirano, Yumi Iwasaku, Tomonobu Iwadata, Satoru Onoda, Nobuko Tosaka, Kenichi Kato, Shusaku Fukaya, Shunji Yoshida

Division of Rheumatology and Infectious Disease, Department of Internal Medicine, Fujita Health University School of Medicine

[Objective] To consider QOL of connective tissue disease (CTD) patients who develop gastroesophageal reflux disease (GERD) [Method] Subjects were 629 cases of CTD outpatients on April 2010 (including 277 RA, 117 SLE, 37 SS, 36 SSc and 30 PM/DM cases, 111 men and 518 women with average age of 55 \pm 15). GERD was surveyed by QUEST (cut off, 4) and QOL was done by GSRS. [Result] GERD complication rates in RA, SLE, SS, SSc and PM/DM were 41.5%, 39.3%, 40.5%, 47.2% and 60.0% respectively, and QOL based on GSRS were lower in GERD group (2.14) than in non-GERD group (1.50). (p<0.0001) [Conclusion] CTD patients develop symptom of GERD in high rates, which has caused deterioration in their QOL.

P3-460

A case of fasciitis complicated with overlap syndrome of SLE and scleroderma

Koji Kitagori, Shuichiro Nakabo, Daisuke Kawabata, Takao Fujii, Naiochiro Yukawa, Hajime Yoshifuji, Koichiro Ohmura, Tsuneyo Mimori

Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

A 49-year-old woman was diagnosed as having systemic lupus erythematosus (SLE) in 1985. She had hematologic disorders including thrombotic thrombocytopenic purpura. In 2008, she developed scleroderma (SSc) and interstitial pneumonia (IP). Anti-U1RNP, Sm, DNA and Scl-70 antibodies were positive. She was treated with corticosteroid (CS) and cyclosporin for overlap syndrome. In March 2010, because chest CT showed IP exacerbation, cyclophosphamide pulse therapy was added. In May, she complained pain of extremities. STIR images of MRI and en block biopsy of femoral muscle showed necrotizing fasciitis. After an increased dose of CS (0.5mg/kg), her fasciitis was improved. Till now, there are few similar case reports suggesting that the present case may be informative.

P3-461

Comparison between adalimumab responders and non-responders in patients with RA

Yoshihiro Yoshida, Yuji Akiyama, Takuma Wada, Fumihiko Miyoshi, Muneko Ota, Mayuko Sakamoto, Yuki Shimada, Akinori Yamamoto, Yasufumi Shindo, Kazuhiro Yokota, Yasuto Araki, Hiroshi Kajiyama, Haruhiko Akiba, Kyoichi Nakajima, Kojiro Sato, Yu Asanuma, Toshihide Mimura

Saitama Medical University, Department of Rheumatology and Applied Immunology, Moroyama, Japan

Purpose: To analyze the efficacy and adverse reactions between adalimumab (ADA) responders and non-responders in patients with

RA.

Patients characteristics at the base line; Two males, 20 females. Mean age: 61.6 years old, mean disease duration: 10.5 years, mean DAS28: 6.01.

Results; Six patients were discontinued by side effects. DAS28 and HAQ score of responders were lower than those of non-responders at the baseline ($P<0.05$). Responders showed shorter disease duration and higher MTX dose compared with non-responders. The ratio of biologics naïve was higher in responders. Four out of non-responders were switched to etanercept: 2, or tocilizumab: 2.

Conclusion; ADA responders tended to be in shorter disease duration, with lower disease activity and biologics naïve and to take more MTX.

P3-462

The clinical analysis of RA patients showed a reduced response to ADA therapy

Koji Nagai, Takuya Kotani, Tohru Takeuchi, Kentaro Isoda, Kenichiro Hata, Shuzo Yoshida, Shigeki Makino, Toshiaki Hanafusa

First Department of Internal Medicine, Osaka Medical College

Objective: To analyse the clinical features of RA patients who showed a reduced response to Adalimumab (ADA) therapy. **Materials and methods:** We investigated 17 RA patients who received ADA in our hospital. Seven patients showed a reduced response to ADA therapy (group A), 10 patients showed a good response (group B). **Result:** We compared the clinical features of group A to group B (age, stage, other biologics therapy, MTX therapy, prednisolone therapy and other DMARDs therapy). In group A, all cases showed a reduced response after 12 weeks. Mean duration of group A was relatively longer than that of group B (13.1 years vs 6.8 years). And rate of combined MTX therapy was lower (42% vs 80%). **Conclusion:** On ADA therapy we should be careful of the case received no MTX therapy after 12 weeks.

P3-463

Clinical efficacy of adalimumab in our hospital

Mamoru Matsumoto¹, Tomoaki Yoshikawa¹, Toru Yamakawa¹, Satoshi Hosoi²

¹Department of Orthopedic Surgery, Yamada Red Cross Hospital, Mie, Japan, ²Suzuka university of Medical Science

The purpose of this study is to assess the curative effects by DAS28-ESR and blood level of MMP-3 on 10 RA patients (2 male and 8 female, mean 59 years old) who were treated with adalimumab (ADA). MTX were used on all cases, which included 5 biologically naïve cases, 4 cases previously treated with Infliximab (IFX), and one treated with Etanercept. DAS28 assessment showed that 4 cases achieved remission, 3 cases had got LDA, and 2 had got MDA. Just one showed the primary failure. Four remission cases included 2 previous naïve and 2 previous secondary failure of IFX. MMP-3 level was decreased on all cases. The curative effects and the persistent rate of ADA with MTX was good as well as previous reports. It was also suggested that ADA was effective against the secondary failure of IFX.

P3-464

Therapeutic experience of adalimumab

Katsuya Kanesaki¹, Kensei Nagata²

¹Nagata Orthopedic Hospital, ²Department of Orthopedic Surgery, Kurume University

(Introduction) Adalimumab injection therapy for RA was evaluated. (Cases) 35 cases were evaluated. Average age of medication initiation was 65.9 years old, and the average duration of disease was 8.19 years. (Results) Injection was continued in 23 cases (65.7%). 12 cases were discontinued; 2 due to deep remission, 1 changed to another biologics, 2 by patients inconvenience and 7 by side effects. Average DAS 28 ESR was changed from 4.62 at the start to 2.92 after 6 months, showing low disease activities. We had 5 cases of deep remission of which 2 were discontinued. (Discussion) Adalimumab is very useful for RA therapy, resulting 7 cases with remission and 15 cases with low disease activities. However, high side-effect rate of 20% was shown that it requires extra cautions.

P3-465

The efficacy and safty of Adalimumab (ADA) monotherapy

Atsushi Kohno¹, Yasue Shimogaki², Kenji Kohriyama³, Takao Takeuchi⁴, Yoshikiyo Toyoda⁵

¹Department of Rheumatology, Osaka Kaisei Hospital, Osaka, Japan, ²Immunity Plaza, Deptment of Rheumatology, Osaka Kaisei Hospital, Osaka, Japan, ³Department of Rheumatology, Shin-Suma Hospital, Kobe, Japan, ⁴Clinical Immunology and Rheumatology Center, Hayaishi Hospital, Osaka, Japan, ⁵Department of Orthopedic Surgery, Osaka Kaisei Hospital, Osaka, Japan

We report a case which showed effectiveness of ADA (80mg bi-weekly, solely) more than the other biological products showing anti-TNF-alpha activities.

[Case] 44years old woman suffering from RA since 2009 (Stage2,Class2)had been administrated ADA40mg/2w+MTX4mg/w for 13 months,but the disease activities was not controled enough. She refused to increase the dosage of MTX, ADA 80mg/2w monotherapy was chosen by her request. After starting ADA monotherapy (80mg/2w), the disease control was maintained in good condition. It is postulated that the administration of 80mg/2w of ADA prevents the production of AAA. This case showed the efficacy and safty of the administration of 80mg/2w of ADA because of preventing AAA.

P3-466

The efficacy and safty of Adalimumab with MTX low dose

Atsushi Kohno¹, Yasue Shimogaki², Yoshikiyo Toyoda³, Kenji Kohriyama³, Takao Takeuchi⁴

¹Department of Rheumatology, Osaka Kaisei Hospital, Osaka, Japan, ²Immunity plaza, Department of Rheumatology, Osaka Kaisei Hospital, Osaka, Japan, ³Department of Rheumatology, Shin-Suma Hospital,Kobe,Japan, ⁴Clinical Immunology and Rheumatology Center, Hayaishi Hospital, Osaka, Japan, ⁵Department of Orthopediatrics, Osaka Kaisei Hospital, Osaka, Japan

It is postulated that the administration of MTX (more than 8mg/w)is required to prevent the production of AAA on the treatment course using ADA in RA patients. However,we report the case that low dose of MTX administration are effective to control the disease activitis of RA patients using ADA.

[case]A 27 years old female suffering from RA for 6 months (Stage2,Class2)was administrated MTX 6mg/w with ADA, after 12 months later,she wanted to get pregnant. After that, ADA has been administreaed without MTX. However ,the disease activities has been maintained in good control for a year and 8 months.In this case,

ADA showed the efficacy and safety without administration of high dose of MTX (more than 8mg/w).

P3-467

Successful adalimumab treatment in a patient with typical Reiter syndrome

Noriko Sasaki, Shinji Sato, Kiri Honda, Eiko Saito, Takayuki Wakabayashi, Chiho Yamada, Yasuo Suzuki

Department of Internal Medicine, Division of Rheumatology, Tokai University School of Medicine, Isehara, Japan

We report a typical Reiter syndrome who manifested gastroenteritis, nongonococcal urethritis, conjunctivitis followed by refractory and persistent arthritis that was improved dramatically by Adalimumab subcutaneous injection. Although treatments with non-steroidal anti-inflammatory drugs, corticosteroid and disease-modifying anti-rheumatic drugs were non-effective, drug free remission was accomplished after adalimumab treatment. It is suggested that TNF- α blocker is an excellent treatment for refractory and persistent arthritis in a patient with Reiter syndrome.

P3-468

Treatment for RA patient who shows insufficient to adalimumab- high dose steroid

Takayoshi Fujibayashi¹, Toki Takemoto¹, Masashi Kawasaki¹, Atsushi Kaneko²

¹Department of Orthopaedic Surgery, Konan Kosei Hospital, Konan, Japan, ²Department of Orthopaedic Surgery, Nagoya Medical Center

We present a 57-year-old woman with RA who was diagnosed as RA at 37 years old. She has been under a poor control for RA with DMARDs and IFX. When her first visit to our institute, she showed CRP/DAS28-CRP was 9.7/6.6. Our first treatment for her was MTX8mg/week and PSL5mg/day, however, RA control got worse. Therefore, we changed the strategy and started ADA40mg every other week. After then the RA activity was improved temporarily. At 8 weeks after administration of ADA, we provided PSL50mg (i.v.) single dose because CRP/DAS28-CRP was 9.4/7.1. After PSL single dose, CRP/DAS28-CRP was 1.4/2.9 by 3 months later, respectively. We thought high dose PSL certainly held down RA activity temporarily or controlled to production of anti-adalimumab antibody (AAA), and the effect of ADA came back.

P3-469

Cold agglutinin disease in a patient with RA during adalimumab therapy

Kyoko Honne¹, Yoko Aoki¹, Takao Nagashima¹, Seiji Minota¹

¹Division of Rheumatology and Clinical Immunology, Department of Medicine, Jichi Medical University, Tochigi, Japan, ²Center for Community Medicine, Jichi Medical University, Tochigi, Japan

A 57-year-old man, diagnosed with rheumatoid arthritis in 2002, had been treated with methotrexate since 2004 and adalimumab was added on since Feb. 2010. Both drugs were suspended in May 2010 due to upper respiratory infection. Severe anemia had suddenly developed in June and he was referred to our hospital. Laboratory data suggested autoimmune hemolytic anemia with a positive direct antiglobulin test and a relatively high titer in cold agglutinin (1:2048), although the titer was lower for the typical chronic cold agglutinin disease (CAD). He was diagnosed with low-titer CAD with a more enhanced agglutinin level in albumin; albumin reduced electrostatic force for RBCs to agglutinate even at physiological temperature.

Prednisolone (1mg/kg) normalized the hemoglobin levels within a month.

P3-470

Study of RA patients' background that affect ADA treatment remission rate (RR)

Toshihiko Hidaka¹, Kazuyoshi Kubo¹, Shota Sakaguchi¹, Hiroshi Kuroda¹, Kunihiro Umekita², Akihiko Okayama²

¹Institution of Rheumatology, Zenjinkai Shimin-no-Mori Hospital,

²Internal Medicine, Department of Rheumatology, Infectious diseases and Laboratory medicine, University of Miyazaki

Objective We examined whether RR of adalimumab (ADA) treatment have correlation with patients' (pts') background or not. **Subjects and Methods** Our 37 RA pts (6 men, 31 women) receiving ADA; rate of pts with DAS28ESR<2.6 (RR) at 1 year (y) treatment, using LOCF method was compared by background: 1) with/without concomitant MTX, 2) stage, 3) RA duration, 4) age and 5) HAQ. **Results** DAS28ESR significantly improved from 4.93 ± 1.01 baseline to 2.89 ± 1.19 at 1 y ($p<0.001$) with RR of 28%. RR by background: 1) with MTX 60%, without MTX 14% ($p<0.05$); 2) stage I/II 58%, III/IV 36% NS; 3) RA <5 ys 69%, ≥ 5 ys 38% ($p<0.1$); 4) <65 yo 56%, ≥ 65 yo 41% (NS); 5) HAQ ≤ 0.5 61%, >0.5 27% (NS). **Conclusion** Initiation of concomitant MTX with ADA can lead to increase in RR.

P3-471

The effect of IL17 on the cell death of cultured murine podocyte

Hiroshi Kajiyama, Mayuko Sakamoto, Muneo Ota, Fumihiko Miyoshi, Yasuto Araki, Kojiro Sato, Yu Asanuma, Yuji Akiyama, Toshihide Mimura

Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University

Background Effects of IL17 on podocytes are not well studied, although the roles of Th17 and IL17 in glomerular injury in lupus nephritis were recently reported.

Methods IL17RA and IL17RC mRNA in cultured murine podocytes were quantified by qPCR. Doxycycline (1 μ g/mL) was added to cultured murine podocytes to induce cell death with expression of toxic protein Vpr, pretreated with 1-100ng/mL of IL17 in the presence of rat anti-murine IL17 or control IgG. After 24 hours, cell death of podocytes were quantified with Cellglo-ATP assay.

Results IL17RA and IL17RC mRNA expression was confirmed in cultured murine podocytes. Vpr podocyte cell death was inhibited with 1-100 ng/mL of IL17, which was neutralized with anti rat-anti-IL17.

Conclusion IL17 potentially ameliorates podocyte cell death.

P3-472

Examination of treatment and the prognosis of lupus nephritis type V

Shinji Morimoto, Souichiro Nakano, Takashi Watanabe, Hirofumi Amano, Yoshinari Takasaki

Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo, Japan

The lupus nephritis to about 60% of the systemic lupus erythematosus (SLE), and 10~15% of those is considered to be WHO type V. It is said that about 10% reach the end stage renal disease. We examined an organization type about the condition of a patient and treatment, prognosis about 18 examples diagnosed as WHO type V

that were able to be decided in kidney biopsy among SLE patients who hospitalized during from 2000 to 2010. There were most of the things which did not recognize abnormality about the condition of a patient serologically, but all examples proteinuria met in more than 3g/day. As for the treatment, it was used an immunosuppressant together except one example. The proteinuria became negative for many cases after treatment.

P3-473

Efficacy of tacrolimus as induction or maintenance therapy in 5 new onset LN

Kazuo Nishi, Takayuki Hoshiyama, Hiroaki Taguchi, Takahiro Suzuki, Yutaka Okano, Satoshi Akizuki
Internal medicine, Kawasaki municipal hospital, Kanagawa, Japan

Patient data: 5 females, age:17-40, UP 0.4-3.84g/d, Cr <1.3mg/d, anti-DNA body >200U/ml, complement <15/ml. Renal biopsy revealed WHO class IV LN in every patient. 2 patients, we started treatment with IVCY (cyclophosphamide 500mg/month 6 course) as induction therapy, and followed tacrolimus (Tac) 3mg/d as maintenance therapy. The other 3 patients, we started treatment with Tac 3mg/day as induction therapy and continued it. All patients were treated with steroid in the same way. (initial dose 0.8-1mg/kg, then tapered gradually) After the initial therapy (7-17 months), all patients sustained remission with Tac and small amounts of steroid. Our cases suggest that Tac might be effective not only for reducing proteinuria during the maintenance period, but also for inducing remission.

P3-474

A case of lupus nephritis treated with combination of Tacrolimus and Mizoribine

Takashi Kida, Aihiro Yamamoto, Amane Nakabayashi, Hidetake Nagahara, Wataru Fujii, Ken Murakami, Kaoru Nakamura, Takahiro Seno, Hidetaka Ishino, Masataka Kohno, Yutaka Kawahito
Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

As an induction therapy for lupus nephritis, we have focused on combination of Tacrolimus (TAC), Mizoribine (MZR), and steroids. A 59-year-old female presented with arthritis, lymphocytopenia and increased proteinuria was diagnosed as SLE. Renal biopsy suggested it was lupus nephritis class IV. We started the treatment of oral prednisolone (PSL 40mg/day) and TAC (3mg/day). After a week, MZR (150mg/day) was added and after another week, dose of MZR was switched (300mg/day, 3/week). Proteinuria was improved immediately. We could reduce the initial dose of PSL and also taper it rapidly, so it made hospitalization shorter. She had no significant side effect of this therapy. The combination therapy with TAC, MZR, and steroids may be effective in the induction of remission of lupus nephritis.

P3-475

Two cases of lupus nephritis successfully treated with mycophenolate mofetil

Kyoko Takano, Michita Suzuki, Eiji Nagasawa, Masao Katayama
Division of Rheumatology, Department of Internal Medicine, Nagoya Medical Center, National Hospital Organization

【Case1】A 30-year-old woman under PSL5mg for systemic lupus erythematosus (SLE) since 12 years old was diagnosed as lupus nephritis (LN) (WHO type IV-S-A/C+type V) at July,15,2009. She

was treated with mycophenolate mofetil (MMF) combined with PSL. Two months later, proteinuria and serum albumin were improved remarkably by addition of MMF. 【Case2】A 21-year-old woman was diagnosed as SLE at July 13,2009 and LN. At first, she received methylprednisolone pulse therapy, however, her nephrotic syndrome was not improved. The additional therapy of MMF improved her clinical findings and proteinuria three months later. 【Conclusion】Several reports indicate that MMF is useful for LN and has low risk of gonadal failure. We suggest that MMF is an alternative choice for induction therapy of young woman with LN.

P3-476

Complete remission of nephritic syndrome in SLE patient using plasma exchange

Takashi Oura, Kazunori Uehara, Masaki Akamine
Hemodialysis Unit, Oura's Lupus Clinic, Naha City Okinawa Japan

In our unit, we combined plasma exchange with extracorporeal ultrafiltration method (ECUM) which potentially removed the excessive water and respectively increased serum drug concentration. The patient was 43 years-old female with edema and ulcers of the extremities. The onset of SLE was found in 2003 and rapidly progressed to NS after a year. She received the above mentioned treatment and completely remitted. In 2007, she suffered from the refractory ulcers of the extremities and severe pain. We started plasma exchange (DFPP) with the combination of conventional drug therapy. The severe pain relieved as ulcers remitted completely. We experienced the complete remission of NS using combination of steroid, immunosuppressant, plasma exchange, and ECUM.

P3-477

Remission induction and maintenance therapy for proliferative lupus nephritis

Eiko Saito, Shinji Sato, Noriko Sasaki, Kiri Honda, Takayuki Wakabayashi, Chiho Yamada, Yasuo Suzuki
Department of Internal Medicine, Division of Rheumatology, Tokai University School of Medicine, Isehara, Japan

We investigated the efficacy and safety of each immunosuppressant in remission induction and maintenance therapy for patients with biopsy-proven proliferative lupus nephritis (PLN). To examine remission induction and relapse rate in each treatment, fifteen patients were enrolled to this study. The remission rate of steroid, IV-CY, Tacrolimus (TAC) therapies were 100% (2/2), 91% (10/11), 100% (2/2).

In maintenance therapies, no relapse were observed among the patients with IV-CY and TAC regimen, while 60% (3/5) of patients relapsed with azathioprine and mizoribine regimen. IV-CY and TAC were suggested to be effective in both remission induction and maintenance therapy.

P3-478

Long-term effects of ARB on kidney function in LN; Evaluation with sC₃C.

Sayaka Namba¹, Satoshi Kadomatsu¹, Mari Ushikubo², Hirotoishi Matsumoto², Taku Yabuki², Kumiko Akiya², Hisaji Ohshima²
¹Department of Kidney Diseases, Tokyo Medical Center, Tokyo, Japan, ²Department of Connective Tissue Diseases, Tokyo Medical Center, Tokyo, Japan

Background) Protective effects of ARB on renal function in CKD have been established. In LN, however, the evaluation of renal

function by sCr is difficult because of the corticosteroid action on muscle. Purpose) To clarify effects of ARB on the renal function in LN, sCyC was evaluated. Subjects) Nine LN patients without serological activities were enrolled and followed for more than 17 mo. Olmesartan was used as an ARB. Mean age and prednisolone dosage was 41.6 and 7.6mg/day, respectively. Results) 1;ARB was stopped in two because of adverse symptoms. Two cases had hypertension. 2;In other 5 cases, sCyC and proteinuria both decreased in all cases. Conclusion) It was suggested that ARB had long-term protective effects on the kidney function when evaluated with sCyC and proteinuria in LN.

P3-479

Pulmonary edema after cyclophosphamide infusion in a case of lupus nephritis

Yumiko Nobuhara¹, Koji Takaori², Misako Uehara³, Eriko Eguchi², Megumi Nakata¹, Kengo Akashi¹, Shunzo Namiuchi¹

¹Department of Rheumatology, Saiseikai Nakatsu Hospital, Osaka, Japan, ²Department of Nephrology, Saiseikai Nakatsu Hospital, Osaka, Japan, ³Division of Rheumatology, Fujieda Municipal General Hospital, Fujieda, Japan

A fourteen-year-old woman was diagnosed as lupus nephritis (IV-G (A)). Prednisolone (0.8mg/kg) was initiated after intravenous pulse methylprednisolone (500mg for 3days). Despite the therapy, her serum creatinine remained high, and proteinuria was increasing. Therefore she was infused 750mg of cyclophosphamide (CY). 8days later, she developed dyspnea. Chest CT showed bilateral pleural effusions and diffuse ground glass opacities. Laboratory findings did not suggest infection. She received diuretics, and recovered soon. Though she had hypoalbuminemia due to nephrotic syndrome, she was not edematous and her body weight had decreased after CY infusion. Echocardiography displayed normal cardiac function, so it is unusual but CY might induced pulmonary edema without cardiomyopathy.

P3-480

Lupus nephritis triggered by parvovirus B19 infection

Eri Kimura, Koichiro Tahara, Aki Shoji, Haeru Hayashi, Tetsuji Sawada

Tokyo Medical University Hospital, Department of Rheumatology

<Case>A 16 year-old-woman presented with fever, malar rash and polyarthritis. She was diagnosed as erythema infectiosum because IgM antibodies against parvovirus B19 were positive. ANAs and anti-DNA antibodies were positive. Although fever and erythema disappeared, the symptoms flared up again. She was admitted to our hospital with fever, arthritis and malar rash. IgG antibodies against parvovirus B19 changed to positive. However, anti-DNA antibodies were 2700IU/ml and complements levels were decreased, she presented with microhematuria and proteinuria. She was diagnosed as WHO class IV lupus nephritis. Development of SLE triggered by parvovirus infection was reported in the literature. We discuss clinical manifestations and relationship between parvovirus B19 infection and SLE.

P3-481

The study of switching to celecoxib in RA patients with NSAIDs-induced GI injury

Junsuke Arimitsu^{1,2}, Keisuke Hagihara¹, Atsushi Ogata¹, Mari Kawai¹, Yoshihiro Hishitani¹, Toru Hirano¹, Yoshihito Shima¹, Masashi Narazaki¹, Toshio Tanaka¹

¹Department of Respiratory Medicine, Allergy and Rheumatic Diseases, Osaka University Graduate School of Medicine, ²Department of Kampo Medicine, Osaka University Graduate School of Medicine

Celecoxib (CEL) is a highly selective COX-2 inhibitor and has been proven to be less associated with gastrointestinal complications (GIC) than NSAIDs. However, the effects of COX-2 inhibitors on the GI tract have not been well examined in patients with pre-existing NSAIDs-induced GIC. RA patients who have been treated with NSAIDs for twelve or more weeks are switched to CEL (400mg/day). Capsule endoscopy (CE) is conducted before and after administration of CEL. CE demonstrated petechiae/red spot: $6.0 \pm 3.4 \rightarrow 2.3 \pm 1.8$ ($p < 0.01$), mucosal break: $4.9 \pm 6.1 \rightarrow 0.5 \pm 0.7$ ($p < 0.01$). Hemoglobin: 1.2 ± 1.6 g/dl \rightarrow 11.6 ± 1.7 g/dl ($p = 0.05$). DAS28 score has not changed before and after treatments. Our results suggest that switching from NSAIDs to CEL is an effective treatment for NSAIDs-induced GIC in RA patients.

P3-482

The association usage of low dose aspirin with upper GI injury in RA patients

Naoki Sugimoto, Eiichi Tanaka, Eisuke Inoue, Daisuke Hoshi, Kumi Shidara, Eri Sato, Yohei Seto, Toru Yamada, Ayako Nakajima, Atsuo Taniguchi, Shigeki Momohara, Hisashi Yamanaka
Institute of Rheumatology, Tokyo Women's Medical University

[Objective] To examine the association usage of low dose aspirin with upper GI ulcer in RA patients. [Methods] The rates of low dose aspirin user and gastro-duodenal ulcer were collected biannually based on self-report questionnaire using IORRA cohort from April 2007 to March 2010. [Results] The number of RA patients was approximately 5,500 in each phase. The rates of low dose aspirin user were 1.2~1.8%, and the rates of concomitant NSAID user were 50~70% among the low dose aspirin user. The incidences of gastro-duodenal ulcer were 4~10% in the both low dose aspirin and NSAID user ($n = 41 \sim 53$) and approximately 2 % in the NSAID alone user ($n = 3,192 \sim 3,363$). [Conclusion] Our results suggest that additional use of low dose aspirin on NSAID in RA patients may increase the risk of upper GI ulcer.

P3-483

Celecoxib improved upper gastrointestinal adverse lesions in patients with RA.

Shigeyoshi Tsuji¹, Tetsuya Tomita³, Hideo Kawai¹, Hideki Yoshikawa³

¹Department of orthopaedic surgery, Hoshigaoka koseinenkin hospital, ²Department of Gastroenterology, Hoshigaoka Koseinenkin Hospital, ³Department of Orthopaedics, Osaka University Graduate School of Medicine

Purpose: We prospectively investigated the effects of celecoxib (CEL) after switching from NSAIDs on the GI tract in RA with endoscopically identified GI mucosal injury. **Methods:** We conducted upper GI endoscopy to examine GI tract injury in RA patients who had been treated with NSAIDs for 3 or more months. GI mucosal injury was evaluated according to the modified LANZA score. Patients with mucosal injury without ulcers were switched from NSAIDs to CEL. LANZA score and DAS28 was evaluated before and at 16 weeks after switching to CEL. **Results:** 82 patients were eligible for the study. Endoscopic analysis revealed GI mucosal injury, including 6 ulcers, in 45 of 82 patients (54.9%). LANZA score/

DAS28 were significantly improved to 1.6/2.94 from pre-switching values of 2.1/3.18 ($p < 0.01$).

P3-484

A case of MTX-LPD accompanied with multiple nodules in the lung and liver.

Seiko Fukuta¹, Makoto Kubo¹, Hiroshi Nakamura²

¹Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan, ²Department of Community Health and Medicine, Yamaguchi University School of Medicine, Yamaguchi, Japan

We report a case of Methotrexate-associated Lymphoproliferative Disorder (MTX-LPD), which was accompanied with multiple nodules in the lung and liver. He was 69-year-old Japanese man. He has been affected with rheumatoid arthritis since he was 42-year-old, and he had taken MTX for 7 years. In July 2010, his doctor detected multiple nodules on the chest x-ray, and the patient admitted in our hospital. On the computer tomography, we found multiple nodules in the lung and liver. Pathological examination with both organs showed, there were no sign to suggest malignant, nor lymphocytic invasion. Because he had taken MTX, MTX-LPD was suspected. After MTX was stopped, the size of nodules were decreased. MTX-LPD is reported one of side effects of MTX. Early diagnosis is essential for this disease.

P3-485

MTX-LPD of oral cavity in a RA patient with MTX therapy: a case report

Isao Nakamura, Takako Fujisawa, Ikuo Minamisawa

Department of Orthopaedic Surgery, Nagano Municipal Hospital, Nagano, Japan

We report a MTX-LPD of oral cavity in a RA patient with MTX therapy. The patient was 69 year-old male. He suffered from RA from 2000. And he took 6mg of MTX every week from 2003. After MTX therapy, his state of RA was well controlled. After removing of his tooth on October in 2009, he came our hospital through dentist's introduction because of bad cavity ulcer. He also had neck lymphonode swelling. By a biopsy of ulcerative oral mucosa, there were many large atypical cells, positive for Vimentin, LCA, L26 and CD30, negative for AE1/E3 and CD3. Furthermore EBV was detected in those cells. According to those results, he was diagnosed MTX-LPD. From a biopsy of neck lymphonode, we could not detect any proof of MTX-LPD. After 3 months from stop of using MTX, ulcerative oral mucosa become well.

P3-486

Clinical courses of RA patients complicated with MTX-LPD at our hospital

Noboru Kitamura, Hirotake Inomata, Hidetaka Shiraiwa, Yoshikazu Kuwana, Masaaki Shiozaki, Takamasa Nozaki, Natsumi Ikumi, Hiromi Karasawa, Yoshihiro Matsukawa, Masami Takei, Takashi Hayama

Division of Hematology and Rheumatology, Department of Medicine, Nihon University School of Medicine

Background) MTX is recognized by an effective drug in RA. However patient, receiving MTX may pose risk of MTX-LPD. We show RA patients who developed a LPD during MTX therapy. (Objects, methods) We examined clinical course of RA patients complicated lymphoma during administrating MTX. (Results) All patients

were advanced RA. Although mean total MTX dose was 537.5mg, there was no correlation in MTX dose and appearance of lymphoma. There were 5 cases of B cell lymphoma, a case of Hodgkin lymphoma and MALT lymphoma. Although lymphoma has improved to 4 patients, 3 patients relapsed and needed chemotherapy. EBV was proven by 5 patients and by all relapsed patients. 1 patient died from lymphoma. (Discussion) It's necessary to note the appearance of the lymphoma during treatment RA using MTX.

P3-487

A case of bucillamine (BU) -induced aplastic anemia with rheumatoid arthritis (RA)

Yumiko Seno, Mutsuto Tateishi, Hideyuki Tachibana, Sayuri Kataoka, Akiko Tochimoto, Manabu Tanabe, Takashi Ogasawara, Takashi Yamada

Division of Rheumatic Diseases, Tokyo Metropolitan Ohtsuka Hospital, Tokyo, Japan

She developed RA in 1983 and effectively treated by BU in 1998. In 2000, laboratory tests revealed thrombocytopenia. BU was discontinued and PSL(30mg/day) was effective. Thereafter, RA gradually exacerbated and BU was readministered in 2004. In July 2005, platelet count decreased again. BU withdrawal and PSL(45mg/day) were ineffective. In September 2005, laboratory findings showed pancytopenia (WBC;2100/ μ l, Hb;4.8g/dl, plt;5000/ μ l). A bone marrow aspiration revealed decreased numbers of myelocytes, erythroblasts and megakaryocytes indicating aplastic anemia. Anabolic steroid and G-CSF were ineffective. ATG was given with daily CyA in March 2006. Five month later, peripheral blood cell counts began to increase, and complete recovery of the cell counts was observed in December 2006.

P3-488

Preferences for involvement in treatment decision making of RA patients

Akiko Aoki¹, Shohei Nagaoka², Akiko Suda², Takako Kawai³, Mitsuhiro Takeno⁴, Yoshiaki Ishigatsubo⁴, Sadayoshi Ohbu⁵

¹Office of Post-graduate Medical Education, Yokohama City University Hospital, Kanagawa, Japan, ²Rheumatology, Yokohama Minami Kyosai Hospital, Kanagawa, Japan, ³Rheumatology, Yokohama Sen-inhokenn Hospital, Kanagawa, Japan, ⁴Rheumatology, Yokohama City University Hospital, Kanagawa, Japan, ⁵Department of Sociology, Rikkyo University, Tokyo, Japan

Introduction: We conducted a questionnaire survey regarding the involvement of patients in treatment decision making. **Methods:** A desired and actual role was chosen from the following descriptions: #1 I prefer that my doctor makes the final decision after showing the best option. #2 I prefer that my doctor and I share responsibility for deciding which treatment is best for me. #3 I prefer to make the decision about which treatment I will receive by myself. **Results:** 83% were women and 70% were 60 years of age or older. While 65% of the patients selected #2 as a desired role, only 30% of them selected #2 in the actual role. The desired role was concordant with the actual role in 63% of the patients. We determined the patients' characteristics which associate the patient preferences.

P3-489

Tight Control with DMARDs for RA occurring at advanced aged.

Yasuhiro Tani, Noriyuki Miyazaki

[Perpose] We evaluated the efficiency and safety of the treatment with DMARDs for rheumatoid arthritis (RA) occurring at an advanced age (70 or over). [Object]There were 16cases. Average DAS28(ESR) is 4.96 (3.66-6.74). [Method] 7 cases were initially received therapy by SASP and 9 cases by MTX. [Result]Tenderness joint count and swelling joint count were improved with DMARDs. Average DAS28(ESR) after 6 month is 2.58(1.38-6.09). In the following after 6 month, 4 cases were received by SASP, 3 cases by SASP and MTX, 8 cases by MTX, 1 case by MTX and Etanercept. There was no complication for following periods. [Conclusion]It may be possible and effective to treat by Tight Control for RA appearing in persons aged 70 or over.

P3-490

Treating rheumatoid arthritis to target in our early arthritis clinic

Taio Naniwa, Kaneshige Sasaki, Shiho Iwagaitsu
Division of Rheumatology, Nagoya City University Hospital

AIM: To evaluate the proportion of RA patients reaching at treatment goal in our early arthritis clinic. PATIENTS: Data of 91 RA patients with symptom duration ≤ 5 years (mean age 54 years, 78 female, mean symptom duration 12 months, mean baseline DAS28 5.17.) treated for at least 3 months in the early arthritis clinic were retrospectively analyzed. RESULTS: 81 patients were on MTX (11.6 mg/week), 33 were on biologics. Oral corticosteroids have been used in 43 patients with a daily mean prednisolone-equivalent dose of 8.3 (1.5-30) mg/day and could be tapered off in 29 patients. At 3, 6, 12, and 24 months, the proportions of patients achieved DAS28 remission/low disease activity state were 22/40, 40/54, 43/64, and 71/80%, respectively. Our treatment approach was tolerable in most patients.

P3-491

IgG4 related sclerosing disease with ocular mass in young adult

Ryutaro Yamazaki, Reika Maezawa, Junya Nagasawa, Satoko Arai, Takayoshi Owada, Kazuhiro Kurasawa, Takeshi Fukuda
pulmonary Medicine and Clinical Immunology, Dokkyo Medical University, Tochigi, Japan

We report a case of IgG4 related disease in the young. 23 -year old male was admitted because of orbital mass and eosinophilia. He had felt blurred vision and noticed exophthalmos for 8 month. Imaging studies showed bilateral orbital mass compressing optic nerves and bilateral pulmonary hilar lymph-node swelling. Sample from orbital mass showed marked lympho-plasma cell infiltration, more than 50% of which were IgG4 positive plasma cells. Serum IgG4 level was increased to 2150mg/dl. He was diagnosed as IgG4 related disease and treated with glucocorticoid that dramatically reduced orbital mass and improved visual activities. IgG4 related disease is usually developed in old ages. However, physicians should include the disease in differential diagnosis of unknown mass even in young patients.

P3-492

A case of systemic lymphadenopathy in a patient with IgG4-related disease

Reina Ogawa^{1,2}, Hiroyuki Hounoki², Koichiro Shinoda³, Shoko Matsui³, Hirofumi Taki², Kazuyuki Tobe³

¹Toyamaken Saiseikai Takaoka Hospital, ²First Department of Internal Medicine, University Hospital, University of Toyama, ³First Department of Internal Medicine, School of Medicine, University of Toyama

A 64-year-old man consulted to the hospital with lower leg purpura and cough. He had a severe hypergammaglobulinemia without monoclonarity. The neck, mediastinal and intraperitoneal lymph nodes (LN) were observed to be swollen on CT. FDG-PET showed an accumulation in the swollen LN. Serum soluble IL-2R and IgG4 were both elevated. Pathological findings indicated that IgG4 positive plasma cells were predominantly infiltrated in the neck LN and the nasal mucosa. Thus, he was diagnosed as the IgG4-related disease. However, infiltration of IgG4 positive plasma cells was scarce in the bronchial mucosa and the skin. He treated with 30 mg of prednisolone with a good clinical response. Systemic IgG4-related lymphadenopathy should be also concerned in a case of systemic lymphadenopathy.

P3-493

Two cases of IgG4-related disease with pleural effusion

Ryosuke Hiwa, Yukio Tsugihashi, Ryuichi Sada, Teruhisa Azuma, Hiroyasu Ishimaru, Kazuhiro Hatta
Tenri Hospital

【Case1】A 74-year-old man with right pleural effusion was referred. Polyclonal plasmacytes were found in the effusion. Serum IgG4 was 1590mg/dl. IgG4-positive plasmacyte was detected in thickened pleura. Pleural effusion decreased with 15mg/day of prednisolone (PSL). 【Case2】A 76-year-old man with bilateral pleural effusion was referred. Atypical cells derived from plasmacyte were noticed in the effusion. Serum IgG4 was 2420mg/dl. IgG4-positive plasmacyte was detected in lymph node of right supraclavicular fossa. The effusion responded to the treatment of PSL (20mg/day) for the comorbid uveitis. 【Discussion】There are few reports of Ig4-related diseases complicated with pleural effusions. In these two cases, the pleural effusion was considered to be associated with IgG4-related diseases.

P3-494

IgG4-related tubulointerstitial nephritis without autoimmune pancreatitis.

Shigehisa Koide, Kyoko Kanayama, Nahoko Kohriyama, Kunihiro Nabeshima, Yukio Yuzawa
Department of Nephrology, Fujita Health University School of Medicine

A 72-year-old man was evaluated for malaise and elevated serum creatinine level (Scr). Two years ago, he was pointed out for abdominal periaortitis.

On physical examination, temperature was 36.8 °C. There were lymphadenopathies on his inguens. His Scr level had gradually increased from 1.4 mg/dL up to 2.2 mg/dL over 3 months and his IgG4 level was high (4715 mg/dL).

Renal biopsy and lymph node biopsy were performed. Both pathologies showed marked infiltrating of IgG4-positive plasma cell and IgG4-related tubulointerstitial nephritis was diagnosed. Oral prednisolone (30 mg/day) improved the renal function and IgG4 levels as well as renal pathology of 2nd biopsy, the lymph adenopathies, and the periaortitis. Through clinical course, there was no episode of autoimmune pancreatitis.

P3-495

A case of IgG4-related autoimmune disease with thrombocytopenia and neutropenia

Takanori Miura

Asahikawa Kosei Hospital

We report a case of 62-year-old woman who has IgG4-related autoimmune disease with thrombocytopenia and neutropenia. In 2008 she was pointed out liver dysfunction, thrombocytopenia and multiple lymphnode swelling but denied further examinations. In 2010, she was referred to our hospital because of gradually developing leukocytopenia. High serum IgG4 and hypocomplementemia was noted, and lymphnode biopsy revealed the infiltration of IgG4-positive lymphocytes. Although ANA and anti-ds DNA antibody were positive, she showed neither skin rash and arthritis. Urine examination revealed normal. She diagnosed as IgG4-related autoimmune disease and developed severe neutropenia (neutrophil 360/ml). Treatment with oral prednisolone (40 mg/day) was started, which was resulted in effective.

P3-496

Multicentric Castleman's disease (MCD) mimicking IgG4-related disease

Megumi Nakata¹, Misako Uehara², Kengo Akashi¹, Koji Takaori³, Eriko Eguchi³, Yumiko Nobuhara¹, Shunzo Namiuchi¹

¹Department of Rheumatology, Saiseikai Nakatsu Hospital, Osaka, Japan, ²Division of Rheumatology, Fujieda Municipal General Hospital, Fujieda, Japan, ³Department of Nephrology, Saiseikai Nakatsu Hospital, Osaka, Japan

A 53-year-old female with elevated IgG4 (828 mg/dl) was admitted in December 2009. CT scan demonstrated the swelling of lacrimal and submandibular glands, splenomegaly, lung nodules, and retromediastinal fibrosis. Laboratory findings showed interstitial nephritis. The histological examination of lymphnode revealed interfollicular plasmacytosis with the infiltration of IgG4-positive cells. Her clinical manifestations were similar to IgG4-related disease. The patient responded insufficiently to the treatment of PSL (1 mg/kg/day) with azathioprine (3 mg/kg/day). Elevation of CRP (10.2 mg/dl) and IL-6 (889 pg/ml) suggested MCD. We report the diagnostic confusion between IgG4-related disease and MCD with references. Diagnostic criteria are indispensable for these diseases.

P3-497

A case of HHV-6 encephalitis during steroid treatment for IAAA

Hidetaka Yajima, Motohisa Yamamoto, Yui Shimizu, Tetsuya Tabeya, Mikiko Ohara, Mikiko Ohara, Yasuyoshi Naishiro, Hiroyuki Yamamoto, Toshiaki Sugaya, Hiroki Takahashi, Yasuhisa Shinomura

First Department of Internal Medicine, Sapporo Medical University School of Medicine

A 73-year-old male suffered from anemia and weight loss. He was diagnosed with inflammatory abdominal aortic aneurysm (IAAA) due to the findings of FDG-PET. He was started to prescribe 30 mg/day of PSL. He suffered from fever, malaise and headache on June 2010, and was admitted on July. On admission, neck stiffness was not presented, but chest CT revealed pneumonia. He was treated with antibiotics. He was suddenly presented with impaired consciousness and convulsion on August. Brain MRI revealed encephalitis at bilateral temporal lobe, and only HHV-6 DNA

was detected by CSF. He was diagnosed with HHV-6 encephalitis. He was prescribed with gancyclovir, and his consciousness was gradually improved. It was suggested that HHV-6 encephalitis might occur in the elderly with immunosuppression.

P3-498

A case of IgG4-related disease accompanied with SLE and Sjögren Syndrome

Keisuke Nakatsuka¹, Kunihiro Yamaoka², Kazuki Someya², Kazuyoshi Saito², Yoshiya Tanaka²

¹Department of internal medicine, Nougata chuuo hospital, Fukuoka, Japan, ²The first Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Fukuoka, Japan

A 72-year-old man was diagnosed as SLE complicated with Sjogren's syndrome in 2004. His anti-SS-A/SS-B antibody was negative. He was treated with high-dose corticosteroid, during tapering, dry mouth exacerbated and urine protein increased. Mizolitin 200mg/d was initiated, although he developed bronchial asthma and remarkable obstructive jaundice on 2010. Since narrowed bile duct at the pancreas head was observed with ERCP suspecting pancreatic carcinoma, pancreaticoduodenectomy was performed. Pathological evaluation resulted in sclerosing cholangitis and auto-immune pancreatitis infiltrated IgG4-bearing plasma cell. With elevated IgG4 793 mg/dl, he was diagnosed as IgG4-related disease and PSL 30mg/d was initiated. Here we report this rare case with SLE followed with IgG4-related disease.

P3-499

A Castleman's disease patient was complicated with IgG4 related disorder

Keisuke Hagihara¹, Atsuyoshi Morishima¹, Yoshihiro Hishitani¹, Mari Kawai¹, Junsuke Arimitsu^{1,2}, Toru Hirano¹, Yoshihito Shima¹, Masashi Narazaki¹, Atsushi Ogata¹, Toshio Tanaka¹

¹Department of Respiratory Medicine, Allergy and Rheumatic Diseases, Osaka University Graduate School of Medicine, ²Department of Kampo medicine, Osaka University Graduate School of Medicine

Differential diagnosis between IgG4 related disorder and multicentric Castleman's disease (MCD) remains controversial. A 69-year-old male diagnosed with MCD in 2002 and joined the phase II clinical trial of tocilizumab (TCZ). He has been treated with TCZ 8mg/kg every two weeks without prednisolone (PSL) from 2002. In June 2009 he presented with right exophthalmia and was admitted to our hospital. Abnormal F-18 FDG uptake showed in the bilateral orbital and prostate glands on PET-CT scan. IgG4 related disorder were diagnosed by elevated serum IgG4 3940mg/dl and abundant IgG4-positive cells. After treatment with mPSL1g for 3days and TCZ8mg/kg, Right exophthalmia were dramatically improved. Now the patient treated with TCZ at 8mg/kg every four weeks in combination with 10 mg/day PSL.

P3-500

Mucosa-Associated Lymphoid Tissue and Lymphocyte Homing in IgG4-Related Disease

Susumu Sugai

Kudo General Hospital

IgG4-related disease may be a disease of mucosa-associated lymphoid tissue (MALT) and the diversity of affected organs is due to the homing difference of lymphocytes. The disease onset is con-

sidered to be the formation of acquired MALT. This occurs by homing of Ag-experienced lymphocytes from MALT. Homing receptors ($\alpha 4\beta 7$) of lymphocytes are induced by Ag-activated dendritic cells in the MALT. The expression of cellular adhesion molecules (MAdCAM-1) of endothelial cells is considered to be caused by Th1 cytokines (INF γ) from Th1 cells activated by dendritic cells and chemokines produced in inflamed microenvironment around post capillary venule. The cause of inflammation may be due to infection by bacteria or virus, or due to the immune response to PAMPS or autoantigens in DAMPS.

P3-501

Early clinical response to Tocilizumab is not associated with functional outcome

Yu Asanuma, Kojiro Sato, Kazuhiro Yokota, Hiroshi Kajiyama, Kyoichi Nakajima, Yuji Akiyama, Toshihide Mimura
Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University

IL-6 is a cytokine implicated in the pathogenesis of RA. IL-6 also stimulates the production of CRP and fibrinogen then increases serum CRP or ESR. Decrease of CRP and ESR are observed soon after administration of Tocilizumab (TCZ), a monoclonal antibody to IL-6 receptor, in patients with RA. Thus, usual disease activity score using CRP or ESR may not indicate real response to TCZ. We evaluated disease activity and physical function in twenty two patients receiving TCZ. DAS28 significantly decreased in TCZ-treated patients for 16 weeks. On the other hand, improvement of HAQ and mHAQ was not achieved by week 16. Improvement of both DAS28 and mHAQ was recognized in patients treated with infliximab (n=54) or etanercept (n=41) after 2 weeks of therapy.

P3-502

Tocilizumab-free trial in RA: Importance of the normalization of MMP-3

Hiroshi Kaneko¹, Satoshi Kamei², Sumie Moriyama², Reo Yoshikawa², Yoshinori Masui², Junwa Kunimatsu², Yuko Takahashi³, Hiroyuki Yamashita³, Iwao Sekigawa⁴, Akio Mimori³
¹Department of Rheumatology, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan, ²Department of Internal Medicine, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan, ³Division of Rheumatic Diseases, Department of Internal Medicine, National Center for Global Health and Medicine, Tokyo, Japan, ⁴Division of Rheumatology, Department of Internal Medicine, Juntendo Urayasu Hospital, Chiba, Japan

We discontinued tocilizumab (TCZ) in 7 cases of TCZ-treated rheumatoid arthritis (RA) who achieved clinical remission (DAS28-ESR<2.6). Bio-free remission was maintained in 4 cases for 24 weeks without TCZ, with 1 still in drug-free remission after 1 year. TCZ therapy was restarted in the 3 who had recurrence, and clinical remission was achieved soon after. The 3 serum MMP-3 and IL-6 measurements (mean \pm SD) up to TCZ cancellation were compared. MMP-3 was 55.7 \pm 21.5 ng/ml in the withdrawal achievement group, and 220.2 \pm 80.6 ng/ml in the non-achievement group (p=0.01). IL-6 levels in the withdrawal achievement group were lower than in the non-achievement group. Given our results, continuous low titers of MMP-3 should be considered an important predictor of bio-free remission in TCZ-treated RA.

P3-503

Analysis of factors impacting improvement of HAQ in tocilizumab treatment

Yoshio Ozaki^{1,2}, Akihiro Tanaka^{1,2}, Keiko Shimamoto², Hideki Amuro², Katsuyuki Kawakami^{1,2}, Yonsu Son^{1,2}, Hirokazu Sawai¹, Tomoki Ito², Takahiko Wada¹, Shosaku Nomura²

¹Department of Rheumatology and Clinical Immunology, Kansai Medical University Hirakata Hospital, Hirakata, Japan, ²First Department of Internal Medicine, Kansai Medical University, Moriguchi, Japan

Tocilizumab (TCZ) shows a greater effect on test data rather than the clinical condition due to its mechanism of action. The goal of rheumatoid arthritis (RA) treatment is to improve Activities of Daily Living (ADL). Here, we searched for factors that affect improvement of Health Assessment Questionnaire (HAQ), an index of ADL, with TCZ treatment. Forty-six RA patients (M:F ratio 11:35; average age, 56.9). HAQ, DAS28ESR, SDAI, CDAI, and various inflammatory cytokines were measured before and after 24 weeks of TCZ administration. Initial values of DAS28, CDAI, SDAI, and IL-17F as well as DCDAI and DSDAI were correlated with DHAQ. In TCZ treatment, improvement of HAQ can be expected in cases with high IL-17F before treatment. CDAI and SDAI are useful indexes of RA disease activity.

P3-504

Efficacy and safety of tocilizumab in rheumatoid arthritis patients

Takahito Kimata^{1,2}, Naooki Katsuyama¹, Masaomi Yamasaki¹, Koh Nakatani², Shoichi Ozaki³

¹Division of Rheumatology, St. Marianna-university of Medicine, Yokohama-city Seibu hospital, yokohama, japan, ²Division of rheumatology, Misato Marine Hospital, Kochi, Japan, ³Division of Rheumatology and Allergy, St. Marianna university of Medicine, Kawasaki, Japan

Objective: Although availability of TNF-alpha antagonist for rheumatoid arthritis (RA), there are still patients with inadequate response. We analyzed whether tocilizumab (TCZ) respond to RA patients. Methods: 29 (5men, 24women) of RA patients were treated at our clinics. DAS28, CDAI and MMP-3 were calculated in all patients. Results: The continuance rate was 82.7%. 18 patients were switched from another biologic agents. 16 patients had treated TCZ with MTX. 8 patients had achieved remission. 5 patients had extended interval of TCZ administration, and 1 of 5 patient discontinued after attainment of remission. The biologic-naive patients and MTX +TCZ patients had a good response. Conclusion: TCZ treatment is effective of RA patients, especially in biologic-naive and MTX+ group.

P3-505

The desirability of using Tocilizumab to treat patients with RA

Kiyomitsu Miyachi
Keigu Clinic, Health Sciences Research Institute

(Objective) The efficacy of Tocilizumab (TCZ) to treat patients with RA was investigated and compared to that of TNF inhibitors. (Methods) TCZ was administered in 6 of these 7 patients within one year of diagnosis of RA. Five patients were previously not treated with any sort of TNF inhibitor prior to TCZ administration. (Results) Initial mean scores (5.67) registered on DAS 28-ESR were reduced to 2.79 following regular use of TCZ for 3 months. Most no-

tably, the white blood count in 5 cases was reduced to less than 2500 within 3 months. (Discussion) Administration of TNF inhibitors was terminated in some patients because of low efficacy. TCZ is thought to be a suitable first line drug for patients presenting with leucocytosis and or thrombocytosis in the early stages of RA.

P3-506

Efficacy and safety of tocilizumab in rheumatoid arthritis patients

Takao Kodera, Toshio Funyu, Toshio Mitomo
Department of Rheumatology, Tohoku KoseiNenkin Hospital

Objective: We examined the efficacy and safety of the biological agent (BIO), tocilizumab (TCZ), the only interleukin-6 inhibitor developed in Japan, in rheumatoid arthritis (RA) patients.

Subjects and methods: Efficacy and safety were examined using DAS28 with CRP in 20 patients (3 men and 17 women, mean age 54.1 years) after 6 months of TCZ treatment in our hospital.

Results: The mean CRP was 5.0 mg/dL before treatment. DAS28 decreased significantly from 3.8 before to 2.8 after treatment. DAS28 improvement tended to be greater in the MTX concomitant group and BIO treatment naïve group. In 12 patients, 16 adverse events occurred but treatment was not discontinued.

Conclusion: Earlier concomitant use of MTX is recommended to increase the remission rate with TCZ treatment.

P3-507

A study of efficacy and safety of tocilizumab in rheumatoid arthritis patients

Kazuo Kamada, Shinichi Mizuki, Naoko Ueki, Fumihiko Konishi, Kensuke Oryoji, Eisuke Yokota
Matsuyama Red Cross Hospital, The Centre for Rheumatic diseases

In this study, we analysed the efficacy and safety in 22 patients with rheumatoid arthritis treated with tocilizumab (Actemra, an anti-IL-6 receptor antibody) from June 2008 to October 2010 in our hospital. Mean DAS28-CRP at 24 weeks decreased less than at baseline from 5.2 to 2.7. DAS remission rates was achieved in 42.9%. In the problem of adverse drug reaction, leukopenia (neutropenia) was observed. However, severe infection was not observed. Tocilizumab may be used safely relatively and effectively for patients with inadequate response to DMARD, as methotrexate.

P3-508

Evaluation of the Long-Term (≥ 1 year) Efficacy and Safety of Tocilizumab

Mutsuaki Kai, Taisaku Kawamoto, Masakazu Kouzuma, Michitaka Yuasa

Department of Orthopaedic Surgery and Rheumatology, Junwakai Memorial Hospital

Objective: To evaluate the results of long-term treatment with tocilizumab (TCZ).

Methods: DAS28 scores, DAS28 remission and steroid reduction were examined in patients administered TCZ (a mean age of 64.4 and a mean duration of 14.5) for one year (14 patients) and two years (7 patients).

Results: In the first year, the TCZ continuation rate was 93%, with no treatment discontinuations for adverse reactions. The mean PSL dose decreased from 5.0 to 1.5 mg/day, and the mean DAS28 decreased from 5.1 to 2.5 ($P < 0.01$). The response was maintained at two years (2.7). At one year, 7/14 patients (50%) had remission. At

two years, 6/7 patients (86%) had good response.

Conclusions: TCZ was therefore found to demonstrate long-term efficacy and maintenance of response, as well as long-term safety.

P3-509

Evaluation of the efficacy and safety of tocilizumab treatment in our hospital

Akiko Suda¹, Kenji Ohmura¹, Shohei Nagaoka¹, Yoshiaki Ishigatsubo²

¹Department of Rheumatology, Yokohama Minamikyosai Hospital, Yokohama, Japan, ²Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

Purpose: The efficacy and safety of treatment with tocilizumab (TCZ) were evaluated in our institution.

Methods: A total of 30 patients who started TCZ therapy for at least 24 weeks were evaluated.

Results: Nineteen patients had received at least one biological agent before TCZ therapy. Six patients received monotherapy. Mean DAS28 (ESR) scores were 5.8 at baseline, 2.4, 2.3, and 1.9. Rates of remission (DAS28 (ESR) of < 2.6) were 70%, 75%, and 83% at weeks 24, 48, and 72, respectively. Treatment continuation rate was 100%. A total of 40 adverse events occurred in 24 patients. Analysis of patients by factors possibly affecting remission revealed no significant differences by patient characteristics.

Discussion: We conclude that TCZ is a beneficial drug in the daily clinical practice.

P3-510

Decreasing effect of corticosteroids after tocilizumab therapy for RA

Hiroshi Kaneko¹, Satoshi Kamei², Sumie Moriyama², Reo Yoshikawa², Yoshinori Masui², Junwa Kunitatsu², Yuko Takahashi³, Hiroyuki Yakashita³, Iwao Sekigawa⁴, Akio Mimori³

¹Department of Rheumatology, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan, ²Department of Internal Medicine, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan, ³Division of Rheumatology, Department of Internal Medicine, National Center for Global Health and Medicine, Tokyo, Japan, ⁴Division of Rheumatology, Department of Internal Medicine, Juntendo University Hospital, Chiba, Japan

We investigated the change of the steroid dosage in 16 cases of rheumatoid arthritis (RA) who were administered by tocilizumab (TCZ). The DAS28-ESR before the TCZ therapy was 5.56 ± 0.08 and it was improved on 2.49 ± 1.16 (clinical remission) at the point of TCZ administration 12 weeks (W). The average steroid quantity before the TCZ therapy was prednisolone 5.53 ± 2.16 mg/day, and then it was improved on 3.28 ± 2.56 mg/day (12W), 2.47 ± 2.74 mg/day (24W), and 0.54 ± 0.08 mg/day at the point of TCZ administration 52 W. We must decrease or stop oral corticosteroid as much as possible because corticosteroid has some adverse effect including osteoporosis and infection. TCZ is able to induce clinical remission immediately and it may have the beneficial effect of corticosteroid loss or cancellation.

P3-511

Study of tocilizumab treatment for patients with rheumatoid arthritis.

Yoshiko Kawasaki¹, Akira Hashiramoto¹, Teppei Hashimoto¹, Maki Kagitani¹, Chihiro Tanaka^{1,2}, Yoshitada Sakai^{1,3}, Nao Shibamura^{1,4}, Shunichi Shiozawa¹

¹The Center for Rheumatic Diseases, Kobe University Hospital, ²The Rheumatic Disease Center, Konan Kakogawa Hospital, ³Faculty of Health Science, Himeji Dokkyo University, ⁴Orthopedic surgery, Kobe Kaisei Hospital

(Objective)To evaluate clinical sequel of the treatment of RA patients with tocilizumab (TCZ). (Method)A total of 24 patients with active RA, treated by TCZ more than 26 weeks, were enrolled at the Center for Rheumatic Diseases, Kobe University Hospital. Patients' profile was age 58.5±11.6, female 19, male 5, Class I 9±0.6 and X-ray stage 2.0±0.8. (Results)Clinical-remission was obtained by 54.2% in total patients, while it was 81.8% in patients who introduced TCZ as a first-biologic DMARD. Rates of treatment-retention were 79.2% at 26 weeks-period and 50.0% at 52 weeks-period in total, while they were 90.9% and 62.5% in patients who introduced TCZ as a first-biologics. The combination use of both MTX and PSL did not affect on the rate of both clinical-remission and treatment-retention.

P3-512

The 1 year results of patients with Bio naïve RA treated with Tocilizumab (TCZ)

Atsushi Kaneko^{1,4}, Yuichiro Yabe^{2,4}, Toshihisa Kojima^{3,4}, Naoki Ishiguro^{3,4}

¹Department of Orthopaedic surgery and Rheumatology, Nagoya Medical Center, NHO, Nagoya, Japan, ²Department of Orthopaedic surgery and Rheumatology, Tokyo Koseinenkin Hospital, Tokyo, Japan, ³Department of Orthopaedic surgery, Nagoya University, Graduate School & Faculty of Medicine, Nagoya, Japan, ⁴Tsurumai Biologics Communication

This purpose of this study is to analyze the data of 53 patients with Bio naïve RA in 21 institutes of the Tsurumai Biologics Communication. We investigated the drug survival rate, the mean of DAS 28ESR, the remission rates, and the reasons for discontinuation. Results. The drug survival rate was 81.1% throughout 1 year. The mean score of DAS28 was 5.15 in the beginning, decreasing to 2.57 after a year. Overall remission rate over 1 year was 53.4%. Within 1 year 10 patients dropped out. The reasons for discontinuations were as follows: 7 patients dropped out for safety reasons, including 6 patients with related infection, 1 patients with severe infusion reaction. In conclusion, Tocilizumab is very effective for Bio naïve RA, however, several patients were complicated with infection.

P3-513

A case of dermatomyositis with cardiac tamponade

Rumiko Miyagi¹, Takayoshi Soga¹, Yoshiaki Ishigatsubo²

¹Department of Rheumatology, National Hospital Organization Yokohama Medical Center, Kanagawa, Japan, ²Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Kanagawa, Japan

A 59-year-old woman, appeared myalgia of upper and lower and a dyspnea, visited to our hospital in 2005. We diagnosed dermatomyositis and interstitial pneumonia. We started a treatment of pred-

nisolone, but pulmonary interstitial shadow did not fade out. So we added cyclosporin A for internal use. And on October, 2010, she revealed much cardiac effusion on chest CT scan and she admitted our hospital in emergency. We performed pericardiocentesis and drained about 1.1L of cardiac effusion. The state of cardiac effusion is exudative, and from the culture of cardiac fluid, infection was negative. The frequency of dermatomyositis with pericarditis is less than pleuritis. So we report with referential deliberation.

P3-514

A case of SLE/DM overlapping syndrome associated with TTP (TMA)

Natsuki Fujio, Tamao Nakashita, Akira Inoue, Shinji Motojima
Rheumatology and Allergy, Kameda Medical Center, Chiba, Japan

A 47 year-old man was admitted to our wards because of erythema and muscle weakness. From skin symptoms and signs, elevated muscle-derived enzymes and EMG finding, combined with positive anti-DNA and anti-sm antibodies and positive lupus band test, a diagnosis of SLE/DM overlapping syndrome was made. Treatment was started with 60 mg/day of PSL and 150 mg/day of cyclosporine A, but 10 days later thrombocytopenia, hemolytic anemia, fragmented cells and TIA-like symptoms developed. TTP (TMA) was suspected and plasma exchange and M-PSL pulse therapy were done. ADAMTS13 activity was 46% and anti-ADAMTS13 antibody was not detected, suggesting atypical TTP (TMA) consistent with CVD-associated TTP. Because cases of SLE/DM overlapping syndrome associated with TTP is rare, we report this case.

P3-515

Acute hemorrhagic necrosis of liver in a patient with polymyositis (PM)

Kengo Akashi¹, Megumi Nakata¹, Misako Uehara², Yumiko Nobuhara¹, Shunzo Namiuchi¹

¹Department of Rheumatology, Saiseikai Nakatsu Hospital, ²Division of Rheumatology, Fujieda Municipal General Hospital

A 68-year-old man with myalgia, elevated acute phase reactants, was admitted to our hospital. He was diagnosed as PM and rectal adenocarcinoma. Operation was performed immediately after administration of intravenous immunoglobulins, and large amount of glucocorticoid (GC) therapy was started after operation. Because of insufficient effect of GC, azathioprine (AZP) was administered. PM was gradually improved, but thrombocytopenia was developed 19 days after the administration of AZP. Then, AZP was discontinued. However, 2 days later his liver enzymes were elevated extremely and he presented DIC. He died the next day. Autopsy demonstrated acute hemorrhagic necrosis of liver, suspected the possibility of the adverse effect of AZP.

P3-516

A case of C-ADM as a paraneoplastic syndrome preceded by interstitial pneumonia

Akira Inoue, Tamao Nakashita, Natsuki Fujio, Shinji Motojima
Rheumatology and Allergy, Kameda Medical Center, Chiba, Japan

A 65-year old man was admitted to our wards because of interstitial pneumonia (IP) associated with skin manifestations compatible with dermatomyositis (DM). Since the patient did not show muscle symptoms or elevation of muscle-derived enzymes, the diagnosis of clinically amyopathic DM (C-ADM) with IP was made. He has been treated with the combination of PSL, CYA and IVCY, result-

ing in improvement. Abdominal CT at the time of stomach cancer operation revealed mild IP when the CT images were reconstructed into lung field condition. The skin symptoms developed later. From the clinical course, he was thought to be a case of C-ADM as a paraneoplastic syndrome preceded by IP, which is rare.

P3-517

The prognosis of DM/PM with esophagus cancer that show paraneoplastic syndrome

Toshio Kawamoto, Keigo Ikeda, Ken Yamaji, Naoto Tamura, Yoshinari Takasaki

Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo, Japan

We experienced the DM / PM patient who improved the myodystrophy and the rise of myogenic enzyme by the complete excision of esophagus cancer. In our hospital, there were other three DM / PM patients with esophagus cancer from 1979 to 2010. We compared performance status of cancer and DM/ PM by various image, examination data and performed therapies and considered about the prognosis of DM/ PM patients with esophagus and other cancers which showed paraneoplastic syndrome. We considered about PM / DM patient was better first to be operated, and second to be administered prednisolone, and in many cases they could lead to remission. But after the remission, there were many cases which were led to worse prognosis, because prognosis of esophagus cancer itself was worse.

P3-518

Treatment of malignancy in dermatomyositis improved myositis and reduced steroid

Aya Oda¹, Tadashi Sakurai¹, Tomomi Tsutsumi¹, Hiroki Yabe¹, Masato Moriguchi², Chihiro Terai¹

¹Division of Rheumatology, Jichi Medical University, Saitama Medical Center, ²Towa Hospital

Background: Which treatment should be first, that for myositis or malignancy is a difficult issue in myositis patients associated with malignancy. We had two dermatomyositis with malignancy in whom resection of cancer improved myositis without steroid. **Purpose:** To study whether treatment for malignancy improve myositis and reduce steroid requirement (SR) in inflammatory muscle diseases (IMD). **Method:** 24 patients with IMD treated in our hospital were evaluated. Duration (DUR) and total dose of steroid (TCS) until normalization of CK were compared. **Results:** IMD patients with malignancy showed shorter DUR and less TCS compared to IMD patients without malignancy. **Discussion:** Treatment of malignancy could improve myositis and reduce SR in MIMD and should be a prior therapy for such a case.

P3-519

A case of ADM / IP complicated by emphysema for which TAC therapy was effective

Yumiko Oka, Michio Fujiwara, Yasuhiko Kita

Department of Rheumatology, Yokohama Rosai Hospital

A 40-yo man developed fever and erythema in Oct 2009. In Nov 2009, he was diagnosed with adult-onset Still's disease, and began prednisolone (PSL) 30 mg/d. He was referred to us for persistent fever. Based on Gottron's sign, mild myalgia, mild CK, and interstitial pneumonia (IP), amyopathic dermatomyositis (ADM) was diagnosed. He received methyl-PSL pulse therapy for progressive IP in Jan 2010, and then PSL 60 mg/d. No improvement of IP or fever

was noted, but erythema and CK were improved. After cyclosporin A (CyA) was added, fever remitted. He continued the drugs. In Feb 2010, subcutaneous/interstitial emphysema developed. After CyA was replaced by tacrolimus, emphysema improved without aggravation of IP. We report this rare case in which tacrolimus was effective for emphysema with ADM.

P3-520

Polymyositis treated with intravenous immunoglobulins as first-choice agent

Kengo Akashi¹, Megumi Nakata¹, Misako Uehara², Yumiko Nobuhara¹, Shunzo Namiuchi¹

¹Department of Rheumatology, Saiseikai Nakatsu Hospital, ²Division of Rheumatology, Fujieda Municipal General Hospital

A 68-year-old man with myalgia, elevated acute phase reactants, was admitted to our hospital. He was diagnosed as Polymyositis (PM) with laboratory findings, EMG, and muscle biopsy. Colon fiberoscopy was undergone because of positive fecal Hb test, a 10 mm polyp was discovered at Rs portion. EMR specimen was diagnosed as adenocarcinoma, tub1 and muc, pSM (3100 µm from baseline), and ly1 suspected. It was necessary to perform operation before large amount of glucocorticoid (GC) therapy for PM. Because PM was deteriorated, intravenous immunoglobulins (IVIG) was administered before operation. There were no perioperative problems, IVIG was enough effective as perioperative treatment for PM. IVIG is an effective treatment for GC-resistant PM. There are few reports for the first-choice agent.

P3-521

Four cases of Sweet's syndrome (SwS: acute febrile neutrophilic dermatosis)

Tsuyoshi Kobashigawa, Yuki Nanke, Toru Yago, Naomi Ichikawa, Hisashi Yamanaka, Shigeru Kotake

Institute of Rheumatology, Tokyo Women's Medical University

Objectives: To describe the clinical features of SwS. **Methods:** We analyzed the clinical features of 4 patients (2 male; mean-age +/- SD: 38.8 +/- 9.3 year-old) with erythema nodosum (EN) visited our hospital in recent 5 years. **Results:** All 4 patients fulfilled the criteria of SwS, with HLA-B54 ($p = 7.0 \times 10^{-6}$). Each 4 patient fulfilled both the international and the Japanese criteria of Behçet's disease (BD), fulfilled the international alone, fulfilled the Japanese alone, and not fulfilled either, respectively. Pathological findings of skin biopsy from EN in each 4 patient typically showed an upper dermal infiltrate of mature neutrophils. All 4 patients were effectively treated with oral corticosteroid. **Conclusions:** Skin biopsy and HLA loci analysis were very important to diagnose SwS.

P3-522

Sweet disease complicated with hemophagocytic syndrome and Kikuchi disease

Kanako Takano¹, Tomohiro Koga¹, Takahisa Suzuki¹, Yoshikazu Nakashima¹, Akitomo Okada¹, Shin-ya Kawashiri¹, Mami Tamai¹, Satoshi Yamasaki¹, Hideki Nakamura¹, Akinari Mizokami², Atsushi Kawakami¹

¹Unit of Translational Medicine Department of Immunology and Rheumatology Nagasaki University Graduate School of Biomedical Sciences, ²Nagasaki Municipal Hospital

21-year-old male visited the hospital complaining fever, right cervical pain, swelling of tonsils and cervical lymph nodes. He was

once successfully treated with antibiotics. After two months, fever and lymphadenitis complicated pancytopenia relapsed and he was admitted to our hospital for further evaluation. Brachial skin biopsy showed the finding of Sweet disease. The presence of hemophagocytic syndrome (HPS) was diagnosed by bone marrow aspiration. Accordingly, prednisolone (30mg) was initiated and induced remission. Cervical lymph node biopsy revealed necrotizing lymphadenitis. Although the precise conditions remain to be elucidated, we described the rare case of Sweet disease complicated with subacute necrotizing lymphadenitis and HPS.

P3-523

Non-episodic angioedema associated with eosinophilia: review of 18 cases

Atsushi Nomura, Yuri Ohara, Yasuhiro Suyama, Hisanori Shimizu, Eishi Uechi, Mitsumasa Kishimoto, Ken-ichi Yamaguchi, Masato Okada

St. Luke's international hospital

Non-episodic angioedema associated with eosinophilia is a disease characterized by peripheral eosinophilia and angioedema of extremities. Young woman predominance, arthralgia and skin eruption indicate importance as a differential diagnosis of rheumatic disease. We investigated characteristics of 18 cases diagnosed in our hospital from July 2003 to October 2010. Ages were 22 to 51 (mean 33.9). Fifteen cases were female. Lower leg edema was seen in all, arthralgia in 8 and pruritic rash in 13 cases. Ten had some kind of allergy. The maximum number of eosinophil were 1136 to 25680/ μ l (mean 6988/ μ l) and its percentage were 16 to 80% (mean 43%). Onset were mostly seen in summer and autumn. Ten were treated with corticosteroid but all cases relieved regardless of treatment

P3-524

Mycobacterium intracellulare arthritis mimicking rheumatoid arthritis

Hiroki Yabe¹, Takashi Hayashi², Keiichiro Nishida³

¹Department of Internal Medicine, Ako Central Hospital, Hyogo, Japan, ²Department of Orthopaedic Surgery, Sayo Central Hospital, Hyogo, Japan, ³Department of Orthopaedic Surgery, Okayama University, Okayama, Japan

We report a 69-year-old man with Mycobacterium intracellulare arthritis of the wrist, initially diagnosed as early monoarticular rheumatoid arthritis (RA) and treated prednisone and methotrexate for 2 years. The patient was admitted to our hospital because of gastric ulcer. Then he had been treated with a tumor necrosis factor (TNF) antagonist for 7 months. After immunosuppressive therapy the tenosynovitis was not improved, tenosynovectomy was performed. Surgical exploration showed granulomatous inflammation of the synovial and tendon sheath. Polymerase chain reaction for Mycobacterium intracellulare was positive from a specimen of synovial fluid. Our case highlights non-tuberculous mycobacterial (NTM) arthritis as an important differential diagnosis of atypical arthritis.

P3-525

anti-tumor necrosis factor therapy in HIV-positive patient with RA

Takashi Esumi

Meijibashi Hospital, Osaka, Japan

We report a case of anti-tumor necrosis factor therapy in HIV-positive patient with rheumatoid arthritis. A 49-year-old Japanese

man with human immunodeficiency virus infection developed polyarthralgia. Serological testing showed that anti-CCP antibody was positive. He was diagnosed RA and started to treat with Bucllamin, but his symptoms did not improve. MTX was then started at 6mg/week. After increasing MTX (8mg/week), his joint symptom decreased. About 4 weeks later, His arthralgia increased again. Therefore in September 2009, anti-TNF therapy with etanercept (50mg/week) was started. He had good response of anti-TNF therapy, and no sign of adverse events. This is the first reported case of RA concomitant with HIV infection treated with anti-TNF inhibitor in Japan.

P3-526

The influence of malignancy on the treatment of rheumatoid arthritis

Keigo Setoguchi¹, Yasunobu Takizawa¹, Junko Maruyama¹, Misato Kawakami¹, Atsuko Murota¹, Kazuyoshi Ishigaki², Noboru Hagino², Takeyuki Kanzaki², Kenji Takagi¹

¹Tokyo Metropolitan Cancer and Infectious disease center Komagome Hospital, Tokyo, Japan, ²Department of Allergy and Rheumatology, University of Tokyo

We investigated the treatment of RA with prior malignancy and after occurrence of malignancy. We enrolled the patients with RA with prior malignancy and malignancy with prior RA between April 2010 and October 2010 in our department. Thirteen (6 females and 7 males) patients had RA with prior malignancy. The average age of occurrence of malignancy and RA was 69.7 y.o. and 74.5 y.o. Patients were treated with SASP or MTX. No patients need biologic agents. Thirty-five (28 females and 7 males) patients had malignancy with prior RA. The average age of onset of RA and malignancy was 54.9 y.o. and 68.0 y.o. 4 patients used biologic agents. All 8 patients with malignant lymphoma were treated with MTX. Patients were treated with DMARDs after operation of malignancy. Most chemotherapy needs no DMARDs.

P3-527

A study of patients admitted by unknown origin fever to our hospital

Akihiko Mukai¹, Mayumi Kawaguchi²

¹Co-op Osaka Hospital, ²Mimihara General Hospital

We investigated about a disease of patients who were hospitalized with unknown origin fever from 2006 to 2010. 64 examples were hospitalized in total. In classification by an original disease, infection, collagen disease, malignancy and unknown were 32, 18, 2 and 8 cases. In infection cases, TBC, pyelonephritis, infectious endocarditis, pneumonia/pleuritis were 5, 9, 4 and 2. In collagen disease, Rheumatoid arthritis, polyarteritis, polymyalgia rheumatica and adult still's disease were 4, 3, 2 and 4. There were three patients who were diagnosed collagen disease at first but final diagnosis was an infectious disease. As for them, all the members were complicated with diabetes. We should distinguish an infectious disease before diagnosing as collagen disease in patients with diabetes.

P3-528

Evaluation of nutritional state in RA patients with newly available tool, GNRI

Takashi Kato¹, Kunihiro Ogane^{1,2}, Ichiro Mizushima^{1,2}, Mitsuhiro Kawano²

¹Division of Nephrology and Rheumatology, Ishikawa Prefectural Central Hospital, Kanazawa, Japan, ²Department of Rheumatology, Kanazawa University School of Medical Science, Kanazawa, Japan

(Introduction) In 1980s, RA was considered as malnutrition due to chronic inflammation. Nutritional state of RA in this era was evaluated with a new tool, geriatric nutritional risk index (GNRI). (Method) Nutritional state of RA cases (N=62) were evaluated with BMI and GNRI and relationship with DAS28-CRP was validated. (Result) Characteristics of 62 cases were as follows: age 59.83±1.75 yo, duration 6.68±10.3 yrs, DAS28-CRP 2.83±0.16, BMI 21.98±0.45, GNRI 104.81±1.26. GNRI and BMI were strongly associated (p=0.7864, p<0.001). DAS28-CRP was related with neither BMI nor GNRI. (Conclusion) Malnutrition was not shown by BMI. GNRI was closely related with BMI as HD patients (ref). Nutritional state was not associated significantly with disease activity. (ref. Am J Clin Nutr 2008; 87: 106-13.)

P3-529

The treatment of RA with chronic kidney disease

Hiroshi Kajiyama, Akinori Yamamoto, Yasufumi Shindo, Yoshihiro Yoshida, Kazuhiro Yokota, Yasuto Araki, Haruhiko Akiba, Kyoichi Nakajima, Kojiro Sato, Yu Asanuma, Yuji Akiyama, Toshihide Mimura

Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University

Background) The treatment for RA with chronic kidney disease (CKD) is not well established.

Method) Estimated GFR (eGFR) was calculated in patients who visited out outpatient clinic from Jan. 11th, 2005 until Sept. 30th, 2010. The treatment for RA with stage 3, 4 and 5 CKD were described.

Results) We classified 112 patients to stage3 CKD (S3:30≤eGFR<60), 16 patients to stage4 CKD (S4:15≤eGFR<30), and 13 patients to stage5 CKD (S5:eGFR<15). SASP was the most prescribed DMARD (S3:S4:S5=33:3:7), followed by MTX (S3:S4:S5=32:0:0). Etanercept was the most prescribed biologics (S3:S4:S5=13:3:2), followed by tocilizumab (S3:S4:S5=3:2:2). MTX, adalimumab and infliximab were not prescribed to patients with stage 4 and 5 CKD.

Conclusion) Characteristics of the treatment of RA with CKD was clarified.

P3-530

Steroid-induced myopathy of RA patient treated with low dose steroid.

Ryo Tanaka

Orthopaedic Surgery, Takayama Red Cross Hospital, Gifu, Japan

Objective: We experienced the steroid-induced myopathy of RA patient treated with low dose steroid. We report the clinical course of this case. Patient: The patient is 70 y.o. female who was treated with steroid (3 to 10 mg) against RA. In 2006, when she consulted our institution because of difficult to stand up, muscle weakness of lower extremities, especially proximal muscle, was present. Steroid-induced myopathy was diagnosed by the MRI, serological and histopathological findings. We started to decrease the steroid. Result: Etanercept was given to the patient, and we could control without steroid. She recovered her muscle power of lower extremities. Conclusion: When the muscle weakness is present during the RA treatment

of low dose steroid, there is the possibility of steroid-induced myopathy.

P3-531

A case report; a girl with multiple knuckle pads suspected arthritis

Suran Yang¹, Akiko Sasaki^{2,3}, Michiaki Takagi^{2,3}, Toshihiko Ogino³

¹Yoshioka Hospital, Yamagata, Japan, ²Yamagata saisei hospital, Yamagata, Japan, ³Yamagata University School of Medicine Department of Orthopaedic Surgery

An 11-year-old girl was aware of PIP joint swelling of six fingers, and presented to our hospital after one year. Hypertrophic sclerosis around joints was not associated with tenderness. CRP, rheumatoid factor and anti-CCP antibody were negative. X-ray image showed no marked bony change. Skin lesions were suspected and consultation to Dermatologist was done. The lesions were diagnosed as knuckle pads because of repetitive mechanical stimulation of her habit of knuckle cracking. Knuckle pad is flat nodule with keratosis. The lesions most commonly develop of PIP joint of finger and toe because of repetitive trauma. The differential diagnosis consists of keloids, calluses and warts. However, the case with multiple lesions is suspected of collagen diseases such as rheumatoid arthritis.

P3-532

A case of SSc-PM Overlap syndrome accompanied with myopathy by sarcoidosis

Mari Ushikubo, Hirotohi Matsumoto, Kazuhide Gomi, Taku Yabuki, Kumiko Akiya, Hisaji Ohshima

Department of Connective Tissue Diseases, Tokyo Medical Center, Tokyo, Japan

Case) A 47-yo woman admitted because of progressive muscle weakness. The skin in the body and face was sclerotic. Weakness in the proximal muscle was shown (MMT 3-4). The serum level of CK was high (6230). Positive tests of anti-nuclear antibody and anti-Ku antibody were detected. A CT scan revealed enlargement of lymph nodes in the body. Muscle biopsy of the rt-biceps showed infiltration of mononuclear cells in the interstitial area and epithelioid cell granuloma, which was seen in the lymph node and the bronchial wall. Corticosteroid (PSL 50mg/day) therapy was effective for the CK level and the muscle strength. Conclusion) The case was a very rare combination of sSSc-PM overlap syndrome and sarcoid myopathy, and helpful for studying pathogenesis of myopathy in autoimmune diseases.

P3-533

Two cases of muscle sarcoidosis

Yuko Toyoda¹, Jun Kishi¹, Katsuhiro Kinoshita¹, Seidai Sato¹, Toshifumi Teduka¹, Masami Kishi¹, Yasuhiko Nishioka¹, Kenji Tani², Saburo Sone¹

¹Department of Respiratory Medicine and Rheumatology, Tokushima University Hospital, Tokushima, Japan, ²Department of General Medicine, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima, Japan

Sarcoidosis is a multisystem granulomatous disorder. The incidence rate of muscle sarcoidosis was reported about 0.4% in systemic sarcoidosis. We experienced two cases of muscle sarcoidosis. Case 1: 58 year-old female. She initially felt muscle pain and then was attacked diplopia. She was introduced to our hospital and then examined by muscle MRI, muscle biopsy, and so on. She was diag-

nosed muscle,neuro,cardio and pulmonary sarcoidosis.

Case 2: 81 year-old female. She was diagnosed pulmonary sarcoidosis 8 years ago, and has been followed. 2 years ago, she had eye and skin sarcoidosis. A few months ago, she had felt stiffness of extremities, and her muscle biopsy revealed muscle sarcoidosis. Both of cases were improved by taking steroid.

P3-534

A case of Sarcoidosis diagnosed by sarcoid myopathy concomitant with Scleroderma

Kunihiro Ogane¹, Ichiro Mizushima¹, Takashi Kato¹, Mitsuhiro Kawano²

¹Division of Nephrology and Rheumatology, Department of Internal Medicine, Ishikawa Prefectural Central Hospital, ²Division of Rheumatology, Department of Internal Medicine, Kanazawa University Graduate School of Medicine

A 65-year-old man had Raynaud's phenomenon and swollen of fingers in December 2009. On the basis of sclerodactyly and positivity of Scl-70 antibodies, a diagnosis of Scleroderma (SSc) was made. Further, myopathy or myositis associated with SSc was considered, because myogenic enzymes elevated. The findings of muscle biopsy showed noncaseating granulomas with multinucleated giant cells. In Addition, serum ACE and lysozyme were elevated, a diagnosis of sarcoid myopathy was made. Serum Cr level gradually increased, renal biopsy demonstrated granulomatous interstitial nephritis. 40 mg/day of PSL resulted in improved the myopathy and nephritis. Sarcoid myopathy is a rare condition in SSc patients, but it should be considered when myogenic enzymes are elevated.

P3-535

Investigation of the actual medical condition in 31 patients with Polycondoritis

Hiroshi Oka¹, Yoshihisa Yamano¹, Kazuo Yudo¹, Jun Shimizu², Noboru Suzuki^{1,2}

¹Institute of Medical Science, St. Marianna University School of Medicine, ²Departments of Immunology and Medicine, St. Marianna University School of Medicine

(Purpose) To investigate the actual medical condition with Polycondoritis (RP) patients in Japan. (Methods) We examined number of medical consultation, monthly medical cost, and public support status by a questionnaire survey. RP patients group supported the survey. (Results) Thirty-one patients (7 male, 22 female) were enrolled in the study. The average age was 45.9 years old. The average number of medical consultants was 2.74. The average monthly medical cost was 16,774 yen per one outpatient. The cost of one inpatient was 200,702 yen. The public help was only 4 cases (12.9%) out of 31 patients. (Conclusion) RP patients consulted the plural number of medical doctors and had to pay plenty of medical cost. Especially inpatients with airway troubles had to pay over 200,000 yen monthly.

P3-536

The clinical analyze of polychondritis as symptomatic in autoimmune disease

Hirotoishi Matsumoto, Mari Ushikubo, Kazuhide Gomi, Taku Yabuki, Kumiko Akiya, Hisaji Ohshima
Department of Rheumatology, Tokyo Medical Center, Tokyo, Japan

Polychondritis is a rare clinical manifestation and seen in relapsing polychondritis (RPC). Since we experienced three cases who

presented polychondritis in autoimmune diseases as a symptom, clinical characteristics were analyzed. Result)1: Age of the diagnosis was an average of 62 years old. 2: Underlying diseases were RA, PN, and ITP. 3: While cartilage inflammation of the auricular was seen in all cases, that of the larynx/trachea and saddle nose was not accepted. Increases in the acute inflammatory responses were detected in all, and the myelodysplasia was seen in one case. 4: Although two cases have improved with steroids, a spontaneous remission was noted in one. Conclusion) Polychondritis was accepted as a part of symptoms in autoimmune diseases other than RPC.

P3-537

A case of relapsing polychondritis with airway lesion treated with ICS and LABA

Ryota Okazaki, Naoto Azuma, Aki Nishioka, Kazuyuki Fujita, Takuya Hino, Chieri Kanda, Mika Okabe, Mai Morimoto, Masahiro Sekiguchi, Masayasu Kitano, Naoaki Hashimoto, Hajime Sano
Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan

A 66-year-old woman was admitted to our hospital because of auricular chondritis, conjunctivitis, polyarthralgia, productive cough and dyspnea. RP was diagnosed according to Damiani's criteria. Pulmonary function test demonstrated an obstructive pattern, and flow-volume curve revealed a constrictive upper airway flow pattern. Chest CT showed a thickened tracheal wall and narrowing of the airway. After steroid therapy was started, her symptoms, pulmonary function, and CT findings ameliorated promptly. But FEV₁% was decreased as steroid tapering. Using inhaled steroid (ICS) and LABA was improved FEV₁% and enabled to taper off steroid. This case report suggests ICS and LABA might be effective in case of having difficulty of tapering systemic steroids in RP patients with airway lesion.

P3-538

Biologics in NinJa 2009

Toshihiro Matsui^{1,3}, Shigeto Tohma^{2,3}

¹Department of Rheumatology, Sagami National Hospital, National Hospital Organization, Kanagawa, Japan, ²Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagami National Hospital, National Hospital Organization, Kanagawa, Japan, ³iR-net

[Aim & Methods] Using data of NinJa 2009, we evaluated the use of biologics in patients with RA. [Results] Among 7085 patients, 1238 patients (17.5%) were under the treatment with biologics as follows; ETN 576 (46.5%), IFX 288 (23.3%), TCZ 202 (16.3%), ADA 144 (11.6%), and ABT 21 (1.7%). Mean value (remission rate) of DAS28-ESR/CDAI was 3.48 (26.2%)/9.22 (19.2%) in ETN, 3.29 (31.6%)/8.27 (24.8%) in IFX, 3.03 (42.9%)/10.38 (16.8%) in TCZ, and 3.79 (29.1%)/11.49 (17.4%) in ADA, respectively. Prevalence of combination therapy with biologics and other DMARDs were 69.8% in ETN, 99.6% in IFX, 38.1% in TCZ, and 75.7% in ADA. Disease activity was lower in biologics-mono therapy group than in combination group except TCZ user. Among over 80 year-old patients, 7.8% of patients were treated with biologics.

P3-539

The report of efficacy and safety of etanercept (ETN) in our hospital

Takumi Matsumoto¹, Takao Katsuragawa¹, Kiminori Hasegawa¹, Hidenori Nakai², Hiroaki Tamura¹

¹Kin-ikyo Chuo Hospital, Department of Rheumatology, Sapporo, Japan, ²Kin-ikyo Sapporo Hospital, Department of Rheumatology, Sapporo, Japan

<objective>We discussed about safety and efficacy of ETN administered to 67 patients in our hospital from June 2005 to March 2010. <patients and methods>The each number of males and females were 13 and 54, mean age was 59±13 y.o.. The each number of Steinblockers stage and class I,2,3,4 were 5,9,32,21, and 2,44,21,0, respectively. 37 cases used MTX (4.1±3.9mg per week). <results>Up to November the first, 2010, 30 cases discontinued ETN because of remission (1 case), 14 complications (4 pneumonia, 3 interstitial pneumonia, etc.), and switch to other biologic agents (13 tocilizumab and 1 infliximab). Persistency rate (12 and 36 mo.) were 84.4 and 72.7%. The number of remission by ETN based on the EULAR response criteria (6 mo. and 12 mo.), were 8 and 12, the number of good response were 19 and 16.

P3-540

Clinical evaluation in patients treated with etanercept (ETN) in our department

Toru Sasaki

Akita Rosai Hospital, Department of Internal Medicine, Odate, Japan

Objective Report on the clinical course of our RA pts treated w/ ETN. **Subjects** 12 pts on ETN since Aug. 2008 & continuing for over 3 mths (mean age & RA duration: 59.3 yo & 7.2 yrs); divided into 2 groups to study disease activity (DA) changes: early stage group (ES-g) (n=8) & advanced stage group (AS-g) (n=4), each w/ mean RA duration of 3 yrs & 18 yrs, respectively. **Results** DAS28-CRP in AS-g decreased from 6.19 to 4.74, while in ES-g it significantly decreased from 4.40 to 2.14, ie. remission level. Each mean treatment period was 15.5 mths and 12.1 mths. **Discussion** As in many clinical studies, ETN was more effective as RA stage was earlier. In 5 of our 6 pts starting ETN after 2009, RA duration was less than 3 yrs, showing the increase of ETN use in early RA pts in actual clinical practice.

P3-541

Investigation of actual conditions of RA patient who is undergoing HD

Nahoko Nishimura, Shogo Banno, Hirohisa Kawai, Shinkichi Suzuki, Yukihiro Kimura, Kunihiro Maeda, Mari Ogawa, Norihiro Suga, Harutaka Yamada, Masahiro Yamamura, Hirokazu Imai
Department of Nephrology and Rheumatology, Aichi Medical University, Aichi, Japan

MTX is contraindication on hemodialysis (HD), and the aggressive therapy by biologics is considered to be difficult because of the increased risk of infection. We found 24 (1.3%) patients with RA among 1780 undergoing HD, and investigated their clinical feature, the therapeutic effect and complication of ant-rheumatic drugs. Following RA, 16 patients failed to end-stage renal disease, and have maintained HD, mainly caused by unknown. Eight patients developed RA during HD. The administered drugs for RA were PSL (18 cases; mean dose 5mg/day), tacrolimus (2 cases), etanercept (4 cases) and tocilizumab (1 case). Etanercept and tacrolimus were effective without serious complication. The biologics is safety available with careful risk management even though undergoing HD.

P3-542

Exacerbation of interstitial lung disease in a RA patient treated with ETN

Aya Yamada, Tomoya Miyamura, Yoshiro Horai, Karin Shimada, Motoko Ishida, Soichiro Takahama, Rumi Minami, Masahiro Yamamoto, Eiichi Suematsu

Department of Internal Medicine and Rheumatology, Clinical Research Center, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan

We report a case of fatal exacerbation of interstitial lung disease induced by ETN in a RA patient. A 75 year-old male developed RA and interstitial lung disease (ILD) in 2008. ETN was started because of the refractoriness to oral disease-modifying anti-rheumatic drugs in February 2010. In May 2010, he developed cough and sputum, and a chest X-ray revealed diffuse ground-glass opacity in the middle to lower lung fields. Laboratory tests showed an elevated CRP level (8.79 mg/dL). Immunosuppressive therapy, combining intravenous cyclophosphamide pulse therapy with methylprednisolone was started. However, about 2 months later, he developed severe respiratory failure and died. We need to be aware of an acute exacerbation of ILD in RA patient treated with TNF- α blocking agents.

P3-543

Diagnose as tuberculous pleuritis during etanercept (ETN) therapy is difficult

Koji Tsuzaki, Yukio Tsugihashi, Ryuichi Sada, Teruhisa Azuma, Hiroyasu Ishimaru, Kazuhiro Hatta

Division of General Internal Medicine, Tenri Hospital, Nara, Japan

A 72-year-old man with rheumatoid arthritis (RA) has been treated with methotrexate and prednisolone since 2008, and with ETN since April in 2009. In August 2009, he had pleural effusion with lymphocyte counts of 93 percent of the white blood cells, and with ADA levels of 108.2 IU/l. Although tuberculin skin test was positive, both Quanti-Feron (QFT) in peripheral blood and IFN γ in pleural effusion were negative. Pleural effusion was thought to be caused by not tuberculosis but ETN. After withdraw of ETN, his pleural effusion decreased. Because his RA got worse, we started infliximab. After that, he developed fever, sputum, and dyspnea. In 2010, he was diagnosed as having a miliary tuberculosis. It is considered that QFT and IFN γ in pleural effusion was false negative during ETN therapy.

P3-544

A case of tuberculosis meningitis during etanercept therapy for RA

Junji Hayashi

Joint Reconstruction and Rheumatic Center, Niizashiki Central General Hospital, Saitama, Japan

We report a case of tuberculosis meningitis during etanercept therapy for rheumatoid arthritis. An 82 year-old woman treated with etanercept for 22 months showed incontinence, gait difficulty, and pyrexia. A lumbar puncture was highly suggestive of bacterial meningitis, but CSF culture produced no growth, and Ziehl-Neelsen stain was negative. She was treated with antibiotics, but showed acute deterioration of general condition, and died after 19 days. Mycobacterium tuberculosis was identified by 4 weeks culture, and diagnosed as tuberculosis meningitis. Only few patients with tuberculosis meningitis during etanercept therapy for rheumatoid arthritis

have been reported. Tuberculosis meningitis should be considered when the neurological signs are appeared during etanercept therapy.

P3-545

A case of RA complicated by myelitis in spinal cord during etanercept therapy

Naoki Shimmyo¹, Takashi Fujimoto², Yasuhiro Akai³

¹Department of Rheumatology, Kashiba Asahigaoka Hospital, Nara, Japan, ²Department of General Medicine, Nara Medical University, Nara, Japan, ³Department of Internal Medicine, Nara Medical University, Nara, Japan

A 60-year-old Japanese woman was diagnosed with RA in 2002. She received various DMARDs, but most of them were discontinued because of poor effectiveness. She was administered etanercept from September 2008. This resulted in rapid improvement of polyarthritis. However, five months after the initial administration of etanercept, she developed weakness of bilateral upper extremities and dysesthesias on bilateral upper extremities and upper chest lesion subacutely. MRI of her spinal cord revealed a high-intensity lesion on T2 weighted image from the first through to the third cervical levels. MRI findings suggested myelitis. High-dose corticosteroid therapy was conducted and effective for her. Among adverse events induced by TNF inhibitors, myelitis is considered to be very rare.

P3-546

Tuberculous peritonitis during etanercept therapy for rheumatoid arthritis

Naoto Azuma¹, Mai Morimoto¹, Takanori Kuroiwa^{1,4}, Kazuyuki Fujita¹, Takuya Hino¹, Mika Okabe¹, Aki Nishioka¹, Ryota Okazaki¹, Masahiro Sekiguchi¹, Masayasu Kitano¹, Naoaki Hashimoto¹, Hajime Sano¹

¹Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, ²Department of Respiratory Medicine, Tanimukai Hospital, ³Center for Infectious Diseases, Osaka City General Hospital, ⁴Department of Internal Medicine, Yukioka Hospital

In August 2010, a 73-year-old woman with rheumatoid arthritis receiving etanercept (ETN) therapy for two years, developed high-fever and abdominal fullness. Though she was not exposed to tuberculosis, isoniazid prophylaxis was administrated for 18 months until August 2008. Antibiotics was not effective. CT image revealed the massive ascites and peritonitis, and Ga scintigraphy demonstrated notable uptake in the peritoneum. Ascites analysis showed an elevated ADA value (105 IU/l). Moreover, PCR and culture for *Mycobacterium tuberculosis* were positive. After initiating anti-tuberculosis therapy, her condition ameliorated and ascites rapidly regressed. Although the tuberculous peritonitis during ETN therapy is rare, this report emphasizes the importance of initial suspicion of tuberculosis.

P3-547

A case of autoimmune hepatitis induced by etanercept

Maki Nishimura, Shinsuke Yamada, Hitoshi Goto, Keiji Okamoto, Koichiro Yoda, Yasuo Imanishi, Masaaki Inaba
Rheumatology, Osaka City University Graduate School of Medicine, Osaka, Japan

24 yo. female RA patient was treated with MTX (8mg/week) unsuccessfully, so Etanercept (ETN) started in Mar., 2008. ETN was effective and induced clinical remission status. However, transaminase test extremely increased in June, 2009. Virus examination

showed negative. all drugs were stopped, but transaminase was not improved. Antinuclear antibody was positive. Liver biopsy was performed, resulting acute exacerbation of chronic hepatitis. According to Simplified Scoring system, we diagnosed autoimmune hepatitis. PSL (40mg/day) was started and was effective. AIH appeared in spite of well controlled of RA, and ETN induced lupus was reported, so it was suspected that ETN was concerned in AIH. AIH should be considered if transaminase increase during treatment of ETN.

P3-548

Aplastic anemia in a rheumatoid arthritis patient after the start of etanercept

Yoshiro Horai, Tomoya Miyamura, Karin Shimada, Motoko Ishida, Soichiro Takahama, Rumi Minami, Masahiro Yamamoto, Eiichi Suematsu

Department of Internal Medicine and Rheumatology, Clinical Research Center, National Hospital Organization Kyushu Medical Center

A 73-year-old female, diagnosed with rheumatoid arthritis (RA) complicated with severe levels of joint destruction, started etanercept (ETN) because of high persistent RA disease activity. Although her articular symptoms dramatically improved, she developed marked pancytopenia after the introduction of ETN. Bone marrow aspirate specimen revealed hypocellular marrow in three hematopoietic series without atypical findings, which was compatible with aplastic anemia (AA). This is a rare case of severe pancytopenia due to AA presumably induced by ETN.

P3-549

An autopsy case of antiphospholipid syndrome complicated by cerebral infarction

Atsushi Noguchi¹, Junya Yamamoto¹, Riki Satoh¹, Satoru Kunisaki¹, Satoshi Jodo¹, Atsushi Fujisaku¹

¹Department of Internal Medicine, Tomakomai City Hospital, Tomakomai, Japan, ²Department of Pathology, Hokkaido University Graduate School of Medicine

A 42-year-old man developed cerebral infarction. Positivity of lupus anticoagulant and anti- β_2 GPI antibody indicated a diagnosis of APS, and anticoagulation and antiplatelet therapy were introduced. Subsequently, progressive decrease in platelet count occurred, and he was treated with high dose prednisolone as the diagnosis of ITP, resulting in clinical remission. However, during the uneventful course, he suddenly exhibited intracerebral bleeding, coma, cardio-respiratory arrest, and died. Autopsy revealed cerebral hemorrhagic infarction without other obvious organ damage. The present case suggested the difficulty of differential diagnosis of APS and catastrophic APS in view of the clinical findings. We discuss the differences between both diseases with review of the literature.

P3-550

A case of catastrophic APS successfully treated with aggressive treatment

Masako Utsunomiya¹, Hideto Oshikawa¹, Kazuki Yoshida¹, Tatsuo Kobayashi¹, Makiko Yamamoto², Mitsumasa Kishimoto², Kazuo Matsui¹

¹Kameda Medical Center, ²St. Luke's International Hospital

A 49-year-old woman developed dark color change in bilateral fifth digits 2 weeks prior to admission followed by acute congestive heart failure and renal failure. She had malar rash, digital ischemia,

livedo racemosa in her legs and weakness in her left leg. She also had thrombocytopenia, positive troponin T, proteinuria and hematuria. On brain MRI, there were multiple high intensity areas. We strongly suspected catastrophic antiphospholipid syndrome (CAPS), so started methylprednisolone pulse therapy and plasma exchange. Later we found low complement, positive antinucleolar antibody and positive lupus anticoagulant, so added IV cyclophosphamide and she attained remission. Because CAPS is a life-threatening disease, if suspected, aggressive treatment is required without delay.

P3-551

A case of antiphospholipid antibody syndrome with bilateral adrenal infarction

Takayasu Suzuka, Kenichiro Hata, Daisuke Wakura, Kentaro Isoda, Takuro Ozaki, Tohru Takeuchi, Shigeki Makino, Toshiaki Hanafusa
Osaka Medical College

A 44-year-old woman had felt paresthesia in her left leg from October 2008. She was admitted into our hospital, because her paresthesia had become worse gradually. The histological specimen of the sural nerve showed angitis. ANA, anti-ds-DNA antibody and antiphospholipid antibody (aPL) was positive. Chest CT showed thymoma, and thymectomy was performed in June 2009. She was hospitalized on September because of general fatigue, nausea and abdominal pain for 2 weeks. Abdominal CT scan and MRI showed bilateral adrenal swelling and thrombus in adrenal vein. She was diagnosed as adrenal infarction caused by antiphospholipid antibody syndrome (APS) with SLE. Serum cortisol level was low, and rapid ACTH test was no response. This is a rare case of APS with hypoadrenalism.

P3-552

Catastrophic antiphospholipid syndrome treated with early intensive intervention

Kiyofumi Hagiwara, Hiromitsu Asashima, Ryo Rokutanda, Shinichiro Nakachi, Yoshimi Matsuo, Shoko Kobayashi, Osamu Akiyama, Shigeko Inokuma

Department of Allergy and Rheumatology, Japanese Red Cross Medical Center

We report a case of catastrophic antiphospholipid syndrome manifested as recurrent central nervous system symptoms, renal dysfunction, and thrombocytopenia that was successfully managed with the combination of steroid pulse therapy, plasma exchange therapy and anticoagulation therapy.

P3-553

A case of diffuse large B cell lymphoma with antiphospholipid syndrome

Yoshihiko Raita

Okinawa Miyako Hospital

68y.o female was admitted to our hospital with complaining of fever and right hip pain. On arrival she was shock state and large hematoma was found around her right femoral bone on CT scan. Laboratory test revealed low platelet count and prominent APTT prolongation which was not corrected by 1:1 mixed test. Serum antibody was positive for anticardiolipin IgG, β 2GP1, and lupus anticoagulant. She was treated by steroid-pulse and plasma exchanges. After starting treatment, ALP elevation was found and diffuse low density area was noted on her liver by abdominal sonography. Liver biopsy showed abnormal lymphocytes which was CD20 positive, made a di-

agnosis of liver origin diffuse large B cell lymphoma.

We report a case of diffuse large B cell lymphoma complicating with antiphospholipid syndrome.

P3-554

Assessment of Synovitis in RA Patients With DMARDs-induced Clinical Remission

Kazushige Seki

Tushimi Hospital

Methods: We studied 12 RA patients receiving disease-modifying antirheumatic drug therapy who were judged to be in remission (DAS28-CRP < 2.3). Imaging of hands and wrists using standardized scoring techniques (grade 0-3) with Power Doppler ultrasonography (PD-US). result: Despite their being in clinical remission, 8 patients (67%) continued to evidence of active inflammation, as shown by PD-US. In symptomatic joint, PD-US showed that 72% had synovitis. Even in asymptomatic joint, PD-US showed that 4% had synovitis. Conclusion: most RA patients receiving disease-modifying antirheumatic drug therapy who satisfied the remission criteria had imaging-detected synovitis.

P3-555

Diagnosis of Early Rheumatoid Arthritis by Ultrasonography

Kaoru Takase, Kouji Kobayashi, Kayo Terauchi, Toshiyuki Watanabe, Reikou Watanabe, Sei Samukawa, Maasa Hama, Ryusuke Yoshimi, Hiroshi Kobayashi, Atsushi Ihata, Atsuhisa Ueda, Mitsuhiro Takeno, Yoshiaki Ishigatsubo

Yokohama City University Graduate School of Medicine, Department of Internal Medicine and Clinical Immunology, Yokohama, Japan

We divided 12 patients with undifferentiated arthritis (female 8 cases, 55.6 y.o.) into 6 patients who the new ACR/EULAR classification criteria for rheumatoid arthritis (RA group) and the others (non-RA group). Bilateral MCP, PIP, wrists, knee, and MTP were examined by ultrasonography (US) in which synovitis was graded with 0-3 gray scale (GS) and power Doppler (PD).

Mean GS in all examined joints was significantly higher in the RA group than non-RA group (1.3 vs 0.7, $P < 0.05$), whereas no difference was found in PD (0.3 vs 0.1, ns). The same comparative study based on the 1987 ACR criteria did not show any difference.

Our data showed that increased GS of US is supportive of early RA.

P3-556

Ultrasonographic assessment is useful to find patients with RA in "Ningen Dock"

Junichi Kaburaki, Yoshihiko Takeda

Shinakasaka clinic

Clinical significance of ultrasonographic assessment for joints was investigated in "Ningen Dock". The subjects consisted of 7 patients with stiffness and positive reaction of serum rheumatoid factor. Three patients satisfied the newly proposed ACR/EULAR criteria out of 4 patients with anti-CCP antibody. Two of them were diagnosed as having RA. Ultrasonographic assessment could distinguish these two RA patients from another 1 patient with Sjogren's syndrome. These data suggested that ultrasonographic assessment is useful to find patients with RA in "Ningen Dock".

P3-557

Real-time Three-dimensional (3D) Ultrasonography in Rheumatoid Arthritis

Kazuhide Tanimura, Akihiro Narita, Yuko Aoki, Akemi Kitano, Fumihiko Sakamoto, Mihoko Henmi, Takeya Ito, Akio Mitsuzaki, Masato Isobe, Jun Fukae, Megumi Matsuhashi, Masato Shimizu
Hokkaido Medical Center for Rheumatic Diseases, Sapporo, Hokkaido, Japan

【Introduction】 US is an imaging modality used to detect synovial hypertrophy, erosions, and synovial fluids by GS and to quantitatively grade vascularity by PD signal. Longitudinal US examination is feasible assessment, which facilitates improved evaluation of disease activity and thus treatment effects with DAS28. **【Methods】** Conventional and real-time 3D US were performed in RA patients with erosions. In addition, X-ray, CT and MRI, were performed to compare detection of erosions and imaging among those different modalities. **【Results】** With real-time 3D US, intraarticular vascular flow could be observed with confirmed extensity. Moreover it produced vascular signals more clearly. Differences were observed between US and other techniques in sensitivity for detecting erosion.

P3-558

Evaluation of the activity of rheumatoid arthritis (RA) with musculoskeletal ultrasound (MSUS).

Kazuki Someya, Kazuyoshi Saito, Kunihiro Yamaoka, Shintaro Hirata, Shizuyo Tsujimura, Masao Nawata, Naoki Yunoue, Takayuki Katsuyama, Eri Hirakawa, Maiko Yoshikawa, Yoshiya Tanaka

The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan.

We examined bilateral carpal joints and 20 finger joints with MSUS semi-quantitative 8 grade scale (FS) and the number of flow-positive joint count (JC) in 50 RA patients. We evaluated the correlation between the FS / JC and Disease activity score 28 (DAS28). The average age is 61.0 years old, duration is 80 months and DAS28 (ESR) is 5.60. FS and JC correlated with DAS28 (ESR), but the result suggested we should evaluate large joints such as elbow, shoulder and knee. On the other hand, we detected some active synovitis which had no tenderness and swelling in 7 patients (5 moderate and 2 low disease activity patients). Recently, it is shown that RA patients who had achieved clinical remission had some active synovitis. And it may bring the destruction of the joints. We showed the utility of MUSU in RA patients with clinical remission or low disease activity.

P3-559

Power Doppler US on RA patients with clinical remission by biologics

Tomoyuki Asano, Masayuki Miyata
Fukushima Redcross Hospital

We performed Power Doppler ultrasonography on RA patients given biologics with clinical remission (DAS28<2.6), to evaluate whether they have inflammation. And we compared echo findings between three different biologics. **Methods**) We performed Power Doppler ultrasonography of 16 joints (MCP1-3, PIP2-3, Rad, Cen, Uln) of RA patients with clinical remission administered three biologics, which are tocilizumab (n=11), adalimumab (n=3) and infliximab (n=3). And Doppler was calculated as total signal points(%) with use of Tanimura's box method. **Results**) Mean of DAS28 of

each biologics was 1.45, 2.04 and 2.12. And mean of total signal points was 55.6%, 18.9% and 20.0%. **Conclusion**) Doppler remained both of three biologics, but of tocilizumab, stronger Doppler was shown than two other biologics.

P3-560

Usefulness of joint ultrasonography in RA patients on etanercept (ETA) treatment

Kazutoshi Aoki, Kentaro Chino
Saitama Social Insurance Hospital, Saitama, Japan

Objective Etanercept (ETA) has high dose-interval flexibility but DAS28 may be insufficient as the indicator for dose reduction/discontinuation. We examined whether joint ultrasonography (US) can accurately measure DA of pts on ETA. **Methods** Our 33 ETA-treated RA out-pts (5 men, 28 women); mean age 56.4 ± 15.3 yo; DAS28 & HAQ + US synovial hypertrophy (SH) & power Doppler (PD) blood flow signal were assessed by quantal scores (0-3). **Results** DAS28-remission pts w/ mean total SH 4.0 ± 3.8 & total PD score 3.9 ± 4.8 ; some correlated w/ DAS28. Non-remission pts w/ 8.0 ± 6.8 & 8.8 ± 5.6 , respectively; some had low scores w/ high HAQ. **Conclusion** US showed findings even in DAS28-remission pts and low SH/PD scores in some non-remission pts considered as providing more accurate local inflammatory data.

P3-561

Evaluation of discrepancy between DAS28 and power Doppler echoic assessment .

Masato Shimizu, Megumi Matsuhashi, Jun Fukae, Akio Mitsuzaki, Masato Isobe, Takeya Ito, Akihiro Narita, Yuko Aoki, Akemi Kitano, Mihoko Henmi, Fumihiko Sakamoto, Kazuhide Tanimura
Hokkaido Medical Center for Rheumatic diseases, Sapporo, Japan

We treated 72 cases of tocilizumab (66 women, six men) on the echo findings were compared DAS28. Target: Age 40-76 60% , stage III is mostly. Disease duration 6-10 years 36% of early cases of 10% 2 years after onset, 4% of the cases over 20 years. 39% cases have not been previously administered biologics. **Results:** DAS28 less than 2.6 of 53 %cases of patients with less than 3.2 was 78.7%, and total vascularity (TV) 0 percent and was 55%. DAS28 is 2.6% less than that of 22% patients showed a worsening of the TV. Group of more than 2.6 33% cases showed improvement. **Conclusion:** The efficacy of tocilizumab can not be determined only by clinical evaluation, echo image evaluation by the joint inflammation is necessary.

P3-562

Evaluation of cervical spine in patients with rheumatoid arthritis

Kensuke Kume, Kanzo Amano, Susumu Yamada
Department of Rheumatology, Hiroshima Clinic, Hiroshima, Japan

Purpose and methods) 48 patients with cervical symptoms in patients with rheumatoid arthritis, we compared that ultrasound findings with dynamic Xp in the atlantoaxial joint of cervical spine in RA. **Results**) BM in 41 cases showed some findings. But PD images, only 13 cases showed findings. The relation between atlantoaxial subluxation in Xp and BM findings were no correlation ($p=0.64$) **Conclusions**) In some case, it is hard to recognize atlantoaxial joint, but careful operation atlantoaxial well above the state can grasp.

P3-563

Proper machine setting for finger joint ultrasonography

Fumihiko Sakamoto, Akihiro Narita, Mihoko Henmi, Akemi Kitano, Yuko Aoki, Takeya Ito, Akio Mitsuzaki, Masato Isobe, Jun Fukae, Megumi Matsuhashi, Masato Shimizu, Kazuhide Tanimura
Hokkaido Medical Center for Rheumatic Diseases

Background: Joint ultrasonography (US) is useful tool for assessing rheumatoid arthritis, however, inter-machine difference is critical issue. We studied several US machines and investigated proper settings for each machine. Methods: The US machines (Hitachi EUB-7500, Aloka 7, Toshiba Xario, GE LOGIQ P6) were used. Same MCP and PIP joints were examined by gray-scale mode (GSUS) and power Doppler mode (PDUS). In the GSUS, settings were examined to visualize bone cortex and flexor muscle tendon clearly. In the PDUS, settings were examined to visualize vascular flow as standard image. Results: Proper settings were established. Discussion: It was rare opportunity that several US machines to be studied simultaneously. Similar images were obtained by each machine.

P3-564

The efficacy of effusion of knee orthosis from measuring using ultrasonograph

Yoshitaka Toda¹, Motohiko Sato²

¹Toda Orthopedic Rheumatology Clinic, ²Department of Orthopaedic Surgery, Soryukai Inoue Hospital

The 31 patient with osteoarthritis (OA) of the knee who showed effusion were measured area of effusion by ultrasonography (US), removed fluid and delivered corticosteroid. Then, the patients were prospectively randomized and treated with a strapped type knee belt (the belt group, n=10), stocking type knee sleeve (the stocking group, n=10) and no orthosis (the control group, n=11). After one week, the area of effusion was significantly decreased in the belt group than in the control group (p=0.005). The significant difference was not found between the stocking and control groups. The strapped type knee belt more improved proprioceptive deficit of knee OA than stocking type knee sleeve. We concluded the knee belt is useful to decrease effusion area after aspiration.

P3-565

Usefulness for diagnosis by ultrasonography in trigger wrist complicated with RA

Kenji Onuma¹, Mamoru Fujita^{1,2}, Naonobu Takahira³

¹Department of Orthopaedic Surgery, Kitasato University School of Medicine, ²Department of Orthopaedic Surgery, Toyohashi Municipal Hospital, ³Kitasato University, School of Allied Health Sciences, ⁴Department of Orthopaedic Surgery, Kyushu University

Case 1: Seventy-one-year-old female complained numbness of left hand and trigger phenomenon of ring finger. Although she was injected corticosteroid in A1 pulley by an orthopaedic doctor before visiting our hospital, trigger phenomenon was not relieved. The mass lesion moving into and out of carpal tunnel was observed by ultrasonography (US) in dynamic state of fingers. Case 2: Thirty-two-year-old female complained numbness of left hand and disturbance of finger motility. When finger flexion, flexor tendon catching in distal end of carpal tunnel was observed by US at a time she fell click. Both patients had immediate relief following carpal tunnel re-

lease and tenosynovectomy. Conclusion: US which could visualize dynamic state was useful for preoperative diagnosis in trigger wrist.

P3-566

T2 relaxation time mapping of articular cartilage of rheumatoid wrists

Atsushi Kitagawa, Tetsuhiro Iguchi, Tomoko Nakamura
Hyogo Rehabilitation Center Central Hospital, Hyogo, Japan

Objective: To evaluate the feasibility of MR imaging-derived T2 relaxation times of articular cartilage in radiocarpal joints in rheumatoid and healthy subjects. Methods: Quantitative T2 relaxation time mapping was performed using a microimaging gradient coils for 24 rheumatoid (mean age: 63.5 years) and 8 healthy (mean age: 36.5 years) subjects. Results: Rheumatoid subjects exhibited mean T2 values of 39.9±6.8 msec, while healthy subjects showed 33.9±1.5 msec (P=0.021). Subjects with findings of the bone erosion or edema exhibited higher T2 values than subjects with no these findings, however no statistically significant differences. Conclusion: These results demonstrate the feasibility of T2 maps and the possibility of detection of early change of cartilage structures.

P3-567

Rheumatoid factor as a biomarker of response to treatment for RA

Takayoshi Owada, Kazuhiro Kurasawa, Junya Nagasawa, Ryutaro Yamazaki, Satoko Arai, Reika Maezawa, Takeshi Fukuda
Department of Pulmonary Medicine and Clinical Immunology, Dokkyo Medicinal University, Tochigi, Japan

Purpose: To clarify whether serum rheumatoid factor (RF) is a biomarker of response to treatment in patients with rheumatoid arthritis (RA).

Subject: RF-positive RA patients at onset, in whom serum RF was periodically examined before and after treatment.

Results: Serum levels of RF were reduced to normal range (<20 IU/ml) after treatment in 19.4% of RF-positive RA patients at onset. RF-negative RA patients after treatments had received more aggressive intervention with disease modifying agents as combination therapy with methotrexate and anti-tumor necrosis factor-alpha inhibitor, and had lower erythrocyte sedimentation rates, compared with RF-positive patients after treatments.

Conclusion: It is possible that serum RF is a biomarker of response to treatment for RA.

P3-568

Analysis of factors affecting HAQ in Bio-untreated advanced-stage RA patients

Ko Katayama

Katayama Orthopedic Rheumatology Clinic

<Objectives:> An analysis of factors affecting HAQ score was performed for Bio-untreated advanced-stage RA patients. <Subjects and Methods:> One-hundred and two patients with RA were divided into three groups: a low HAQ group (0.5 ≤ mHAQ, mean 0.16, n = 39), a medium HAQ group (1 ≤ mHAQ < 0.5, mean 0.81, n = 27), and a high HAQ group (mHAQ ≥ 1, mean 1.66, n = 36). <Results:> In the low, middle, and high HAQ groups, mean DAS28 was 4.64, 5.19, and 6.16, mean modified Larsen score for small joints was 1.55, 1.77, and 1.81, and the mean number of affected medium-sized and large joints was 3.2, 4.7, and 6.6, respectively. <conclusion> Factors affecting mHAQ in advanced-stage RA were dura-

tion, disease activity, Larsen score, number of affected medium-sized and large joints, Ochi's classification.

P3-569

Discrepancy between inflammatory reaction and radiological findings in RA

Akira Katagiri¹, Toshiyuki Kaneko¹, Takuya Nemoto¹, Masato Yamada¹, Noboru Iida¹, Yoshinari Takasaki¹

¹Department of Internal Medicine and Rheumatology, Juntendo University Shizuoka Hospital, ²Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine

【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 classification passage and the examination value was evaluated about 170 cases. **【Results】** Ten cases that progress the bone lesion in spite of serological remission was existed, however MMP-3 value was not high, and titer of anti CCP antibody was not recognized significant difference. The pattern that inflammatory reaction was positive in spite of radiological remissions during all observation term were 8 cases, however the average of MMP-3 value was 257.0. **【Discussion】** We consider that it is necessary of regulatory image evaluation.

Sponsored Symposium

SS1-1

The Place of Opioids in RA Therapy

Hiraku Kikuchi

Department of Orthopaedics Surgery, Sakai Hospital Faculty of Kinki University School of Medicine

Pain is the greatest defense mechanism but the worst symptom. Both nociceptive pain, which is physiological, neuropathic, and pathological, may occur when the inflammatory pain of RA persists, and treatment with anti-RA drugs, biological preparations, etc., designed to achieve an early remission is important in order to break the vicious of chronicity. However, chronic pain patients currently account for 13.4% of the entire population, and it has been reported that 34% of RA is plagued by chronic pain. The usual choices of analgesics are : (1) NSAIDs, (2) acetaminophen, (3) opioid, (4) other analgesics. According to OARS guidelines the safety odds ratio for gastrointestinal adverse events is 5.36 with NSAIDs for internal use and 1.45 for external use, with COX-2 inhibitors drops to 0.55, but the odds ratio for cardiovascular/renal adverse events with COX-2 inhibitor is 1.19, and the odds ratio for any kind of adverse event with opioids is 1.4, and 3.6 for constipation. The risk of complications is even higher in the elderly and patients concomitantly treated with a steroid. Accurate diagnosis and specialized counseling are important to the treatment of chronic pain in RA, and (1) Neurotrophin injection, (2) anti-RA drugs, (3) anticonvulsants, (4) opioids are considered as drugs therapies, (5) psychotropic drugs and antidepressants (6) psychotherapy are cited for the psychogenic pain component. Opioid drugs are used in the treatment of approximately 30% of chronic pain patients in other countries, whereas treatment with opioids has just begun in Japan, and it will be necessary to deepen the discussion on their proper use. When it comes to considering the proper place of opioids in RA therapy at this symposium, we survey the actual circumstances of the use of acetaminophen, codeine phosphate, fentanyl patches, etc., in the treatment RA chronic pain patients in our clinic, and conduct a clinical evaluation (XP and bone and joint markers).

SS1-2

Opioid treatment for the locomotive syndrome

Kenji Miki^{1,2,3}

¹Dept. of Orthopaedic Surgery, Amagasaki Central Hospital, ²Center for Pain Management, Osaka University Hospital, ³Dept. of Rheumatology, Yukioka Hospital

1. The importance of musculoskeletal pain. The Japanese Orthopaedic Association's focus on "locomotive syndrome" has been enlightening. Locomotive syndrome is a condition that develops due to various musculoskeletal disorders. Nearly 80% of patients with musculoskeletal disorders have pain and frequently seek medical attention for pain management. The National Livelihood Survey in 2007 found that one of the top five symptoms of musculoskeletal disorders is pain (back pain, stiff neck, pain in the joints of the hands and feet) that affects more than twenty million elderly Japanese patients. Musculoskeletal disorders can result from either a musculoskeletal disease itself or age-related musculoskeletal dysfunction. Proper treatment of musculoskeletal pain is critical to reduce pain-related morbidity and mortality, restore the ability to perform activities of daily living, reduce caregiver burden and improve overall quality of life. 2. Opioid use and chronic musculoskeletal pain. Chronic musculoskeletal pain is usually treated with anti-inflammatory drugs. Recently, opioid drugs have been approved in Japan to treat non-cancer chronic pain. The mechanism of action of

opioids is due to binding with μ opioid receptors to induce their potent analgesic effects. These drugs have several significant side effects, including the potential for abuse and addiction; however, when used to treat pain, the risk of addiction and abuse is relatively small. Since being approved, physicians prescribing opioids to treat musculoskeletal pain has increased. I would like to explain the use of opioids to treat musculoskeletal pain and present some tips to properly select cases and avoid side effects. 3. The expected future of painkillers. Chronic musculoskeletal pain results from many complex factors and its management is difficult. Currently, new agents are being developed to treat chronic pain, which will improve the management of patients with chronic musculoskeletal pain. However, until those drugs are available, the use of opioids to treat chronic musculoskeletal pain is an efficacious option.

SS1-3

Current Status and Issues of Chronic Pain in Japan

Mikio Fukui, Narihito Iwashita

Pain Management Clinic, Department of Anesthesiology, Shiga University of Medical Science

In the West, "Pain" has been recognized as the fifth vital sign to improve the quality of life. Many epidemiological large-scale surveys related to chronic pain were conducted. After The Decade Of Pain Control And Research which started in January 2001 in USA, chronic pain measures have been done as a national policy. In "Pain in Japan 2010" performed in this country in 2010, the prevalence of chronic pain in Japan is about 22.5% over 20 years among the entire Japanese adult population. The total of 23150 thousand of Japanese adult people was estimated to suffer from chronic pain. Among them, 70% of patients is not found to be properly controlled and 34.5% is estimated to interfere with daily activities due to the chronic pain. In patients with chronic pain such as fibromyalgia which has not been clearly elucidated the cause, also a large effect on the brain, has been suggested by various brain imaging techniques. The Ministry of Health in Japan, in 2009, "Study Group on Chronic Pain" was formed. "Measures of chronic pain in the future", was proposed in September 2010 from the Ministry of Health. Efforts to take appropriate measures for chronic pain began as a society in Japan. A chronic pain is no longer a physical problem, and a psychiatric factor and psychological factor and a social factor. Therefore, in a pain practice, it is necessary to interdisciplinary approach often beyond the framework of the specialty. Performing the epidemiologic survey of a chronic pain, the establishment of the Japanese pain assessment tools for chronic pain, the pathogenesis elucidation of chronic pain, an establishment of an education system, promote public awareness activities, the create of the treatment guidelines, and a multidisciplinary/interdisciplinary approach establishment to build a medical care system for the treatment of chronic pain is necessary. These studies should be preferably supported by a governmental organization and a pain-related scientific society of Japan

SS2-1

Pathological roles of T cells in rheumatoid arthritis and abatacept

Kazuhiko Yamamoto

Department of Allergy and Rheumatology, The University of Tokyo Graduate School of Medicine

Rheumatoid arthritis (RA) is a chronic inflammatory disorder. Autoimmune responses are believed to play important roles. Concentrating on specific elements of the abnormal immune response, several lines of evidence suggest the important roles of T cells in the

pathogenesis of RA. Genetic information is one of them. HLA-DR that presents an antigen to T cells was reported to be the strongest genetic factor, but other genes should also play important roles. Protein tyrosine phosphatase, non-receptor type 22 (PTPN22), cytotoxic T lymphocyte antigen 4 (CTLA4) and CCR6 are well known RA-associated genetic factors. On the other hand, biological treatments that act via tumour necrosis factor (TNF)-alpha blockade, have been effective in RA, indicating cytokines might be the main controlling element in RA. However, activated T cells predominate in the disease processes of RA and the same clones were found to exist in different joints of a patient. Therefore, one rational approach to therapy is to modulate or target T cells. In this regard, several clinical trials have been performed to prove the effectiveness of anti-CD4 on RA. However, no clear positive data was obtained until recently, suggesting T cells might not be the main target of the treatment of established RA. In this respect, abatacept is a first-in-class agent that targets T-cell modulation via the co-stimulatory CD80/CD86:CD28 pathway. Preclinical studies and clinical trials have demonstrated both the rationale and efficacy of abatacept. Abatacept is currently approved for the treatment of RA. In this talk, abatacept will be highlighted as an important insight of the pathogenesis of RA and also important treatment option in the therapeutic repertoire for RA.

SS2-2

Latest Findings on Abatacept Data from Clinical Studies in Japan and Overseas

Tsutomu Takeuchi

Division of Rheumatology, Department of Internal Medicine, School of Medicine, Keio University, Tokyo, Japan

The pathology of rheumatoid arthritis (RA) has not been fully clarified. The disease is characterized by abnormal immune response to some self-antigens and by persistent inflammation. Activated T cells activate other immune cells, including B-cells and macrophages, promote the production of inflammatory cytokines such as TNF- α , IL-1, and IL-6, and develop inflammation and tissue destruction. In consideration of these pathological conditions, drugs that inhibit inflammatory cytokines, such as TNF and IL-6, have been developed. Being completely different from these established approaches, abatacept inhibits the activation of T cells, which is a more upstream event. As a drug that aims to normalize the abnormal immune responses, abatacept is expected to exhibit a clinical benefit which differs from that of cytokine inhibitors. In the ATTAIN Study, the efficacy of abatacept was investigated in patients with RA who were resistant to TNF inhibitors. In this study, response rates of ACR 20, 50, and 70 in the abatacept + DMARD group were 50.4%, 20.3%, and 10.2%, respectively, being significantly higher than those in the placebo + DMARD group. As a drug that acts on T cells located in the upstream of inflammation, abatacept is expected to be particularly effective for treatment of early RA. In the AGREE Study, the efficacy of abatacept + MTX was investigated in patients with early RA that had developed within the previous 2 years who had not undergone previous treatment with MTX. After 1 year of administration, 46.1% of the patients treated with abatacept + MTX achieved remission (DAS28-CRP < 2.6), 61.2% of patients showed no progression of joint destruction, and 49.1% of patients showed normalization of HAQ (HAQ score \leq 0.5). In this symposium, I will introduce the latest findings on abatacept obtained from these overseas data, together with Japanese clinical study results.

SS2-3

The Abatacept in Japan -From the points of survivability and safety-

Naoki Ishiguro

Department of Orthopedic Surgery Nagoya University, School of Medicine

While biological medicines, with their excellent efficacy, have revolutionized the treatment of rheumatoid arthritis (RA), discontinuation of treatment with these drugs due to secondary failure and adverse drug reactions has posed a significant problem in clinical practice. In our investigation of treatment persistence rates with the first biological medicine that we administered, the median persistence time did not exceed 5 years. The major reasons for discontinuation of treatment are secondary failure and adverse drug reactions. Treatment persistence rate can be regarded as the integral value of efficacy and safety. Given this background, it is natural to hope for better results from biological medicines that have different mechanisms of action. Differing from established cytokine inhibitors, abatacept has a unique mechanism of action that selectively inhibits T cell activation. Its usefulness has been investigated in a great number of clinical studies, mainly conducted overseas, in patients with various disease types, from early RA to TNF-inhibitor refractory RA. In the placebo-control ATTEST study on efficacy of abatacept and infliximab in patients with MTX-refractory RA, infliximab exhibited efficacy at the early stage but caused secondary failure in some patients after 1 year. Meanwhile, high ACR response rates were maintained over 1 year in patients treated with abatacept, suggesting the drug's superior ability to maintain effect over the long term. This characteristic was also demonstrated in the results of the AIM study on efficacy of abatacept in long-term administration in MTX-refractory RA, which showed that the drug's efficacy was maintained for 5 years and that more than 60% of the patients continued to receive the same treatment. In this symposium, together with Japanese clinical study results, I will present treatment persistence, safety, and the prolonged effect of abatacept and discuss its position in RA treatment.

SS2-4

Positioning in the RA Treatment of Abatacept - early RA-

Yutaka Kawahito

Kyoto Prefectural University of Medicine

The goal of the current rheumatoid arthritis (RA) treatment is clinical remission, and the definition of remission standard that is severer than a conventional standard was announced by ACR/EULAR in ACR2010, but this is not a drug free remission standard. At present, the rate of drug free remission by TNF inhibitors is not so high. So the continued remission is a substantial goal worldwide. The tight control including biologics at the early stage of RA is the common treatment strategy to achieve the continued remission. Abatacept is a selective co-stimulation modulator that inhibits T-cell activation by binding to CD80/86, and modulating its interaction with CD28 which is a co-stimulatory signal necessary for the full activation of T cells. The use of abatacept at early stage of RA has a possibility to cause immunological remission. In ADJUST trial, abatacept delayed progression of undifferentiated arthritis /very early RA in some patients. An impact on radiographic and MRI inhibition was seen, which was maintained for 6 months after treatment stopped. These findings suggest that it is possible to alter the progression of RA by modulating T-cell responses at a very early stage of disease. Thus it is possible to alter the progression of RA by modulating T-cell responses at a very early stage in RA. In this symposium,

I want to talk about positioning by the RA treatment of abatacept including expectation.

SS2-5

Our experiences with ABT and the examination for extensions of dosing intervals

Takafumi Hagiwara

Matsubara Mayflower Hospital, Rheumatology, Kato, Japan

We've participated in ABT trials since Phase I, prescribing ABT to over 40 patients since ABT became available to present.

ABT has a new mechanism of action that selectively modulates activation of T-cells by binding to antigen presenting cells. With this unique mechanism, ABT is considered a 'Bio-DMARDS'; a new category of drugs. In our hospital, ABT plays a broad role such as the 1st-biologic agent used before cytokine blockers in some cases or being switched to from existing cytokine blockers when patients don't improve.

Since ABT doesn't mask inflammatory markers such as fever or CRP value, in cases infection occurs, it's easy to treat patients.

Among 28 patients participating in the trial, the persistence rate at the end of the trial (about 3yrs.) was 82.1%; higher than other biologics previously available. Also 11 patients (39.3%) achieved a high clinical remission rate defined by DAS28-CRP < 2.3 and maintained it at the end of the 3-year-clinical trial.

To study the possibility of increasing dosing intervals, we evaluated disease activity of 15 patients who experienced the washout period (3 months) with ABT. For the ABT 10mg/kg group, all 8 patients achieved LDA within 6 months and 4 out of 8 patients maintained their LDA after the 3-month-washout period. For the ABT 2mg/kg group, 2 out of 3 patients that achieved LDA maintained their LDA after the washout period. We evaluated the differences between the LDAS maintained group (6 patients) and the flare up group (5 patients) during the washout period. Patients who couldn't maintain their LDAS tended to have a longer period of washout (avg.: 14.3 weeks vs. 11.0 weeks) and a higher IL-6 before ABT was administered (avg: 22.2pg/mL vs. 10.4pg/mL).

ABT has the same efficacy as other biological agents that had been on the market longer. Our experience shows there's a possibility of reducing costs for patients by extending administration intervals of ABT to ≥ 4 wks. for patients who've achieved LDA or remission.

SS2-6

Treatment of RA by Abatacept in Our Clinic and Future Possibilities

Shigeru Honjo¹, Mayumi Kaneko¹, Mitsuhiro Kawano²

¹Honjo Rheumatism Clinic, ²Department of the second internal medicine, Kanazawa University, Kanazawa, Japan

We have been using abatacept (ABT) in our clinic since the clinical trial study. However, due to its short history, we are still working to determine its position in treatment. Drawing on the drug's properties and our experience in using it, I will discuss patients who have been treated with ABT to date. We have been treating a group of 30 patients (28 females, 2 males) with a mean age of 60.3 years (range: 37 to 85 years). Six of these 30 patients were bio-naïve and 24 patients were shifted from biotherapy. Efficacy and safety results for these two groups will be presented using data covering up to 12 weeks of treatment. Of the patients who discontinued ABT in a Japanese clinical trial, one patient has been drug-free and one has been bio-free for 1 year. Some patients have resumed ABT-therapy due to progression of the disease or based on their proposal. Treatment was resumed safely and good responses have been observed. This is as-

sumed to be attributable to low frequency of appearance of ABT antibodies. Also, in a Japanese clinical trial in which ABT was re-administered after the washout period, no increase was detected in incidence of adverse events such as infusion reactions. ABT has demonstrated high efficacy and safety in not only bio-naïve patients but also in those who switched from biotherapy. Considering its action mechanism, it may be possible to lead patients treated with ABT to a drug-free/bio-free state. It is also suggested that ABT is low-risk when re-administered or discontinued.

SS2-7

Treatment for RA patients with inadequate response to TNF- α inhibitors

Koichi Amano

Saitama Medical Center, Saitama Medical University, Kawagoe, Japan

Rheumatoid arthritis (RA) is a chronic, progressive and disabling autoimmune disease affecting between 0.5 and 1% of the adult population. Management of RA has improved dramatically following the introduction of TNF- α antagonists. However, despite the efficacy of these agents, some patients either do not respond or fail to maintain initial response. Abatacept is a dimeric fusion protein composed of the extracellular domain of CTLA4 fused to the Fc region of human IgG1. Abatacept binds to the B7 molecule to block interaction between CD28 and B7 leading to downregulation of T cell activation. Abatacept was approved for the treatment of RA in September 2010. This selective T cell co-stimulation modulator has a unique mechanism of action, which is linked to the pathogenesis of RA. A number of clinical trials have been conducted to evaluate the efficacy and safety of abatacept in patients with RA. The ATTAIn study demonstrated statistically and clinically significant improvements in the signs and symptoms of RA, physical function, and HRQoL outcomes, along with an acceptable safety profile in patients with RA who had already failed to respond to one or more TNF- α antagonists. The results of the ARRIVE study were comparable with or without a washout of DMARDs, supporting direct switching from anti-TNF therapy to abatacept as an option in clinical practice. Abatacept provided considerable efficacy benefits irrespective of previous anti-TNF therapy experience, but the magnitude of improvement was greater in patients who had previously tried only one anti-TNF agent. The two-year ATTEST study suggested that efficacy benefits increased when patients were switched from infliximab to abatacept. Abatacept provides an important treatment option with the potential to achieve complete remission in patients with RA. Continued vigilance and recording of future safety signals is important as is the collection of safety data on the more recently introduced non-TNF biological DMARDs.

Luncheon Seminar

LS1

Best Use of MTX with Safety Consideration for RA- Based on JCR Recommendations -

Yasuo Suzuki

Division of Rheumatology, Department of Internal Medicine, Tokai University School of Medicine, Kanagawa, Japan

A recent paradigm shift of the treatment of RA is to aim for remission by the tight control strategy using DMARDs as early as possible in the disease process. Among the DMARDs, MTX is considered the anchor drug and should be used as a first-line drug. In Japan, more than 10 years have past since Rheumatrex® was introduced into the market in 1999 and most Japanese rheumatologists now accept that MTX is the first choice of DMARDs. However, an upper limit of MTX dose for RA is set to 8mg/week that is about a half of Western Countries. Since the results of RCTS comparing different dosage of MTX in RA treatment showed dose dependent efficacy between 5mg and 20mg/wk, 8mg/wk of MTX is not enough to suppress RA completely. Despite the fact that the maximum dose of MTX was limited to 8mg/week, reports of serious adverse effects have been accumulated every year. The Japan College of Rheumatology (JCR) has demanded improving dosage of MTX for several years. In 2010, there was a significant progress in the application for increasing the upper limit of MTX dose, and an increase in dose of MTX up to 18mg/wk is now under deliberation by the board of review. If MTX is used in adequate doses up to 16mg/wk with due safety considerations, higher efficacy and remission rate will be obtained. The JCR published Recommendations for the Use of Methotrexate in the Treatment of Rheumatoid Arthritis on September 21, 2010. 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 peri-operative period, 8. Pregnancy and nursing mothers, 9. Minimization of side effects; risk factors, monitoring and treatment for serious side effects. All rheumatologists need to understand how to use MTX and how to minimize the side effects.

LS2

Progress of RA treatment targeting on remission

Yoshiya Tanaka

The First Department of Internal Medicine, School of Medicine, University of Occupational & Environmental Health, Japan

It is today's global consensus that remission is the treatment goal for rheumatoid arthritis (RA). The EULAR recommendations for the management of RA 2010 have stated clinical remission as the treatment goal for all patients with RA. The big question for rheumatologists today is what treatment strategies we are to practice for each individual patient to achieve this goal. The evolutionary expansion in treatment options for RA has enabled a greater proportion of patients to attain remission. Biologics targeting TNF have brought about clinical, structural, functional, and even biologic-free remission as treatment goals for RA. We have also learned from various studies with infliximab that structural remission can be obtained without the achievement of clinical remission. Thus, clinical remission is a benchmark; it is critical to derive a treatment strategy for each individual patient, ensuring structural and functional remission. The new criteria to define clinical remission were presented at the ACR 2010. It is based upon scientific evidence that by satisfying these criteria today, we may raise the rate of structural/ functional

remission in the future. In this seminar the gateway of RA treatment (new classification criteria), the treatment goal (new remission criteria) and the strategy to realize the best treatment of RA aimed for structural/ functional remission will be described. Furthermore, the RRR study demonstrated that approximately 50% of the patients who discontinued infliximab could maintain low disease activity for more than 2 years. We finally discuss what treatment strategy could be the best to obtain biologic-free remission.

LS3

The treatment of rheumatoid arthritis - How to use DMARDs, NSAIDs and steroid -

Yutaka Kawahito

Kyoto Prefectural University of Medicine

The primary target for treatment of rheumatoid arthritis (RA) is a state of clinical remission and the definition of clinical remission became a more stringent one than a conventional remission standard. The application to the treatment of the biological agents made it possible to achieve remission relatively easily and importance of tight control from the onset early stage of RA is pointed out. However we cannot use these biological agents for all RA patients due to side effects and economical problems. Moreover, disease-modifying anti-rheumatic drug (DMARD) has efficacy for combination therapy with biological agents and its monotherapy is still effective for patients with mild disease activity, if we can detect patients with early RA stage with the ACR/EULAR new classification criteria. According to these matters, it is very important that rheumatologists can use many DMARDs effectively and with safety. We also need the knowledge of non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoid for controlling pain and ADL in clinical practice. COX 2 inhibitors minimize gastrointestinal toxicity. The administration of low dose of glucocorticoid is seemed to have the merit for joint destruction within 2 years after the onset of RA. In this seminar, I give an outline including advantage and disadvantages of the usage of DMARDs, glucocorticoid, and NSAIDs.

LS4

Vaccination with 23-valent Pneumococcal Polysaccharide Vaccine for Rheumatoid Patients

Minoru Kanazawa

Department of Respiratory Medicine, Saitama Medical University

Streptococcus pneumoniae is the chief cause of pneumonia, covering 30-40% of all causative organisms of community-acquired and healthcare-associated pneumonia (HCAP). In rheumatic diseases, the presence of the primary disease, pulmonary complications, administration of immunosuppressants and biological drugs are thought to increase risks for pneumonia. The present adult pneumococcal vaccine (Pneumovax NP) is effective for reinforcing phagocytosis by inducing type-specific antibody production including 23 types of capsular polysaccharides. Pneumonia preventive effects are strongest in young and middle-aged persons with normal immune level, but decrease in elderly persons and patients with reduced immune competence. With the elderly and patients with chronic underlying disease, many reports prove the efficacy of the pneumococcal vaccine in observational studies. Although randomized study results show effectiveness for invasive pneumococcal infections such as bacteremia and meningitis, they have not demonstrated efficacy for all types of pneumonia. Last year, prospective studies were successively reported from Japan, indicating vaccine effectiveness in high-risk pneumonia patients. Meanwhile, the Japanese government is still sensitive to adverse events of vaccines; then Japan is behind in

the use of these vaccines. However, the government recently decided to fund pediatric pneumococcal (7-valent protein conjugate vaccine), Hib meningitis, and cervical cancer vaccines. With the adult pneumococcal vaccine, about one-fourth of all municipalities in the country currently subsidize the vaccination fees for the elderly. The Japanese College of Rheumatology recommends the pneumococcal vaccine in its TNF inhibitory therapy guidelines for rheumatoid arthritis, but the practice of vaccination is still uncommon. Given that the vaccine lasts 5 to 9 years per shot, cost-effectiveness is excellent. In addition, revaccination is now allowed; those with high risk of pneumonia are recommended to consider vaccination even before age 65. In Japan, the pneumococcal vaccination rate over age 65 is estimated at 10%; considerably lower than the U.S. at 61%. Considering its effectiveness, vaccination should be actively recommended to patients with pulmonary complications and those undergoing rheumatism therapy.

LS5

How to choose conservative treatment suitable for patients with each disease stage of OA

Harumoto Yamada

Department of Orthopaedic surgery, Fujita Health University

OA is a disorder with high heterogeneity and different pathological state exists by each disease stage, so it is very important to choose correctly the most suitable conservative treatment for the present patient. In early stage of OA, destruction of cartilage is still limited, and repair activity of cartilage is preserved. Foot arch support with lateral wedge, control of body weight, and training of quadriceps femoris muscle may improve clinical symptoms of knee OA in early stage. Clinical manifestation sponsored by NIH (GAIT study) was not able to demonstrate significant clinical improvement even if both glucosamine and chondroitin were used. In advanced stage of OA, degeneration of cartilage cannot be recovered, symptoms increase for the secondary synovitis due to the debris caused by bone and cartilage destruction. NSAIDs are first the line drug in OA treatment of this disease stage, but according to the meta analysis, a short-term effect for pain relief by NSAIDs should not put too much confidence. COX-2 selective NSAIDs are recommended as the first choice in the guideline for OA treatment for its reduced rate of gastrointestinal disturbance. As for the intraarticular injection therapy of hyaluronic acid (HA), significant clinical improvement for OA symptom has been confirmed by several meta-analyses. It has been shown HA injection therapy is more effective for the patients with higher knee score (severe clinical symptom including pain). There is not clear evidence that HA injection therapy inhibits disease progression of OA, but suppressive effect for cartilage breakdown has been shown by pilot study in which arthroscopy is adopted as the evaluation method. In the guideline for OA, injection therapy of corticosteroid is shown to be effective for the patients with advanced and terminal stage OA. Corticosteroid may suppress synthesis of cartilage matrix and induce pathological state similar to Charcot's joint, so use of this drug should be limited to one injection in a few months. It is important to choose most suitable conservative treatment for each patient in consideration of pathological disease state, and use of OA guideline may provide great advantage to get clear information and evidence.

LS6

RA treatment from the viewpoint of osteoimmunology

Hiroshi Takayanagi

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- α , 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- β . These mechanisms provide a molecular basis for novel therapeutic strategies including the antibodies against IL-6, IL-23 and IL-17.

Antirheumatic drugs have relatively minor effects on bone destruction, but when they are used in combination with other antirheumatic drugs or biological pharmaceuticals, they exert synergistic effects, which can be explained by their effects on RANKL expression and its signal transduction.

LS7

Anti-neutrophil Cytoplasmic Antibodies Tests: Which Tests Should be Used in Clinical Practice

Masaharu Yoshida

Division of Nephrology, Hachioji Medical Center of Tokyo Medical University

Serological testing for anti-neutrophil cytoplasmic anti-bodies (ANCA) has become an important tool for supporting a diagnosis of systemic necrotizing small vessel vasculitis: Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS) and oligo-symptomatic forms of these. These so-called ANCA-associated vasculitides most often necessitate the institution of therapies with cytotoxic as well as corticosteroids, and hence, a firmly established diagnosis is mandatory to avoid unnecessary and risky treatment. In the laboratory of today the most appropriate way to detect the presence of vasculitis-associated ANCA is by using both indirect immunofluorescence and direct enzyme immuno-assay for antibodies to proteinase 3 (PR-3) and myeloperoxidase (MPO). The diagnostic specificity of these latter assays towards systemic vasculitis can only be secured by setting a suitably high cut-off value, chosen in collaboration with clinicians after testing carefully selected disease control sera. When classical cytoplasmic ANCA as well as a significant level of PR-3-ANCA are found in a given serum this combined result strongly indicates vasculitis. Similarly, the combination of perinuclear ANCA and a significant level of MPO-ANCA is close to 100% specific for vasculitis. MPO-ANCA can be found in MPA and CSS more frequently than WG. The association of MPA with MPO-ANCA is reported to be in the range of 40-90%, and MPA with MPO-ANCA is reported to be frequently associated with necrotizing glomerulonephritis and/or pulmonary capillaritis. An array of different methods for their detection were designed, resulting in great variations in ANCA testing to discuss the methodologies used and to compare results in order to agree on a strategy to harmonize techniques including affinity assay of ANCAs and produce more reproducible results.

LS8

Treatment strategies using new biologic and non-biologic DMARDs for RA

Kazuyoshi Saito

The First Department of Internal Medicine, University of Occupational & Environmental Health

RA is a representative autoimmune disorder characterized by inflammatory synovitis, erosive arthritis and articular degradation. RA affects 0.7 million Japanese and in spite of treatment, it is still possible for progressive joint destruction to occur, as well as deformity, disability. American College of Rheumatology (ACR) and European league against of rheumatism (EULAR) has proposed the new criteria which are aimed at classification of newly presenting patients in 2010. The statement recommend the patients with erosive disease typical of RA with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA and the initial treatment should be begun with methotrexate (MTX). Such early intervention with MTX and introduction of biologics supposed to improve outcome of treatment of RA. So far now, three TNF inhibitors, Infliximab, etanercept and adalimumab, and IL-6 blockade tocilizumab, CTLA-4Ig abatacept are available in Japan and have been successful at improving the signs and symptoms of RA and, thereby, have set a new standard for disease control of RA and have the potential to protect joints from structural damage or to improve quality of life. Although these biologics have brought about a paradigm shift in the treatment of RA, the rate of clinical remission is about 40-50% and the new therapy for the rest of patients should be established. New biologic DMARDs including Baminercept which targets lymphotoxin-beta, Denosumab(anti- RANK ligand Ab), Ofa-tumumab (full human anti-CD20Ab), Belimumab (anti-BlyS Ab) are being developed that either provide alternative methods or different targets of action. On the other hands, low molecular compounds such as Tasocitinib (Jak inhibitor), Fostamatinib (syk kinase inhibitor), Masitinib (KIT inhibitor) are also in various stages of clinical trials. Some of these agents that hold promise as better arthritis treatments.

LS9

Early recognition of cardiopulmonary complications and combination therapy with pulmonary vasodilators may modify the natural course of diffuse cutaneous systemic sclerosis.

Hidehiro Yamada

Division of Rheumatology and Allergology, Department of Internal Medicine, St. Marianna Medical School, Kawasaki, JAPAN.

Cardiopulmonary complications of systemic sclerosis (SSc) include pulmonary arterial hypertension (PAH), interstitial lung disease (ILD) and cardiac fibrosis (CF). Recent study showed that they were leading causes of death in patients with SSc. Unlike idiopathic PAH, SSc-related PAH is often complicated with ILD and CF in a various degree of severity. Furthermore, severe ILD sometimes induces hypoxia-driven pulmonary hypertension, and CF-related left ventricular diastolic dysfunction can leads to pulmonary venous hypertension (PVH). Right heart catheterization should be performed to differentiate these pathogenesis when SSc patients are suspected to have pulmonary hypertension by non-invasive examination including doppler echocardiogram. Recent multicenter prospective study reported that the incidence of PAH, ILD-related PH and PVH were 0.61, 0.15 and 0.61 cases per 100 patient years, respectively. ILD and CF in patients with dcSSc are well recognized to develop within 3-6 years of disease onset as well as skin sclerosis and renal crisis. Recent study has shown that some patients with early dcSSc

who had not shown a detectable tricuspid regurgitation at baseline developed severe PAH within 2 years. This confirms the importance of regular screening for PAH even in early dcSSc patients. The latest studies and our experience indicate that exercise echocardiogram and cardiopulmonary exercise testing are most effective methods for early detection of both PAH and PVH. We experienced eight patients with early dcSSc who showed an improvement of progressive ILD as well as skin sclerosis after combination therapy with bera-prost, endothelin receptor antagonist and PDE5 inhibitors. These findings suggest that therapeutic intervention with combination therapy for PAH could inhibit the progression of skin sclerosis and cardiopulmonary complications of dcSSc when introduced within 2 years of onset before the disease becomes irreversible.

LS10

Role of Leflunomide in Treatment of Rheumatoid Arthritis

Hiraku Kikuchi

Department of Orthopaedic Surgery, Sakai Hospital Kinki University Faculty of Medicine

RA Classification Criteria revised by EULAR/ACR in 2010 improved sensitivity in early disease, and treatment target shifted to clinical remission by introduction of biologics. Leflunomide (LEF) is an immunosuppressant for RA. Its efficacy is comparable with the global standard dose of MTX, although it has not been widely used in Japan since lung complication was reported at an early stage. We reported previously that LEF administration for 6 months can potentially slow down joint destruction. Katayama et al. also reported the superiority of LEF compared with the Japanese standard dose of MTX. After All Case PMS finished, all rheumatologists had access to LEF without PMS contract. We review recommendable administration way of LEF that can control joint destruction with much better economy than biologics.

Patient and methods: Fifty six RA patients, who received LEF for ≥ 1 year. Disease progression of joint destruction in radiological images and bone remodeling markers were compared between before and after treatment for > 1 year.

Results: Of the 56 patients, 8 needed to switch to a biologic to calm disease activity, 6 discontinued due to suffering complication after more than 3 years, 4 discontinued drug after achieving remission, and 30 patients could uphold low disease activity after decrease of dosage to 20 mg alternate-days. Average levels of clinical parameters changed as follows. CRP: 2.0 \rightarrow 0.8 mg/dL, MMP-3: 212 \rightarrow 178 ng/ml, CTX-II: 465 \rightarrow 339 ng/mmol, NTX: 49.5 \rightarrow 37.2 ng/mmol, BAP 23.1 \rightarrow 23.9 mg/L. Progression of joint destruction was confirmed in 3 cases by radiological image and high CTX-II (> 800 ng/mmol). Total knee arthroplasty was performed in 2 cases.

Discussion: Average values of clinical tests indicate retardation of joint destruction. Dose of LEF down to 20 mg alternate-days may be recommendable administration for Japanese RA patients with high incidence of complications. Case with high CTX-II needs alternate more vigorous treatment in early treatment.

LS11

An Update on the Management of Glucocorticoid-induced Osteoporosis

Yasuo Suzuki

Division of Rheumatology, Department of Internal Medicine, Tokai University School of Medicine, Kanagawa, Japan

Glucocorticoids were widely used for the treatment of various disorders. Since glucocorticoid-induced bone loss is most rapid during the initial 3 – 6 months, primary prevention of bone loss is espe-

cially important. The Japanese Society of Bone and Mineral Metabolism have devised a guideline for the management and treatment of GIOP (2004). In the guideline, fragility fracture, low bone mineral density, and prednisolone 5mg/ day or more were brought together in the flow chart as a risk factor that needed the intervention of the drug therapy. Bisphosphonates as a 1st-line drug play a central role in the management of GIOP and active vitamin D3 and vitamin K2 are 2nd-line drugs. Recent clinical studies have indicated teriparatide [recombinant human PTH (1-34)] is efficacious in the secondary prevention of GIOP and teriparatide treatment increased BMD more compared to alendronate treatment in GC- treated patients with high risk for fracture. The American College of Rheumatology (ACR) published 2010 Recommendation for the prevention and Treatment of GIOP. In the recommendations, fracture risks were categorized into high, medium, and low risk, based largely on the FRAX tool for postmenopausal women and men age over 50 years. For patients at high risk, alendronate, risedronate, and teriparatide are recommended. In this seminar, an update on the management of GIOP would be discussed while introducing the efficacy of teriparatide and ACR 2010 recommendations.

LS12

Treatment of Systemic Sclerosis Up-to-date

Kazuhiko Takehara

Kanazawa University Graduate School of Medical Sciences

Systemic Sclerosis (SSc) is a connective tissue disease characterized by various organ fibrosis and the pathogenesis of this disorder is not yet unknown. However, several treatments for SSc are developing in recent years. The development of proper treatment strategy for each cases is important and at the same time we should consider the clinical features and patient background. In all cases, we should consider bellows.

1. Clinical types (diffuse cutaneous vs. limited cutaneous)
2. Disease specific antinuclear antibodies (Anti-topoisomerase? antibody, Anti centromere antibody, Anti-RNA polymerase antibody etc)
3. Skin Score (Modified Rodnan Total Skin Thickness Score, MRSS)
4. Disease stage (early vs. late)
5. Internal organs
6. Quality of Life (QOL)

In this lecture, I present my idea of the treatment strategy showing case presentations. Some of the patients were treated for pulmonary arterial hypertension. I want to stress that so-called EBM (evidence-based medicine) can not establish whole treatment strategy of such a rare treatment-difficult disease as SSc.

LS13-1

Abatacept – A new biologic agent to regulate T cells by inhibiting costimulation

Takao Fujii

Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University

Autoreactive T cells are involved in the pathogenesis of various autoimmune diseases. In rheumatoid arthritis (RA), the fact that oligoclonal T cell subsets infiltrate in synovial tissue indicates T cell involvement in RA synovitis. The infiltrated T cells may stimulate monocytes, macrophages, and synovial fibroblasts to secrete proinflammatory cytokines, B cells to produce immunoglobulin, and activate osteoclasts. Genomic susceptibility of *PTPN22*, *CTLA4*, and *STAT4* variants to RA, which are associated with T cell activation,

strongly suggests that T cell abnormality plays an important role of autoimmunity in RA.

T cells show various functions toward other immune cells by contact-dependent manner, which is a cognate interaction of T cell receptor (TCR)-antigenic peptide on HLA class II and co-stimulatory molecules, and contact-independent manner (bystander help). The former will contribute high titer of immunoglobulin secretion and tolerance, mainly mediated by Th2 and regulatory T cells, respectively. The latter will be mediated by cytokines derived from Th1 and Th17 cells. The effector pathway of these activated T cells, however, may be complex in RA, because it will differ from each individual or disease phase.

Abatacept is a fusion protein between extracellular CTLA (cytotoxic T-lymphocyte antigen)-4 and human IgG1 Fc domains. For T cell activation mediated by antigen-presenting cells, cognate interaction of TCR- antigenic peptide on HLA class II and CD28-CD80/86 (B7-1/7-2) co-stimulation is required. Abatacept can inhibit CD28-binding to CD80/86 by CTLA-4 domain, which has much higher affinity to CD80/86 than CD28.

Till now, while a huge number of reports have shown that treatments targeting T cells are effective in patients with RA, abatacept is a new biologic agent to regulate T cells by inhibiting co-stimulatory molecules. For “unmet needs” of RA patients, beneficial effects of abatacept will be expected.

LS13-2

Clinical evidences of abatacept in the treatment of rheumatoid arthritis

Keiichiro Nishida

Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences

Abatacept (ABT, ORENCIA®) is a soluble human fusion protein consisting of the extracellular domain of CTLA-4 linked to the modified Fc portion of human IgG1. ABT inhibits full T cell activation by binding to CD80/CD86, blocking interaction with CD28, and exhibits anti-rheumatic effects. ABT has been shown to be efficacious, and has an acceptable safety profile in patients with moderate to severely active RA in several clinical trials. Phase IIB study and AIM trial showed the effectiveness of ABT added to methotrexate (MTX). AGREE study showed significant inhibition of structural damage progression with ABT plus MTX versus placebo plus MTX at 1 year (Westhovens R, 2009). ARRIVE trial is the first to demonstrate the efficacy and safety of ABT in patients who switched directly from TNF antagonist therapy without undergoing wash-out, and resulted in improvements in disease activity, physical function and quality of life (Shiff M, 2009). ATTEST trial is the only published randomized clinical trial to assess the effects of two biologic therapies in the same study. After 12 months, a greater reduction in ACR response and DAS28 (ESR) was observed with ABT plus MTX than with infliximab (3mg/kg) plus MTX. Phase III AIM trial showed the long-term clinical efficacy over 5 years of treatment with ABT, suggesting ABT could be considered as a first-line biologic DMARD in the treatment of RA. Several trials demonstrated that the incidence of overall adverse events (AEs) was generally comparable for ABT- and placebo-treated patients. Weinblatt et al. analyzed the data from 4149 patients with 12,132 patient-year of exposure up to 7 years and indicated that the safety profile of ABT remains stable with increasing duration of exposure (EULAR, ACR2010). However, some trials indicate the higher frequency of serious AEs with ABT (Kremer, 2006). In the current seminar, the

best use of ABT in the treatment strategy for RA will be discussed based on the results of clinical evidences.

LS14

Sharing up-dated information on JIA with adult rheumatologists

Syuji Takei

School of Health Sciences, Faculty of Medicine, Kagoshima University

JIA is a chronic arthritis with unknown clinical causes which occurs at the age of less than 16 years. JIA is classified into seven subtypes. However, JIA correspond to 1/30 to 1/40 of adult RA, it is not an uncommon disease for rheumatologists. Since no disease specific markers to JIA, e.g., anti-CCP antibody, are available up to now, differential diagnosis from other diseases is more important than RA. Since drug-free remission can be achieved in about half of JIA patients by giving appropriate medical interventions at an early stage of the disease, the early diagnosis of JIA is of great importance at clinical settings. Diagnosis of systemic JIA (sJIA), differentiation from auto-inflammatory diseases (AID) is of clinically importance. Both the symptoms and laboratory findings of AID are very similar to sJIA. Among 13 patients with AID genetically analyzed at our department, 9 were diagnosed as sJIA. Because neutrophils and macrophages, are known to be related to innate immunities, significantly increased in the acute phase of sJIA, and because no auto-antibodies are synthesized in sJIA, sJIA has now come to be looked upon as AID. Elucidation of the patho-physiological mechanisms of sJIA has given much evidence that sJIA is AID and that treating the disease with anti-IL-6 therapy is one of the rational therapies. Actually, over 300 patients with sJIA have been treated with tocilizumab (TCZ), and an excellent clinical effectiveness for a rather long period of time with the treatment has been manifested. MTX has been approved as the first line DMARD in Japan for the treatment of the polyarticular JIA. To MTX inadequate responders, TCZ and etanercept (ETN), an anti-TNF agent, are being accumulated. Due to the possibility of carcinogenesis by anti-TNF therapy particularly in children and adolescence, the FDA has claimed a box warning. Nevertheless, subsequent investigations carried out employing different types of databases have not affirmed this possibility.

LS15-1

Towards the standardization of musculoskeletal ultrasound.

Shigeru Ohno

Center for Rheumatic Diseases, Yokohama City University Medical Center, Yokohama, Japan

Musculoskeletal ultrasound (MSUS) is regarded as one of the most operator dependent modalities in clinical practice. Considering the Kappa values of various examinations, we can understand that this belief is not necessarily true. But the need for standardization of MSUS is a matter of the greatest importance. Many factors are associated with the reliability of the evaluation of MSUS. Factors of operators, patients, setting of machines and the environment of MSUS should be considered in the standardization of MSUS. Standardizations of positioning of the patient, settings of environment and machines can be achieved by following the recommendations in the guidelines. The most difficulty lies on the factors associated with the operator. The expertise and experience of the operator will determine the value of the diagnostic information obtained. How thoroughly the operator does the examination, the experience and knowledge of the abnormal findings and the judgement of artifacts easily affects the inter-observer reliability. Although the procedure

itself can be standardized by guidelines, the correct interpretation of the image is mandatory. Self-learning by textbooks and guidelines are of limited value and direct education by experts and training courses organized by experts providing hands on experience are useful. Many education courses are provided by European countries but variation of training and practice between countries are reported. The standardization of training and education is required.

I would like to discuss the importance, pitfalls and obstacles towards the standardization of MSUS.

LS15-2

Ultrasound image acquisition in the evaluation of synovial lesion in rheumatoid arthritis

Kei Ikeda

Department of Allergy and Clinical Immunology, Chiba University Hospital, Chiba, Japan

Ultrasonography (US) has been recognized as a useful tool in the management of rheumatoid arthritis (RA) and is spreading rapidly among rheumatologists. Among various pathologies of RA which US can detect, synovial pathologies are the most important and evaluation of synovitis plays a pivotal role in US assessment of RA. However, very few guidelines and textbooks for ultrasound published in European nations specifically focus on RA. Furthermore, none of them provides with detailed and systematic information about RA synovitis in many different joints. In this lecture, the optimal image acquisition methods focusing on the detection and evaluation of synovitis will be discussed.

LS16

Osteoarthritis: Update of diagnosis, treatment, and molecular mechanism

Hiroshi Kawaguchi

Orthopaedic Surgery, University of Tokyo, Tokyo, Japan

Osteoarthritis (OA), one of the most common skeletal disorders, is characterized by cartilage degeneration and osteophyte formation in joints. Despite its high prevalence and social needs, there is no disease-modifying treatment for this disorder. This is because the therapeutic target is undetected, and this is because the molecular backgrounds remain unclear. Considering that most of risk factors approved so far are related to accumulated mechanical stress on joint, we believe that elucidating the signaling lying downstream of the mechanical stress will disclose the molecular backgrounds of OA. To realize it, several experimental OA models in mice by producing instability in the knee joints have been developed to apply approaches from mouse genetics. Although the mouse genetics studies revealed that proteinases like MMP-13 and ADAMTS-5 are the principal initiators of OA progression, clinical trials of the proteinase inhibitors have to date been unsuccessful for the treatment, turning the interest of researchers to the upstream signals of proteinase induction. These signals include endochondral ossification signals such as Runx2, C/EBP β , HIF-2 α (EPAS1), carminerin, osteoprotegerin, β -catenin, syndecan-4, hedgehog, etc. The proteinases produced during the endochondral ossification process cause cartilage degradation at the center of the joint and osteophyte formation at the periphery. At the periphery, vascularity is accessible from the synovium or tendon, which completes endochondral ossification and forms osteophytes, just as it does at the embryonic and growth plate cartilage. However, in the center, the vascularity is not accessible from the edge, so that it may end up with cartilage degradation without being replaced by bone. Molecules related to the endochondral

ossification might become therapeutic targets altering the course of this disabling disease.

LS17

Usefulness of Immunosuppressant therapy for connective tissue diseases.

Yoshinari Takasaki

Department of Internal Medicine and Rheumatology, Juntendo University Faculty of Medicine

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

Therefore, it is needed to develop a new type of immunosuppressant which is targeting the particular molecule associated with immune disorders in connective tissue diseases, and a new approach to use the drugs. In this session, we will discuss about the usefulness of immunosuppressant therapy for connective tissue diseases based on the problems as mentioned above.

LS18

Influence of glucocorticoid on the development of osteoporosis in rheumatoid arthritis

Masaaki Inaba

Department of Metabolism, Endocrinology, and Molecular Medicine, Osaka City University Medical School, Osaka, Japan

Osteoporosis is the disease of bone, which leads to an increased risk of fracture. In osteoporosis, in addition to the reduction of bone mineral density (BMD), bone microarchitecture deteriorates with the amount and variety of proteins in bone altered to impair bone quality. It has been recently recognized that excessive acceleration and reduction of bone turnover might cause increased bone fragility resulting from impaired bone quality. Osteoporosis associated with rheumatoid arthritis (RA) is classified into two categories: generalized bone loss, which may result from immobility, the inflammatory process *per se* and/or treatments such as glucocorticoid; and para-articular demineralization, which is probably due to inflammatory cytokines locally released from inflamed joints. RA patients are often treated with glucocorticoid, which contributes with great degree to the development of osteoporosis. Glucocorticoid is known to increase fracture rate shortly after its administration without any appreciable effect on BMD, glucocorticoid-induced impairment of bone quality is hypothesized to cause bone fragility. Supportive of this notion is our data showing that the threshold of fracture might be significantly greater in those with glucocorticoid treatment than those without. Furthermore, RA patient with glucocorticoid showed

significantly greater fracture rate at vertebrae than those without irrespective of similar BMD at lumbar spine. Treatment for glucocorticoid-induced osteoporosis (GIOP) is particularly important because of its high rate of fracture and as much as approximately 90% prevention against the development of GIOP-based fracture by preventive administration of third generation bisphosphonate. The possible important effect of PTH (1-34) is also supposed in GIOP treatment. Taken together, preventive therapy is needed to effectively reduce GIOP-induced bone fracture also in RA patients, even in low-dose glucocorticoid.

LS19

The use of PTH in the treatment of osteoporosis

Satoshi Soen

Department of Orthopaedic Surgery and Rheumatology, Nara Hospital, Kinki University School of Medicine, Ikoma, Japan

Osteoporosis is a leading cause of fractures in women and men but is underdiagnosed and undertreated. Antiresorptive therapies have historically been used to treat this condition. Teriparatide (recombinant human parathyroid hormone) is an anabolic agent labeled for use in postmenopausal women and men with osteoporosis who are at high risk for fractures. Clinical trials indicate that teriparatide increases predominantly trabecular bone in the lumbar spine and femoral neck; it has less significant effects at cortical sites. The combination of teriparatide with antiresorptive agents is not more effective than teriparatide monotherapy. After a maximum of eighteen months of teriparatide therapy, the drug should be discontinued and antiresorptive therapy begun to maintain bone mineral density. Glucocorticoids (GC)-induced osteoporosis (GIOP) is the most common cause of secondary osteoporosis, which leads to an increased fracture risk in patients. GC can cause a rapid bone loss, decreasing bone formation and increasing bone resorption. The decreased bone formation is mainly due to the GC-induced apoptosis of both osteoblasts and osteocytes, while the increased bone resorption is due to the increased life-span of pre-existing osteoclasts. Bisphosphonates are clearly effective in preventing and treating GIOP but anabolic therapeutic strategies are the new promising therapeutic alternative. Experimental and clinical studies indicate that teriparatide is efficacious for the treatment of GIOP, being able to induce an increase in bone mass in these patients. Intermittent administration of teriparatide stimulates bone formation by increasing osteoblast number. Teriparatide has been demonstrated in several clinical studies to significantly decrease the incidence of fractures in patients affected by GIOP. It has recently received an indication for GIOP in USA and Europe and its label indication has also been expanded.

LS20-1

Pitfalls of Pulmonary Hypertension in the Treatment of Connective Tissue Diseases

Sumiaki Tanaka

Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine

Since the approval of bosentan in 2005, a series of effective oral agents such as sustained release beraprost, sildenafil, tadalafil and ambrisentan have become available for the treatment of pulmonary arterial hypertension (PAH) in Japan. These therapeutic agents are improving the prognosis for PAH patients. This fact led pulmonary hypertension (PH) to get our interest increasingly, among those involved in the treatment of connective tissue disease (CTD).

As a result, a significant progress has also been made in the treatment of CTD-associated PH (CTD-PH), leading to the introduction

of screening using cardiac ultrasonography in patients with systemic sclerosis (SSc) and mixed connective tissue disease (MCTD) to diagnose latent PH. This has elucidated the epidemiology of PH in the patients with CTD. Because it has become more common to make a differential diagnosis of PH, the diversity of CTD-PH has become more widely recognized. The CTD-associated PAH (CTD-PAH) treatment guidelines have also been formulated and the prognosis of CTD-PAH has kept improving. In addition, the usefulness of bosentan and sildenafil in the treatment of fingertip ulceration has been reported, which has drawn our interest further.

Meanwhile, the increased interest in PH and the easiness of treating PAH with the oral medications mentioned above sometimes change to a pitfall trap. One of such examples is the administration of a PAH medication to treat PH associated with left ventricular failure. With easy-to-use and more effective PAH medications being available today, it is important to make a correct diagnosis of PH properly to ensure the appropriate use of PAH medications.

In this presentation, I will present cases of pitfalls of PH and therapeutic results of CTD-PAH observed in our division. Based on these cases and results, I will discuss the characteristics and important points of PH treatment in CTD patients, and concerns that have become apparent.

LS20-2

Pathology and Diagnosis of CTD-PAH

Yasushi Kawaguchi

Institute of Rheumatology, Tokyo Women's Medical University

In this talk, I would like to discuss the efficacy of endothelin receptor (ETR) antagonists, dual and selective types. As you know, there are two types of specific endothelin-1 receptor, type A and type B. In Japan, we have two strategies for inhibiting endothelin-1 signal transduction using dual receptors antagonist and single receptor antagonist (selective ETR type A antagonist). An efficacy of two antagonists on pulmonary arterial hypertension (PAH) has been considered to be almost similar. However, the effects of those agents on tissue fibrosis have not been determined.

I explored the roles of ETR type B expressed on cultured fibroblasts. And then I found the involvement of the signal via ETR type B in the fibrosis.

In conclusion, dual ETR antagonist should be selected in the treatment of PAH with connective tissue disease complicated in tissue fibrosis.

LS21

Surgical Management and Rehabilitation for the Rheumatoid Elbow

Katsunori Inagaki

Department of Orthopaedic Surgery, Showa University School of Medicine, Tokyo, Japan

To date, concept of the treatment of rheumatoid elbow has been changed and developed. Surgical management including arthroscopic synovectomy and elbow arthroplasty has been evolved as well. A reliable surgery must address a spectrum of pathology, have reliable outcomes, and be reproducibly performed. Total Elbow Arthroplasty (TEA) is now most reliable surgical procedure for Larsen Grade III and IV rheumatoid elbow. Between 1999 and 2010, we carried out a TEA on 70 patients in our practice by single surgeon. Clinical results of these series is quite well, the outcome for rheumatoid arthritis is particularly grafting with 95% survival at 7 years. The design, linked and unlinked, and materials of the total elbow prosthesis has been improved in the last several decades. Although there has been

the issue of TEA, with or without cement, selection of the implant: linked or unlinked, for the severe bone loss or osteoporotic stove pipe bone, overall results and patient's satisfaction and QOL after TEAs are quite high. It is important to have knowledge of implant specificity from the view point of elbow biomechanics: kinematics, laxity and intrinsic stability. The surgeon should know the surgical indication including selection of the implant, and right rehabilitation before and after surgery.

LS22-1

Pathogenesis and treatment of SLE: an Update

Takahiko Horiuchi

Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences

Introduction of corticosteroids and cyclophosphamide in the clinic greatly contributed to the improvement of prognosis of systemic lupus erythematosus (SLE). However, the quality of life (QOL) of the survivors of SLE has become an problem in recent years. For example, osteoporosis and arteriosclerosis are representative side effects caused by corticosteroids. In addition, there remain SLE patients that are resistant to conventional therapies. In order to overcome the limitations of the conventional therapies, new treatment modalities are being tried for SLE patients.

I would like to present the recent progress concerning the pathogenesis of SLE clarified by the epidemiologic study and genetic analysis. In addition, new therapies on SLE are presented. Among these treatments, molecular targeting therapies and hematopoietic stem cell transplantation (HSCT) are included. The issues to be solved in performing SLE study will also be presented.

LS22-2

Efficacy and safety of tacrolimus for steroid refractory patients with SLE

Masaya Mukai, Makoto Kondo

Department of Rheumatology, Sapporo City General Hospital, Sapporo, Japan

Purpose: We evaluated the efficacy and safety of Tacrolimus (TAC) for steroid refractory patients with SLE.

Method: We picked up the SLE patients treated with TAC. We checked retrospectively the reason of adding TAC, steroid dose, and the levels of complement, anti-DNA antibody, and SLEDAI. We defined the efficacy as following: A-1; steroid could be decreased less than the dose once increased in relapse, A-2; steroid could be decreased more than 50% at the dose of starting TAC without relapse, A-3; steroid could be decreased more than 20%, A-4; steroid could be decreased less than 20%, B; steroid could not be decreased but the symptoms and/or laboratory data were improved, C; steroid dose and symptoms were not changed, D; SLE was worsen. E; TAC was discontinued because of side effect, and F; impossible to judge.

Results: We found 63 patients treated with TAC from 228 patients with SLE. They were 8 males and 55 females, and their average age was 36.6 ± 12.7 year-old. All patients had some difficulty to taper their steroid dose such as elevation of anti-DNA antibody 29 cases (46.0%), hypocomplementemia 8 cases (12.7%), proteinuria 8 cases (12.7%), skin lesions 20 cases (31.7%), arthritis 2 case (3.1%), and thrombocytopenia 2 cases (3.1%). The efficacy was as follows: A-1; 3 cases (4.8%), A-2; 14 cases (22.2%), A-3; 23 cases (36.5%), A-4; 3 cases (4.8%), B; 8 cases (12.7%), C; 2 case (3.2%), D; 6 cases (9.5%), and E; 4 case (6.3%). Forty-three cases (68.3%) could be decreased their steroid doses. Adverse effects were occurred in 7 cases. A female case with uncontrolled lupus nephritis died because of

bacterial endocarditis.

Conclusion: We considered that TAC was very effective for the many clinical features of SLE including nephritis and was relatively administered in safe. Especially, TAC was most effective for severe skin lesions, especially chilblain lupus. We found that TAC could induce steroid tapering effect for steroid refractory patients with mild SLE.

LS23

Management of Chronic Nonmalignant Pain - Multimodal Treatment of Moderate to Severe Pain and the Role of Ultracet -

Richard Langford

Barts and The London NHS Trust, London, UK

Chronic pain is highly prevalent (19% in a large survey in Europe) but frequently under-estimated.¹ Musculoskeletal pain in the elderly is common with major impact on quality of life.²

Treatment is often multidisciplinary and based on management of the pain and underlying disorder: lifestyle advice, physiotherapy, cognitive behavioral therapy, acupuncture, pharmacological approaches and interventional procedures. Successful pharmacological treatment depends on appropriate selection and titration of analgesic drugs, and is based on the mechanism (inflammatory, neuropathic, visceral, psychological), the magnitude of pain and patient specific factors such as co-morbidities and intolerability issues. Simple analgesics are often tried first, though paracetamol (as known as acetaminophen) has a narrow therapeutic window, and non-steroidal anti-inflammatory drugs are often poorly tolerated gastro-intestinally (GI), and in long term use they may lead to life-threatening complications: peptic ulceration, perforation and bleeding, thrombotic events (myocardial infarction; stroke) and renal failure. By contrast, opioid analgesics do not cause serious cardiorenal or GI complications, even in long-term use, although tolerability may be an issue due to nausea, dizziness, somnolence and constipation. Hence, multimodal analgesic treatments are recommended to minimise the opioid dose, and fixed-dose combinations of codeine with paracetamol have been widely used. The recently developed combination of 'Ultracet' also known as "Tramcet" in Japan (tramadol 37.5mg and paracetamol 325mg in each tablet) has been shown to achieve similar analgesic efficacy to existing comparators (paracetamol/codeine or tramadol) and improved tolerability in a variety of musculoskeletal conditions such as osteoarthritis, including flares, and low back pain.³⁻⁶ It is hypothesised that combining multiple (including tramadol's mono-aminergic) mechanisms of action and complimentary pharmacokinetic profiles permit reduced doses to achieve similar analgesia, with a wider safety margin and fewer opioid related side-effects. The 'Ultracet' combination has also been shown to be of value in acute pain after hand surgery. In healthy human volunteers, it has been shown to cause less somnolence or effect on cognitive function than paracetamol/codeine. Other advantages of tramadol over codeine, relate to less reliance on the CYP2D6 enzyme for metabolism to active analgesic entities, and reduced risk of constipation. The Ultracet (paracetamol/tramadol) combination offers an effective, safe and well-tolerated analgesic option.

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3. Schug S. Clin Rheumatol 2006; 25 (suppl 1): 16-21

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LS24-1

The treatment strategy for the patients with established rheumatoid arthritis

Naoki Ishiguro

Department of Orthopedic Surgery Nagoya University, School of Medicine

Rheumatoid arthritis (RA) is a chronic inflammatory disease, and the causes are still unknown. Also RA is considered as the disease that may lead to several joints damages (related to each other) that substantially abolish important aspects of the individuals' daily life in their typical forms. The RA is associated with pain, stiffness, fatigue, impairment to perform everyday tasks, disability, loss of employment, loss of quality of life and even premature death. Now it is widely accepted that it is the most important goal of treatment to substantially suppress the disease activity and inflammation, and consequently to avoid or at least delay of structural damages of joints. For the established RA (ERA) patients, the term 'cure' appears to be a very ambitious goal with relatively low probability of occurring. So actual goal would be 'clinical remission' (a state of minimal disease activity) or low disease activity (alternative goal for established RA). Moreover, it had been proven that even patients with RA in clinical remission show substantial progression of radiographic damage and synovitis detectable by magnetic resonance imaging (MRI) and ultrasound. In the case of ERA, these conditions would be more likely, compared to early RA. However, the biologics DMARDs treatment provide the paradigm shift in RA therapy, even in ERA cases, we can achieve 'clinical remission' in more than 30% patients. In this lecture, I will focus on the management of the patients who have ERA.

LS24-2

Therapeutic strategies in early-stage RA

Atsushi Kawakami

Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences

Early and aggressive treatment is indispensable for the achievement of better prognosis of RA. Early diagnosis is required for the early therapeutic intervention. 2010 RA classification criteria is useful for this purpose if the patients are scored as higher than 6 points synthetic DMARDs are recommended. Especially MTX is a better choice for the subjects who possess poor prognosis factor including autoantibodies and high inflammatory markers. However, differential diagnosis of OA, Sjögren's syndrome and PMR is required in clinical practice. Plain radiograph is not sufficient to detect joint injury at earlier stages of RA, however, MRI and ultrasonography are good devices in such cases which are able to visualize synovitis and bone changes. Therapeutic response is better in early-stage RA than established RA and an induction of clinical remission is a major goal in early-stage RA. The clinical remission is important to prevent structural damage in RA. There are several composite measures to evaluate clinical remission in RA such as DAS28, SDAI and CDAI. The latter 2 are more stringent than DAS28, however, SDAI remission as well as CDAI remission are actually be achieved in early-stage RA if the proper anti-rheumatic therapies are introduced. Biologic DMARDs are added in cases who do not respond well to synthetic DMARDs. T2T algorithm is recommended to guide the patients into clinical remission. Patients' life style is considered for the choice of biologic DMARDs. Recently, an interruption of anti-rheumatic therapies are become to be evident after the clinical remission is induced in RA patients. Early-stage RA patients may be

advantageous in this issue as compared with established RA. Disappearance or significant reduction of PD signal in PDUS and that of bone edema in MRI may support the physician's decision in this case. Recent evidences of the therapies in early-stage RA will be reviewed in this seminar.

LS25

Long-term outcome and the future possibilities of tacrolimus in the RA treatment

Koichi Amano

Saitama Medical Center, Saitama Medical University, Kawagoe, Japan

Tacrolimus has been developed in Japan as an immunosuppressive drug to inactivate T cells, which are deeply involved in the pathogenesis of rheumatoid arthritis (RA). Tacrolimus has been approved for RA and lupus nephritis in April 2005. The clinical data of 287 RA patients who had been treated with tacrolimus had been accumulated and were analyzed for the efficacy and safety. The demography of the patients: the average age was 61.8. The average disease duration was 10.8 years. Eighty one percent of the patients had some complications; osteoporosis 40%, hypertension 22%, diabetes 12%, interstitial lung diseases 12%. Synthetic DMARDs were used in 50 %; MTX 37%, salazosulfapyridine 11%, bucillamine 7%. Only 10% had biologic DMARDs. Glucocorticoids were prescribed in 82% of the patients. The average initial dosage of tacrolimus was 1.5 mg/day. The rate of continuation of tacrolimus at 2 year was about 60%. Safety: Adverse events (AEs) were seen in 56% of the patients; laboratorial abnormalities 25%, infection 16%, gastrointestinal 10%, metabolic 7%, cutaneous 5%, renal 4% and hepatobiliary 3%. Re-evaluation revealed 13% had renal disorders and 9% showed impaired glucose tolerance. Malignancies were reported in 8 cases (4 lung, 1 prostate, 1 colon, 1 bile duct cancer and 1 lymphoma). Efficacy: ACR-20 response rate at 24 week for 116 patients who could be evaluated was 40% and ACR-20 at 1-year (n=85) was 50% and ACR-20 at 2-year (n=63) was 50%. Conclusion: Considering the patients' background (most of them were older with longer disease duration and had some complications), the efficacy of tacrolimus may be good and tacrolimus seems to be well tolerable with little major safety problems. Renal dysfunction and glucose intolerance should be monitored carefully during tacrolimus therapy. According to the several literatures, tacrolimus will be useful for MTX-intolerable patients and combination with MTX may be good for patients with inadequate response to MTX.

LS26-1

Cardiovascular events in RA - Influence by inflammation and NSAID-

Yutaka Kawahito

Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

The use of biological reagents made it possible to achieve clinical remission of patients with rheumatoid arthritis (RA). Nonsteroidal anti-inflammatory drug (NSAID) is now positioned as a supportive treatment for rheumatoid arthritis. But the use of NSAIDs is required for benefits of pain relief and important at the start of treatment. Selective COX-2 inhibitors as safe medicines for gastrointestinal tracts have been coming up, because they don't suppress COX-1 activity which guides production of physiological PG. However, the cardiovascular safety of selective COX-2 inhibitors has recently been questioned, it is becoming clear that non-selective NSAIDs as well as selective COX-2 inhibitors have side effects of

cardiovascular (CV) events. CV events are popular as a complication for patients with RA and onset risk is reported to be same as in patients with diabetes mellitus in western country. In this seminar, I demonstrate the effect of NSAIDs to arteriosclerosis and CV events, and relationship between arteriosclerosis and inflammation due to RA.

LS26-2

Mechanism for NSAID-induced gastric ulcer

Tohru Mizushima

Graduate School of Biological Sciences

We recently showed that NSAIDs such as indomethacin and celecoxib have direct cytotoxicity (ability to induce necrosis and apoptosis in gastric mucosal cells) due to their membrane permeabilizing activities, which is involved in NSAID-induced gastric lesions. We show here that under conditions where indomethacin and celecoxib clearly induce necrosis and apoptosis, loxoprofen do not have such effects in cultured gastric mucosal cells. Loxoprofen exhibited much lower membrane permeabilizing activities than did indomethacin and celecoxib.

LS27

Effective usage of etanercept in dairy practice - RA case studies

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Norihiro Nishimoto

Laboratory of Immune Regulation, Wakayama Medical University, Wakayama, Japan

Treatment landscape of rheumatoid arthritis (RA) changed entirely after biologics, which show potent anti-inflammatory activity and preventing effect against joint destruction, became available clinically. TNF inhibitors, such as etanercept, infliximab and adalimumab, tocilizumab that blocks IL-6 receptor, and abatacept that inhibits T cell activation, are available in Japan, and these medications increase treatment options for RA.

Etanercept is one of the most popular biologics in use worldwide. Post-marketing surveillance of etanercept enrolling about 14,000 Japanese RA patients and the following long-term use in daily practice elucidated that the treatment is generally well tolerated. In the COMET trial in which patients with early onset RA were treated with etanercept, excellent efficacy in terms of remission rate and preventing structural damage was shown. Besides, aggressive treatment also produced long-term benefits including improvement of QOL.

However, RA patients often have various complications, and we feel reluctant to have aggressive treatment with biologics for such patients. Treatment option of the second line biologic has not been fully determined yet for patients with the first anti-TNF failure. Since safety of biologics has not been established for fetus and infants, introduction of biologics has to be considered carefully for patients who wish to become pregnant.

In this seminar, I, as a self-proclaimed expert on IL-6 inhibitor, will introduce several controversial cases i.e. (1) a patient refused to use etanercept, (2) a refractory patient wished to become pregnant, (3) a patient failed to respond to the first anti-TNF agent, (4) a refractory patient with severe lung disease, (5) a patient repeatedly suffered from tonsillitis, (6) an aged patient showed no febricity with bacterial pneumonia, to show how to choose the treatment based on my daily practice experiences, and finally discuss an effective usage of etanercept.

LS28

A New Wave in Treating Gout and Hyperuricemia by a Novel Xanthine Oxidase Inhibitor (XOI) Febuxostat – sUA ≤ 6.0 mg/dL-

Hisashi Yamanaka

Professor of Medicine and Rheumatology, Director of Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Gout is a syndrome including acute arthritis, tophi, renal impairment and urinary stones caused by urate deposition with persistent hyperuricemia (HU). It has also been noted that patients with gout and HU are prone to obesity, glucose intolerance, and hypertension. Though the incidence of gout and HU has been globally increased, there is no internationally-agreed treatment guideline. We are promoting standardization of treatment based on "Guideline for the management of hyperuricemia and gout" (revised in 2010) 1) developed in the Japanese Society of Gout and Nucleic Acid Metabolism. Gouty attacks are more likely to occur when serum urate level (sUA) persists over 7.0 mg/dL. Incidence of recurrent gouty attacks, however, was reduced below 20 % when sUA is maintained under 6.0 mg/dL 2). Thus patients with HU are recommended to target and maintain sUA under 6.0 mg/dL. As it is known that the risk of lifestyle-related diseases increases as elevation of sUA, treatment with urate-lowering (UL) drugs should be considered if concomitant diseases (renal impairment, hypertension, CVD, metabolic disease, etc) exist in HU patients even without gouty attacks. Allopurinol has been widely used for treatment of gout and HU. It is well tolerated, but has some safety issues and inconvenience requiring dose adjustment for patients with renal impairment. Under such circumstances, a novel UL drug, febuxostat, which is the new XOI and has already launched in the US, Canada and EU, receives attention. Febuxostat needs no dose adjustment for patients with mild to moderate renal impairment since it has dual excretion mechanism. Clinical results indicate that febuxostat demonstrates a potent serum UL effect and keeps the sUA below 6.0 mg/dL for long time. Besides, febuxostat was effective and tolerated in the patients with mild or moderate renal impairment without dose adjustment 3) In this lecture, current views on the management of gout and HU with a new XOI, febuxostat, will be provided.

LS29

CR type TKA with medial constrained plastic insert

—in order to gain sufficient flexion angle by CR type TKA—

Koh Shimizu

Institute of Orthopaedics, Chiba Rohsai Hospital, Ichihara, Japan

Further improvement of the flexion angle is necessitated in TKA, although pain relief and tolerance are sufficient in the majority of cases due to improvement of implants and surgical procedure. Recently, PS type TKA has increased in Japan, due to the lesser difficulty of its surgical procedure, and easier induction of good flexion angle and kinematics. However, in the U.S.A., the CR type TKA has been more popular compared to the PS type TKA, due to incidences of some problems with the PS type, including wear of the post, dislocation, and low tolerance. Following this tendency, it is expected that the CR type TKA will also increase in Japan; however, a CR type TKA with good flexion angle is needed to accommodate the Japanese lifestyle. Medial constrained type TKA has good potential in gaining deeper flexion.

There were three kinds of CR type TKA included: flat type, both medial and lateral plastic inserts are flat and joint line is perpendicular to the tibial axis; constrained type, both medial and lateral plastic

inserts are constrained and joint line is perpendicular to the tibial axis; and medial constrained type, medial plastic insert is constrained and lateral is flat, and joint line is 87 degree to the tibial axis, and these three kinds of CR type TKA were compared.

Postoperative flexion angle was best in the medial constrained type, followed by constrained type and flat type; and although statistical differences existed between the three types, clinical results were sufficient in all three types. Furthermore, a correlation between the joint line and flexion angles were observed in the flat type and constrained type implants. These results suggest that the angle of the joint line affects the flexion angle. In kinematics analysis of the knee by fluoroscopy, knees with the medial constraint type implant revealed more anatomical and physiological motion, including medial pivot motion and lateral roll back motion, compared to those with the flat type and constrained type.

Although use of the medial constrained type implant will produce the best results, there are other factors, such as surgical techniques and rehabilitation, which will affect the end results.

LS30

Current concepts in Total Joint Arthroplasty for Rheumatoid Arthritis Patients in Europe

Beat R. Simmen

Upper Extremity and Hand Surgery Schulthess Klinik Zurich, Switzerland

The destruction of the large joints in rheumatoid arthritis (RA) patients is common and has been a challenge for the orthopedic surgeon, not only in Europe, for many years. Total hip arthroplasty and total knee arthroplasty with a high survival rate at 10-year follow-up may now be considered as gold-standard procedures for RA patients. Also at other joints, the development of new prosthesis designs have improved the outcome and the survival rate after joint arthroplasty in RA patients. This positive development has been proven with statistically sound data from the rising numbers of national registries in Europe, especially those long-established arthroplasty registries from Scandinavian countries.

In addition, the outcome success is also supported by the use of patient-reported evaluations (e.g. quality of life, subjective joint function) that have gained importance in the outcome documentation of joint arthroplasty and other therapies. Based on these evaluations, evidence has been provided that the pre-operative status of the joint/extremity determines the extent of post-operative functional gain. Thus, postponing joint arthroplasty for too long will give less functional benefit.

Clinical observations in RA patients indicate that the course of the disease has become milder during the latest past decade. Less severe symptoms as well as the declining need for joint arthroplasties are most likely the result of more potent drugs. According to our own experience, the number of arthroplasties due to underlying RA remained stable, whereas the number of large joint arthroplasties due to advanced osteoarthritis increased from 1997 to 2007. This fact emphasizes the positive trend in times of generally increasing rates of joint arthroplasties.

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 (OA) patients for example.

LS31

Diagnosis and Treatment of Infectious Diseases Learnt from Clinical Cases

Hiroshige Mikamo

Department of Infection Control and Prevention, Aichi Medical University Graduate School of Medicine, Aichi

In Harrison's Principles of Internal Medicine published in 1981, there is a description with "Bacterial infections are the most easily diagnosed and easily managed of all disease processes...". Everyone does not believe this description now. On the contrary, everyone has thought that to treat infectious diseases would be difficult since various problems have been always appearing. Although it has seemed that infectious diseases had been suppressed according to spread of the concept of public health and development of excellent antimicrobial agents, and so on, emerging and re-emerging infectious diseases have appeared all over the world. Appropriate antimicrobial chemotherapy would be based on understanding "host-parasite-drug relationship". While, various guidelines presented by each medical society would be useful to practice appropriate antimicrobial chemotherapy. However, we should not forget that all guidelines were established on the basis of clinical cases. Koch's postulates are four criteria designed to establish a causal relationship between a causative microbe and a disease. Koch's postulates are as follows; (1) The microorganism must be found in abundance in all organisms suffering from the disease, but should not be found in healthy animals. (2) The microorganism must be isolated from a diseased organism and grown in pure culture. (3) The cultured microorganism should cause disease when introduced into a healthy organism. (4) The microorganism must be reisolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent. In other words, a case would lead to the gold standard. In this seminar, I would be willing to offer the opportunity to think diagnosis and treatment of infectious diseases by presenting actual clinical cases.

LS32

Significance of intra-articular injection as a local therapy for rheumatoid arthritis

Koichi Nakagawa

Department of Orthopaedic Surgery, Toho University Sakura Medical Center

Recently, medication therapy for rheumatoid arthritis (RA) has been established with the advent of biologics, which provide better control of systemic inflammatory response. However, localized inflammation could persist with further degeneration of bone and articular cartilage, especially in weight-bearing joints such as the knee joints. In such cases, a local therapy is needed to get rid of the symptom.

Local therapies for RA include intra-articular injection, joint lavage, arthroscopic synovectomy and so on. Among them, intra-articular injection should be the first choice because it can be done easily at outpatient clinic. Corticosteroids and hyaluronate sodium are commonly-used medication for intra-articular injection. Intra-articular corticosteroid injection is known to have risks of side effects such as osteonecrosis and crystal-induced arthritis. On the other hand, hyaluronate sodium is thought to be useful for RA with less risk of adverse effect, because it has already been applied to osteoarthritis safely for a long time.

When hyaluronate sodium is used for RA, selection of the cases is the most important. The first requirement is to control general inflammation by medication. To promise a certain level of effect with hyaluronate injection, it is preferable that local warmth and swelling of the affected joint is minimal. If the local swelling is due to joint effusion, but not to synovial hypertrophy, the effect of hyaluronate sodium is more promising. In addition to careful palpation, ultraso-

nographic examination is useful to determine the indication. While the number of severe RA cases with multiple joint destruction has decreased, the cases with localized joint pain due to persisting osteochondral lesions have been increasing. Local therapies including intra-articular injection are expected to become of particular importance for the treatment of such RA cases.

LS33

Genetic study on rheumatic diseases

Kazuhiko Yamamoto

Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo

Rheumatic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are considered to be multifactorial disorders. Several genetic and environmental factors are contributing to the pathogenesis. Technical advances in human genetics, especially genome wide association study (GWAS), have enabled the screening of the whole human genome for disease susceptibility genes. The information from these genetic studies has contributed to a greater understanding of molecular mechanisms underlying autoimmunity. We now know that several autoimmune susceptibility genes are shared between diseases but some genes appear to be unique. Several susceptibility genes fall within a discrete biological pathway, such as the nuclear factor kappa-B, suggesting that the pathway is essential for the development of the disease. Among the genetic predisposition factors, some variants were found to be restricted to specific ethnic groups. Other genetic factors were revealed to exert different magnitudes of risk for disease among different populations. These might be explained by their interactions with other genetic and environmental factors.

However, GWAS reveals common variants in common diseases. It has also recently been reported that rare variants contribute to common diseases such as autoimmune diseases. Thus, further studies should be done before we can understand precise mechanisms of rheumatic disorders and utilize these findings on personalized medicine.

Evening Seminar

ES1-1

Achieving normal physical function by remission induction of RA with infliximab

Hideto Kameda

School of Medicine, Keio University

The therapeutic goal of rheumatoid arthritis (RA) is the prevention of organ damage leading to disability, morbidity and mortality. Therefore, a prompt diagnosis as RA before developing irreversible joint damages, the understanding of disease activity as the time-differentiated organ (joint) damage, and the effort on remission induction by the right deadline according to the severity of each patient. However, some patients are still referred to us with an advanced disease, and low disease activity, instead of remission, may be a realistic goal for those patients. Thus, “Treat to Target” should be tailor-made for each patient.

Nowadays methotrexate (MTX) is the anchor drug for RA treatment. However, more than 70% of RA patients were not sufficiently controlled with MTX, requiring further therapy such as concomitant anti-TNF biological agents. MTX at a dose of 16 mg/week or greater can be approved in Japan in 2011. Similarly, the dose of infliximab should be strictly titrated according to the residual disease activity after the initial loading, because the optimal dose and interval of infliximab administration must be different among RA patients. The maintenance of serum infliximab concentration may be chiefly affected by the amount of molecules binding to infliximab such as serum TNF content and the development of anti-infliximab antibody.

When we take cost-risk-benefit balance into account, it would be better for us to choose other therapeutic strategies in maintenance phase than those in remission induction phase. RRR study suggested that infliximab could be successfully withdrawn in nearly a half of patients after sustained remission for 6 months. To further decrease the rate of disease flare after discontinuation of infliximab, BuSHIDO trial, in which the efficacy and safety of the addition of bucillamine upon infliximab withdrawal have been investigated, is ongoing. These clinical trials can facilitate an earlier introduction of infliximab for RA patients.

ES1-2

Orthopaedic therapeutic strategy for “no functional damage of the joints” in RA

Keiichiro Nishida

Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences

Recent advances in pharmacologic therapy against rheumatoid arthritis (RA) made “Treatment toward less joint damage and better physical function” possible even for the at least two groups of patients with moderate to high disease activity. One group is consisted of patients with early active arthritis, who reached clinical remission by intensive management before joint damage developed, and no progression of joint damages. These outcomes can be achieved by “early diagnosis” by ACR/EULAR 2010 new classification criteria, and “tight control of disease activity.” ACR/EULAR definition of remission uses SDAI and CDAI as more strict measures of disease activity. However, one should caution that impact on physical function is considerably different whether a joint swelling remains in a small joint or a large joint. It is noteworthy that identification of clinically discerned joint swelling or judgment for active synovitis requires high resolution imaging modality such as MRI and sonography.

Another group is consisted of patients with established long-standing disease, who achieved low disease activity (LDA) as an acceptable alternative therapeutic goal, even after considerable joint damages. These patients may have irreversible physical disability due to prior joint damages, or progressive joint destruction in spite of LDA. As these conditions have been regarded as an ideal indication for surgical intervention, the number of surgery is increasing among these patients with LDA, which is well controlled by biologic-DMARDs. Obviously, patient's demands are bound for re-acquisition of higher grade of ADL. The combination of surgical intervention with intensive pharmacologic therapy is an important strategy for RA patients with LDA to make "no functional damage of the joints" possible by the reconstruction of irreversible joint function to meet each patient's needs.

ES2-1

Prevention of dislocation and eccentric motion in Kudo Total Elbow Replacement

Katsunori Inagaki

Department of Orthopaedic Surgery, Showa University School of Medicine.

The current focus of the resurfacing total elbow replacement is restoration of normal kinematics without compromise of stability. It would appear that an appropriate design and positioning of the humeral and ulnar component are essential to reduce the risk of dislocation and aseptic loosening.

Kudo unlinked total elbow replacement is technically demanding surgery. We would advise particular care when inserting both the trial and definitive components in order to be certain that there is no mal-rotation of ulnar component and accurate positioning of valgus / varus humeral component such that the anatomical axis of movement should more closely replicated to native anatomy of the elbow. While instability has been observed with unlinked total elbow replacement, the loosening rate depends upon the prosthetic design. Use of reasonable design of implant and appropriate surgical technique would decrease dislocation and eccentric motion, decrease stress on the ulno-humeral articulation and therefore possibly reduce polyethylene wear, osteolysis, and loosening.

ES2-2

Surgical techniques of Kudo type-5 Total elbow arthroplasty

Toshihito Mori

Department of Orthopedic Surgery, NOH Sagamihara Hospital, Sagamihara, Japan

Total elbow arthroplasty is very much useful for pain relief from severely damaged rheumatoid elbow and osteoarthritis in the elderly as well as its functional restoration. Total elbow prostheses in our current use are divided into two: linked type and unlinked type. Kudo total elbow prosthesis, which is of unlinked superficial replacement type with intrinsic constraint, can be applicable to severe mutilating elbow with bone graft, to achieve a long-term stability. Since 1993, Kudo type-5 prosthesis has been used. Humeral component is made of cobalt chrome alloy, with a portion of stem being coated with porous titanium alloy for cementless use. The non-porous titanium coated humeral stem can be selected for cemented use. Ulnar component is strengthened by metal-backing at the artificial joint of UHMW polyethylene, which requires cement for fixation. Surgical indications and techniques with Kudo elbow prosthesis and cautions for surgery are explicated in the K-elbow surgery procedures manual by Dr. Kudo. In the present seminar, I would like to introduce you to what I pay attention to when I perform the surgery.

Primary precautions:

1. To properly insert the humeral and ulnar components, it is essential to understand anatomy and design of Kudo elbow prosthesis. Keep in mind the following: Articular surface of humeral component covers trochlea and capitulum of humerus; medullary cavity of humerus is located slightly laterally; and, articular surface axis of humerus is internal rotated by about 5° from the proximal humerus.
2. Kudo elbow prosthesis is designed so that ulnar component and rotation axis of joint are located slightly lower as compared to the normal joint. To prevent ulnar component from being inserted with the end elevated, it is necessary to adequately resect olecranon. Without adequate resection of olecranon process, the ulnar component may be inserted with the end elevated, causing dislocation and limited extension.
3. It is most critical to suture the lateral fascia on the back of olecranon without fail, to prevent post-operative dislocation. Also, it is essential to confirm the tightness of joint by the push-up test following the suture.

ES3-1

Treating ra to target: A new concept to optimize care for rheumatoid arthritis

Josef S. Smolen

Division of Rheumatology, Department of Medicine III, Medical University of Vienna, and 2nd Dept of Medicine, Hietzing Hospital, Vienna, Austria

The "Treat-to-Target" (T2T) concept for the management of rheumatoid arthritis (RA) combines several insights obtained during the last years. Firstly, in clinical remission progression of joint damage and thus progression of irreversible disability are halted – thus remission is the primary therapeutic target. Secondly, it was repeatedly shown that a systematic approach to control examinations using composite disease activity indices and adapting treatment if a predefined therapeutic target is not reached conveys much better clinical, functional and radiographic results than an unstructured approach. And thirdly, if patients do not attain low disease activity or remission within the first 3-6 months of a new therapy, they are unlikely to reach that status subsequently. The T2T concept leads to optimization of care for RA – for the sake of the patient and as a clearly formulated aid for the treating physician during decision making.

The new EULAR recommendations for the management of RA comprise the T2T concept in regards to the therapeutic aims, but suggest particular agents and sequences of therapeutic modalities and stratifications. Among these agents, positioned in context with available evidence, are biological agents such as tocilizumab.

Also, meanwhile ACR and EULAR have newly defined remission and this definition is very stringent. Remission is now defined as an SDAI ≤ 3.3 or a maximum of 1 tender, 1 swollen joint, 1cm of pt. Global assessment and 1mg/dl CRP. This definition together with new therapeutic agents and treatment strategies will allow to optimize outcomes in RA

ES3-2

Effectiveness and safety of Tocilizumab in patients with Rheumatoid Arthritis in daily clinical practice (the REACTION study at 52 weeks)

Tsutomu Takeuchi

Division of Rheumatology, Department of Internal Medicine, School of Medicine, Keio University, Tokyo, JAPAN

Rheumatoid arthritis (RA) is a chronic inflammatory disease mediated by the production of various cytokines such as tumor ne-

crosis factor (TNF), interleukin-1 and interleukin-6 (IL-6). Tocilizumab (TCZ) is a humanized anti-human IL-6 receptor monoclonal antibody that was created in Japan. TCZ inhibits both of soluble form and membrane bounded IL-6 receptor-mediated signaling transduction through gp130 pathway. TCZ is widely started to use in the treatment of RA refractory to DMARDs and TNF blockers. However, at the time of approval, limited data were available about the efficacy and safety in daily practice in the real world. Therefore, we conducted to investigate the efficacy and safety of TCZ through a multicenter retrospective study (REACTION study -52weeks) in Japan. Clinical remission which defined as DAS28-ESR<2.6 was achieved in 42% of patients, and 55% of the patients reached low disease activity criteria after 52 weeks TCZ treatment. The estimated yearly progression of mTSS was also significantly improved from 26.0 at baseline to 1.1 at week 52 ($p<0.0001$). Cumulative probability analysis showed that progression of joint damage was inhibited in 62.8% of patients. After 52 weeks TCZ treatment, the HAQ score decreased from 1.56 at baseline to 1.29. Defined as HAQ score ≤ 0.5 , functional remission was achieved by 26.4% of patients. In a multiple regression analysis, baseline HAQ score before TCZ treatment was an important factor that influences clinical, structural and functional remission at 52 weeks with TCZ. Currently, the safety profile of TCZ in the real world has been established by the interim analysis report which consists of 3,881 patients from all patient survey and is similar to the information from the clinical trials. Update information for safety and efficacy of TCZ will be presented in this symposium.

ES4

What should the goal of PAH treatment be?

Hiroshi Matsubara

Department of Cardiology, National Hospital Organization, Okayama Medical Center, Okayama

During the last decade, several therapeutic agents have been developed for the treatment of pulmonary arterial hypertension (PAH). However, a recent registry analysis in France demonstrated that the prognosis of patients with idiopathic pulmonary arterial hypertension (IPAH) who received various therapeutic agents was not improved compared with calcium-channel blocker monotherapy. Therefore, the strategy and goal for the treatment of PAH should be re-evaluated.

We have already demonstrated that improvement in hemodynamic parameters such as mean pulmonary arterial pressure (mPAP) and cardiac index through clinical intervention is closely related to the long-term survival of IPAH patients. In our facility, 28 IPAH patients whose mPAP was below 45 mmHg after clinical intervention all survived for more than 10 years. In contrast, the 5-year and 10-year survival rates of 18 patients who failed to meet this criterion were 70% and 30%, respectively. This suggests that improvement in hemodynamics, especially a rapid and sufficient decrease in mPAP, was important for the successful treatment of IPAH. For this purpose, we believe that all therapeutic options should be considered at the start of treatment.

If oral therapy does not produce sufficient clinical benefit within 2–4 weeks, we start intravenous PGI₂. However, even in such cases, long-acting drugs that can be administered orally still seemed to be promising because they made it possible to reduce the amount of PGI₂, alleviating its adverse effects. Our treatment strategy was also effective in the treatment of PAH associated with systemic lupus erythematosus or mixed connective tissue disease. In this seminar, we present data to verify the validity of our therapeutic goal, and we

suggest that the strategy for the treatment of PAH should aim to improve the long-term survival of patients.

ES5-1

Mechanisms of action of abatacept and its use with concomitant methotrexate

Hideto Kameda

School of Medicine, Keio University

Abatacept is a fusion protein of CTLA-4 and IgG1-Fc, which is believed to be effective in immune-mediated diseases such as rheumatoid arthritis (RA) through the binding to CD80/86 on the cell surface of antigen-presenting cells and the inhibition of CD28-mediated co-stimulatory signals in T cells, leading to the activation of T cells.

The AIM study investigated the efficacy of abatacept with concomitant methotrexate (MTX) in patients with MTX-refractory RA. In the AIM study, the ACR 20 response rate at 6 months was significantly better in the abatacept group than in the placebo group (67.9% versus 39.7%; $p<0.001$). In addition, the rate of patients who showed an improvement in HAQ-DI score by 0.3 or greater at 1 year was higher in the abatacept group than in the placebo group (63.7% versus 39.7%, $p<0.001$), and the radiographic progression assessed by Genant-modified Sharp score was 0.25 versus 0.53, respectively ($p=0.012$).

The ATTEST trial compared the usefulness of abatacept to infliximab at a dose of 3 mg/kg with 8-week interval in MTX-refractory patients. The mean DAS28-ESR was approximately 6.8 at baseline, and it decreased by 1.48 in the placebo group, by 2.25 in the infliximab group, and by 2.53 in the abatacept group (both $p<0.001$ versus placebo) at 1 year. Over 1 year, serious adverse events (9.6% versus 18.2%) and serious infections (1.9% versus 8.5%) were lower with abatacept than infliximab.

In the AGREE study, patients with RA for 2 years or less were randomly assigned 1 : 1 to receive abatacept + MTX, or placebo + MTX. At year 1, a significantly greater proportion of abatacept + MTX-treated patients achieved DAS28-CRP<2.6 (41.4% versus 23.3%; $p<0.001$) and there was significantly less radiographic progression (mean change in Genant-modified Sharp score 0.63 versus 1.06; $p=0.040$) against MTX alone.

Thus, abatacept has been proved to be clinically and radiographically effective in both MTX-naïve and MTX-refractory patients with RA with fair safety profiles.

ES5-2

Treatment of Rheumatoid Arthritis Update: Efficacy of Abatacept in Refractory RA

Mitsumasa Kishimoto

Section of Allergy and Rheumatology

With regard to treat to target, the ultimate target of RA treatment is said to be achieving a remission or low disease activity in all patients as swiftly as possible. However, since achievement of this target is difficult in some patients, development of new therapeutic drugs has been sought.

Abatacept selectively inhibits full T cell activation by blocking the costimulatory pathway. Its mechanism of action is completely different from that of established cytokine inhibitors.

In the ATTAIN study in patients who failed TNF inhibitors, ACR 20, 50, and 70 rate in the abatacept + DMARD group were 50.4%, 20.3%, and 10.2%, respectively, which were significantly higher than those in the placebo + DMARD group. A low level of disease activity or remission rate increased in the abatacept group during the

period from Month 6 to Year 3. Meanwhile, a discontinuation rate due to poor response was as low as 12.9% at Year 1, 5.4% at Year 2, and 2.4% at Year 3. These results have demonstrated that the success rate for the abatacept treatment target may increase through long-term administration.

From the results of the ARRIVE study, it is suggested that wash-out is not always necessary when switching from TNF inhibitors to Abatacept.

In the ADJUST study in patients with undifferentiated inflammatory arthritis (UA), 46.2% of abatacept and 66.7% of placebo group were diagnosed with RA at Month 12, showing no significant difference between the two groups. Since no similar results have been reported for other biologics, further accumulation of data is awaited regarding abatacept treatment in patients with early RA.

In the U.S., abatacept is used in more than 60 thousand patients. In this symposium, I will demonstrate some important points about using abatacept in patients with refractory RA.

ES5-3

Evidence for Abatacept in Japan

Mitsuhiro Iwahashi, Jiro Yamana, Keisuke Kobayashi, Rie Sasaki, Motoaki Kin, Seizo Yamana

Institute of Rheumatology, Higashihirosima memorial hospital, Higashihirosima, Japan

Abatacept (ABT), a selective T-cell costimulation modulator, was approved in Japan in July 2010 as the fifth biological medicine for treatment of rheumatoid arthritis. In the phase II study of ABT in RA patients who had an inadequate response to methotrexate (MTX), placebo, ABT 2 mg/kg, or ABT 10 mg/kg were administered on Days 1, 15, 29 and then every 4 weeks. The ACR 20 response rate at Day 169, the primary endpoint, was 21.2% in the placebo group, 62.7% in the ABT 2 mg/kg group, and 77.0% in the ABT 10 mg/kg group, demonstrating that the response rate in patients treated with ABT was significantly higher than that in patients treated with placebo. The remission rate, DAS28-CRP < 2.6, was 1.5% in the placebo group, 14.9% in the ABT 2 mg/kg group, and 24.6% in the ABT 10 mg/kg group. In the phase III study, body weight (BW)-based fixed doses equivalent to 10 mg/kg (BW < 60 kg: 500 mg, 60 kg ≤ BW ≤ 100 kg: 750 mg) were administered to 13 patients who had participated in the phase I study and 178 patients who had participated in the phase II study. The treatment persistence rate at 48 weeks was as high as 100% in the patients who had participated in the phase I study and 93.8% in the patients who had participated in the phase II study, demonstrating the drug's excellence in terms of both efficacy and safety. In the phase III study, efficacy of ABT monotherapy was investigated in 26 patients who had no tolerance to MTX and had inadequate responses to DMARDs. At 48 weeks, the treatment persistence rate was 69.2% (18 patients) and the ACR 20 response rate was 88.9% (16 patients) (65.4% in the LOCF analysis). Incidence of serious adverse events in the phase II study was 1.5% in the placebo group, 0% in the 2 mg/kg group, and 3.3% in the 10 mg/kg group. In this symposium, I will stratify and analyze the data on Japanese clinical studies describe current experiences at our hospital, and discuss the position of ABT in treatment of RA.

ES6

The 9th Scientific Meeting of the Riumachi Frontier (RA Frontier)

Nobuyuki Miyasaka^{1,2}

¹Representative Organizer of the RA Frontier, ²Department of Medicine and Rheumatology, Tokyo Medical and Dental University

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 eight 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 4 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.

ES7

The meaningfulness of switching biologics for Rheumatoid Arthritis treatment

Tsutomu Takeuchi

Division of Rheumatology, Department of Internal Medicine, School of Medicine, Keio University, Tokyo, JAPAN

We can judge the efficacy in about three months after treatment when biologics (especially, TNF inhibitors) are used for rheumatoid arthritis (RA) treatment, and it is the time to be able to judge the first failure (no response) for ACR20 unachieved or no response in EULAR criteria. In these cases, increase of dose shortening of interval and concomitants as the increase of the efficacy are assumed. In general, escape phenomenon as second failure exists in DMARDs treatment, and a similar phenomenon is recognized in biologics too. The second failure is defined "the effectiveness judged in 2-3 months is lost". The second failure is distinguished from the first failure and decreasing efficacy. It might be caused by increase of disease activity, inadequate dose and production of antibody, especially, the decrease of trough value through production of antibody decrease. Actually, it is suggested that the inverse correlation is admitted between the half-life of infliximab and the disease activity in DAS28, based on the analytical result of RISING study and the outcome of ATTACT study. Moreover, the antibody (chimeric antibody and anti-adalimumab antibody) not only shortens the half-life of the drug but also can cause infusion reaction and injection site reaction. Therefore, the treatment for second failure is very important, rather than not causing second failure. In EULAR2009 recommendation, it is assumed, "it is necessary to administer other TNF inhibitors, abatacept, rituximab or tocilizumab to the RA patients whose TNF inhibitor firstly doesn't succeed". There are many reports that efficacy on RA patients who contain first failure, second failure and decreasing efficacy is reported by the switching to other TNF inhibitors or biologics for different target molecules. However, it has not

arrived to present a clear method of the switching in that case. In conclusion, if the administering biologics cannot be continued due to first failure, second failure, decreasing efficacy and adverse events, switching biologics is thought to be important choices as treatment methods.

ES8-1

The perioperative complications in RA patients treated with tocilizumab

Shigeki Momohara

Department of Orthopaedic Surgery, Institute of Rheumatology, Tokyo Women's Medical University

Tocilizumab is a humanized anti-human IL-6 receptor monoclonal antibody, which has been demonstrated to improve the symptoms of rheumatoid arthritis (RA). A recent article suggested that the milder course of disease has been due to improved medical treatment. Therefore, the success in the treatment of patients with RA using tocilizumab confirmed that IL-6 plays an important pathological role in RA, and further studies were required to determine the long-term safety and efficacy of tocilizumab treatment. However, it has been unclear whether the use of tocilizumab constitutes an independent risk factor for post operative surgical site infections. Some reports of joint surgeries in RA patients treated with tumor necrosis factor (TNF) alpha blockers have demonstrated no increase in the incidence of post-operative infection. On the other hand, other report suggests higher complication rates when using TNF blockers. These conflicting data left the effect of TNF blocker therapy on the risk of post-operative infection during orthopedic intervention unclear. Meanwhile, the perioperative mechanism of tocilizumab is also currently under review. Unfortunately, there were just two manuscripts reporting about features after joint surgery in RA patients treated with tocilizumab (Hirao M, et al. Ann Rheum Dis. 2008;68:654, Hiroshima R, et al. Mod Rheumatol. 2010 Sep 8). Therefore, this time we organized TOPP (TOcilizumab in Perioperative Period) Study, and collected data from 27 hospitals where the RA-related surgeries under the treatment of tocilizumab were performed. The aim of this study is to establish the perioperative management of tocilizumab. It is necessary to keep the characteristic manifestations of this biological agent in mind to find the complication like surgical site infection after surgery.

ES8-2

Out-of-box strategy for the prime therapeutic goal in patients with rheumatoid arthritis

Jun Hashimoto

NHO Osaka Minami Medical Center

Biological agents successfully relieve many patients from their suffering various diseases including rheumatoid arthritis (RA). People who developed the biologics and succeeded their clinical application have contributed the world immeasurably. And then we have to treat skillfully the patients with RA using these biologics efficiently as many as we can. Two strategic courses of intended action are needed to achieve our role.

One is the strategy for wide and adequate use of biologics aimed to relieve many patients with RA into remission or low disease activity. Since it might be the existing state of affairs that not all of patients with RA have the chance to be adequately treated with expertise of the rheumatologists or orthopaedic surgeons both in Japan and other countries, this strategic course might be the fundamental to improve the skill of the most doctors, resulting in improved average outcome of treatment. Another is out-of-box strategy for the

prime therapeutic goal in patients with RA available in era of biologics, which is being introduced in this lecture. This strategy aimed to both functional and/or cosmetic recovery could be performed with co-ordinated therapy by rheumatologist and orthopaedic surgeon. This must be indicated both in patients who fail to achieve remission or low disease activity and in cases with remission. Both of two strategies are required for much improvement of the treatment for RA in era of biologics. And these strategies are based on comprehensive and multidisciplinary team therapy with rheumatologist, orthopaedic surgeon, nurse, physical therapist and other many co-medicals.

ES9

Roles of rheumatologists in providing best clinical practice for PH

Masataka Kuwana

Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

Recently, prognosis in patients with connective tissue diseases (CTD) has been markedly improved by introduction of molecular-targeting drugs and progress of supportive therapies, but pulmonary hypertension (PH) still remains one of intractable conditions. Since a various forms of PH, including pulmonary arterial hypertension (PAH), PH owing to left heart disease, PH owing to interstitial lung disease (ILD), and chronic pulmonary thromboembolism, can be found in patients with CTD, it is critical to identify etiology of PH before initiating treatment. PAH is the most common form of PH in CTD patients, and patients with SSc or MCTD are at an extremely high risk of developing PAH while SLE is fairly common in Japanese patients with PAH-CTD. 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 drugs, such as prostanooids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors, have prolonged time to clinical worsening and survival. These treatments are able to prevent ongoing pulmonary vascular changes, but are incapable of reversing vascular remodeling. To further improve prognosis of PAH-CTD, 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, goal-oriented aggressive treatment strategy has been shown to improve functional outcomes. Effective PH management requires joint forces between rheumatologists, cardiologists, and pulmonologists. Rheumatologists play important roles in this collaboration by active screening of PH as part of the routine practice for identifying patients with early PH, detection of CTD patients in those with newly diagnosed PH, adequate classification of PH, and optimization of treatment regimen by taking disease activity of accompanying CTD and peripheral vascular disease into consideration.

ES10

The 13th Annual Meeting of Society for Surgery of the Rheumatoid Hand

Society for Surgery of the Rheumatoid Hand

The 13th Annual Meeting of Society for Surgery of the Rheumatoid Hand

"Rheumatoid Thumb Deformities"

1. Roll of the thumb
2. review

Hands-on Seminar

HS1

Ultrasonographic evaluation of synovial pathology (lecture + live demonstration)

Kei Ikeda

Department of Allergy and Clinical Immunology, Chiba University Hospital, Chiba, Japan

Musculoskeletal ultrasound (US) depicts a range of pathologies by illustrating soft tissue and bone surface. In rheumatoid arthritis (RA), synovial inflammation, subsequent structural damage, and differential causes of symptom can be assessed with US. Evaluation of synovial inflammation with US, especially, allows accurate diagnosis and activity assessment, and therefore, contributes to better clinical outcome.

Synovitis is depicted as either synovial hypertrophy or increased synovial fluid. Although these two findings are often indistinguishable from each other in small joints, synovial hypertrophy is more specific to synovitis and synovial hypertrophy accompanied by increased Doppler signals represents ongoing synovial inflammation. Therefore, synovial Doppler flow is important in the assessment of disease activity of RA. However, it should be noted that the assessment of synovial blood flow could be influenced by many factors. Different joints should be assessed differently for accurate estimation of inflammation according to their synovial shape, threshold for increased blood flow, and normal vessel distribution.

In this seminar, fundamentals of evaluating synovial lesions with US in rheumatology practice will be shown by a short lecture and a live demonstration with healthy subject accompanied by a presentation of pathologic images of rheumatoid patients.

HS2

Musculoskeletal ultrasonography by orthopaedic surgeon in clinic

Keiichiro Nishida¹, Ryuichi Nakahara²

¹Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, ²Department of Orthopaedic Surgery, Okayama University Hospital

The major implication of musculoskeletal ultrasonography (US) has been well recognized with the paradigm shift of pharmacological treatment for rheumatoid arthritis (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 is 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.

It is not difficult for orthopaedic surgeons, who are familiar with normal and pathologic anatomy, to understand the information derived from US image. Experience of arthroscopic surgery facilitates us to understand three-dimensional localization and distribution of inflammatory synovitis. The diagnostic advantage is not restricted to RA, but other musculoskeletal disorders, such as bone fracture, rotator cuff tear, tendon and ligament injury, trigger finger and tenosynovitis, soft tissue tumor, or osteoarthritis. Time consumed for US examination is technically dependent but soon shortened later, and can be controlled by physician. It is important to note that US gives

full play to its ability when rheumatologists perform US examination by themselves in outpatient clinic.

HS3

Basic technic and usefulness of ultrasound for musculoskeletal system

Michihiro Ogasawara

Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine

As early diagnosis and treatment for rheumatoid arthritis has been considered to be critical for prognosis of bone and joint, not only clinical assessment but also imaging modality has become important as it is able to create the correct image of joint inflammation using ultrasonography with B mode and power Doppler mode. Although conventional X-ray is the gold standard modality make us recognize soft tissue swelling, para-articular osteoporosis, joint space narrowing and bone erosion at a glance, it is hard to find early change particularly in non-tangential direction and phenomenon on going. This means X-ray only show the past change accumulated on the bone and joint. On the other hand, MRI have higher sensitivity for detection of bone erosion and destruction than X-ray and make it possible to have a differential diagnosis in early stage and activity assessment by detection of the synovitis and bone edema with contrast agent. However, there are disadvantages of high cost, long imaging time and low accessibility for multiple joints.

Ultrasonography does not have these disadvantages described above and promises to be a useful tool to assess multiple joints at one time. B mode method can visualize the articular structure and have higher sensitivity to detect early bone change which can be undetectable with X-ray. Power Doppler mode can detect minimum blood flow in synovitis and make it possible to distinguish joint swelling between with and without synovitis. Using ultrasonography in daily medical practice improve the level of medical care for arthritic patients. Today, let me show you the basic technic and usefulness of ultrasonography.

HS4

Musculoskeletal ultrasonography in daily clinical setting

Yohei Seto

Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

New imaging techniques such as musculoskeletal ultrasonography (US) and magnetic resonance imaging (MRI) have not only proven their correlation with conventional disease activity measures, but also determined data which gives insight to articular pathology at disease onset, early treatment response, disease remission and prediction of future bone damage, showing their utility to detect subclinical joint inflammation and damage which had not been able to be evaluated by conventional examination or laboratory tests.

As it is not simple to diagnose and evaluate patients with inflammatory arthritis due to the lack of a single gold standard, physicians need to apply various measures to assess disease activity and outcome. Introduction of biologic agents in last decade has resulted in great evolution in the treatment of inflammatory arthritis, whereas new classification criteria and remission criteria have just been proposed by American and European rheumatologists because of the needs for more precise evaluation of disease status to use these agents appropriately. It has also been in progress to develop methods for disease assessment by imaging such as global US scoring system and quantification of joint inflammation, but still on the way to reach a consensus. Furthermore, complicated US scoring system

could spoil its advantage such as convenient, rapid and real-time use at clinic.

Apart from application of global scoring, US is still a very powerful modality to confirm joint counts and useful to improve physician's physical examination technique and patient education. When applied for these purpose at outpatient clinic in our institution, US could be adapted to evaluate various joint areas taking acceptable time for the examination. US examination complimentary to clinical assessment could be easily and usefully applied to daily clinical setting.

HS5

Ultrasonographic evaluation of remission in rheumatoid arthritis

Yohei Seto

Institute of Rheumatology, Tokyo Women's Medical University

Remission has become achievable goal for patients with rheumatoid arthritis (RA) with biologic agents and tight control strategies. Though various definitions have been applied in clinical trials and daily practice, remission defined by traditional criteria does not always result in non-progression of joint damage and physical dysfunction.

New ACR/EULAR definitions for remission were proposed in 2010, defined by analyzing likelihood ratios comparing the proportion of patients in remission having the good outcomes to the proportion of patients in non-remission who achieved those. New definitions mainly consist of 28-joint count and patient's global assessment, and would predict good radiographic and functional outcomes in which remission state is defined more stringent compared to that defined by DAS28. Whereas joint count of feet or new imaging modalities such as ultrasound (US) and MRI was excluded after careful consideration, there might remain dissociation between remission state and deterioration of structural damage and function in individual patient and individual joint.

US is non-invasive technique which enables evaluation of multiple joints in short time at bedside, and has been determined to be superior to physical examination in terms of sensitivity and reliability. Increasing data has been produced regarding its utility in assessment of disease activity including remission and in prediction of prognosis. Though standardization of the technique has not reached a consensus, several US global scoring systems have been determined to be potential outcome measures, which would need further investigations for association with new definitions. It would also be the option to utilize US complimentary to clinical examination when applying new definitions.

Review of current data and the cases of US examination in the evaluation of remission are to be presented.

HS6

Ultrasonography for Evaluating Rheumatoid Inflamed Joints is Useful in Rheumatology Clinic.

Akira Sagawa

Sagawa Akira Rheumatology Clinic

Recently Rheumatoid Arthritis (RA) has now been considered to be one of the curable diseases, if the treatment started in early disease period. This phenomenon owes to progress of new and effective treatment representing biologic agents such as TNF- α inhibitor, IL-6 receptor inhibitor and T cell modulator. Therefore we should find new RA patients and diagnose correctly as early as possible, then start proper treatment for the patients diagnosed as RA. In these circumstances, newly proposed RA Classification Criteria of 2010ACR/EULAR is now very useful for screening and diagnosing

early RA patients from others. This criteria comprises from four items such as 1.Number of Joints with Synovitis, 2.Seropositivity, 3.Duration of disease, 4.ESR, CRP. Among these items, most important and fundamental item is the presence of synovitis for screening RA. In order to find and diagnose synovitis, imaging tools such as MRI and ultrasonography has now been shown very effective besides physical examination. Today's topic is the usefulness of ultrasonography for evaluating rheumatoid inflamed joints in rheumatology clinic.

Annual Course Lecture

ACL-1

Differential Diagnosis of Systemic Rheumatic Diseases

Shoichi Ozaki

Division of Rheumatology and Allergology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan

Systemic rheumatic diseases (SRD), also called systemic autoimmune diseases or connective tissue diseases, develop through the interaction of genetic and environmental factors. This interaction breaks self-tolerance and induces autoimmunity and inflammation, which result in the damage of multiple organs including connective tissue such as joint, muscle and blood vessels. The key to the diagnosis of SRD is to suspect your patient to have SRD.

Many SRD can be diagnosed by precise and complete history taking. In present illness, it is important to get the information about manner of disease onset, the state immediately before the onset, time course, accompanying symptoms, and response to antibiotics or glucocorticoid in case of recent administration of these drugs. In past history, histories of drug administration, infection, operation, and various related diseases are important. Since some SRD have genetic predisposition, familial history about autoimmune diseases should be investigated.

Physical examination should be done thoroughly, not only in regions of patients' complaints but also through whole body from head to toes. The majority of SRD can be diagnosed by complete history taking and physical examination.

Laboratory tests and other diagnostic procedures are employed to confirm clinical diagnosis. Among them, some autoantibodies are specific for individual SRD and can serve as diagnostic tools. These include antibodies for nuclear components such as double-stranded DNA and Sm, for cytoplasmic components such as myeloperoxidase and proteinase 3, and for citrullinated peptides. HLA typing gives good information in some SRD. Imaging studies are also useful in evaluating organ lesions. Pathological examination of biopsy specimen is crucial for final diagnosis and useful in determining therapeutic regimen.

In this lecture, the above mentioned strategies will be reviewed from the viewpoint of differential diagnosis of SRD.

ACL-2

Basic research on the pathogenesis of rheumatoid arthritis

Hiroshi Takayanagi

Department of Cell Signaling Tokyo Medical and Dental University / JST, ERATO

The method to prevent bone destruction in rheumatoid arthritis has never been established to the full satisfaction. This is partly because virtually all the antirheumatic drugs were developed based on their effects on immune reactions. Thus, even in the age of biology, it is crucially important to understand the mechanism underlying bone destruction, which will surely benefit the development of future therapeutic strategies. How does abnormality of the immune system induce skeletal damage in autoimmune disease? Although the infiltration of CD4⁺ T cells in the rheumatoid arthritis (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. IL-17-producing T helper cells (T_H17 cells) have been identified to be the exclusive T cell subset that has the ability to induce osteoclastogenesis. IL-17 induces RANKL, the key cytokine for osteoclastogenesis, on synovial fibroblasts and also stimulates local inflammation leading to over-

production of inflammatory cytokines such as TNF- α , 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, TGF- β and IL-23. These mechanisms provide a molecular basis for novel therapeutic strategies including the antibodies against RANKL, IL-6, IL-23 and IL-17. Recent finding on the transcriptional regulation of Th17 development will also be discussed.

ACL-3

Juvenile Idiopathic Arthritis: Clinical Approach

Shumpei Yokota

Yokohama City University School of Medicine, Department of Pediatrics

Most part of chronic arthritis in childhood is juvenile idiopathic arthritis (JIA). Recent development of biologic response modifiers or biologics is attributed to the concept shift of the diagnosis and treatment of JIA. The earlier the diagnosis is, the better the prognosis will be expected. The accurate diagnosis approach includes an early detection of joint inflammation, an estimation of magnitude of inflammation, and a presumption of prognosis. It is an important issue to start the standard treatment regimen in order to choose the children who are not responded well to the first line treatment. Those who are unresponsive to the treatment will be the group for biologics. Clinically, the children affected with arthritis are firstly interviewed when the joint pain starts in the morning and whether the both sides of joints are affected, and then received physical examination on each joint around 70 sites. The ultrasound examination will be helpful to detect active joint inflammation. Then, the classification of JIA should be reminded according to the WHO/ILAR criteria. The blood examination includes CRP and ESR as the inflammatory markers, rheumatoid factor, anti-nuclear antibody and anti-CCP antibody for the estimation of prognosis, and MMP-3 as the cartilage destruction marker. The treatment schedule will be the next matter to be considered. The world-wide standard for the first line treatment regimen is the weekly methotrexate (MTX, 10 mg/kg) (+ prednisolone 5-10 mg/day). Rehabilitation for the joints unaffected and the ophthalmological examination are recommended. Two to 4 weeks after the initiation of the therapy, the efficacy of MTX can be estimated by physical and ultrasound examination on the next visit. In case a patient with polyarticular JIA still has active arthritis after 3 months treatment, the application of biologics will be considered; polyarticular JIA patients with positive anti-CCP antibody are those who would be applied the biologics much earlier. Children are the people on developing and maturing, and the restricted movement by joint pain and swelling will deeply hurt them and strongly affect on their life. Thus, rheumatologists should be careful in choosing the appropriate treatment for JIA patients with prospect in the future.

ACL-4

Diagnosis of Rheumatoid Arthritis by 2010ACR/EULAR Criteria and Imaging Diagnosis

Akira Sagawa

Sagawa Akira Rheumatology Clinic, Sapporo, Japan

Recently Rheumatoid Arthritis (RA) has now been considered to be one of the curable diseases, if the treatment started in early disease period.

This phenomenon owes to progress of new and effective treatment representing biologic agents such as TNF- α inhibitor, IL-6 receptor inhibitor and T cell modulator.

Therefore we should find new RA patients and diagnose correctly as early as possible, then start proper treatment for the patients diagnosed as RA.

In these circumstances, newly proposed RA Classification Criteria of 2010ACR/EULAR is now very useful for screening and diagnosing early RA patients from others. This criteria comprises from four items such as 1.Number of Joints with Synovitis, 2.Seropositivity, 3.Duration of disease, 4.ESR, CRP.

Among these items, most important and fundamental item is the presence of synovitis for screening RA. In order to find and diagnose synovitis, imaging tools such as MRI and ultrasonography has now been shown very effective besides physical examination.

Today's topic is the diagnosis of early RA by 2010ACR/EULAR criteria using imaging method.

ACL-5

Drug therapy for rheumatoid arthritis

Hideto Kameda

School of Medicine, Keio University

The therapeutic goal of rheumatoid arthritis (RA) is to prevent organ damage, especially joint destruction, the decrease in the activity of daily life, and the lifetime shortening. Therefore, we need to regard "disease activity" as the time-differentiated organ damage, and consequently, properly evaluate and control the activity and severity of RA. Clinical remission should be the state in which RA patients should not experience any disability for a long time. Although it is a realistic goal of RA treatment, a less stringent control may be an alternative for some patients with co-morbidities and pre-existing organ damages. Nowadays methotrexate (MTX) is the anchor drug for RA. However, other disease-modifying anti-rheumatic drugs (DMARDs) than MTX are suitable for some patients with co-morbidities, pregnancy wish, or little activity and severity. Accumulating recent evidences indicate that the efficacy of MTX as well as anti-cytokine biological agents largely depends on whether a sufficient dose of those agents are given for each patient or disease. Patients who are unable to receive MTX at all, or sufficiently, due to co-morbidities, in turn, tends to remain high-risk without enough efficacy of anti-TNF biologics and consequent prevention of organ damage. Thus, further alternative therapeutic agents are needed for those patients. In terms of cost-risk-benefit balance of view, remission induction and maintenance therapy should be separately considered. Biological agents, as well as the inhibitors of JAK and Syk, may be best applied for remission induction. By contrast, conventional DMARDs including MTX are suitable for a long-term use in the maintenance phase. In this context, we are performing BuSHIDO trial, in which the addition of bucillamine to MTX has been examined for the efficacy on the decrease in the flare rate after the successful discontinuation of infliximab.

ACL-6

Treatment of rheumatic disease covered by health insurance: From the medical economic perspective

Nobumasa Miyake

Miyake orthopedic clinic, Shizuoka, Japan

The introduction of biological products (hereinafter "Bios") has given a whole new look to RA outpatient treatment. On the other hand, these drugs are not being prescribed to patients as much as they should. The major reason for this is not so much the patients' concern for adverse reactions but the drug's high prices. Bios cost a total of approximately 100 billion in Japan, and, because of this, medical service fee is estimated to have reached 390 billion.

A burden that a disease places on a country is called a Burden of Disease (hereinafter “BD”). BD is expressed in terms of calculation of costs. BD’s direct costs include health insurance costs which are direct medical fees, and fees for alternative treatment used other than drugs. Direct non-medical fees include costs for nursing care, home remodeling, and self-help devices, etc. BD’s indirect costs refer to labor losses. In other words, they are losses from fees required for going to a hospital, discontinuation of work due to worsening of a medical condition and retirement from work.

Indirect costs are generally said to be approximately twice as much as direct costs. A doctor’s most important role is to reduce these labor losses even at the expense of medical costs.

The best time to start Bios therapy is an early stage of RA. Becoming Bio-free will contribute the most to reducing BD. And second best time to start Bios therapy is the stage before impairment of leg joint. It is the biggest factor that raises indirect costs or labor losses. Moreover, the ideal time to start using Bios should differ, depending on individual patient’s lifestyles.

Based on EBM, the inherent role of a physician is to choose the best treatment at a particular juncture. You are encouraged to carry out clinical practice while keeping in mind the alleviation of the burdens placed on our country as well as on the patients.

ACL-7

Recent Surgical Treatment for Rheumatoid Arthritis

Hisaaki Miyahara

Dept. of Orthopaedic Surgery, and Rheumatology, Kyushu Medical Center, Fukuoka, Japan

Remission is realistic goal of current early aggressive therapy with MTX and biologics for rheumatoid arthritis (RA). Not only clinical remission, but functional remission must be reached. By the recent use of biologic agents, severity of the disease is decreasing. However, non-responders to medications and the patients who cannot use them due to comorbidities still exist. The use of biologic agents inhibits progression of joint destruction, but joints with higher grade of destruction at baseline show gradual deterioration. Therefore, surgical intervention is needed to get complete functional improvement or remission. Recent surgical treatment for rheumatoid arthritis, operative indications, timing and procedures are discussed in this lecture.

Synovectomy: The improved control of the inflammatory process by new drugs such as biologic agents has lead to a decrease of acute painful synovitis and therefore to a decrease of synovectomies. Early stage synovectomy is now rarely performed except for a few joints with residual synovitis for which medication is not effective.

Arthroplasty: Sauve-Kapandji’s operation is recommended as stabilizing procedure for the unstable wrist. Resection arthroplasty is applied to the forefoot deformity.

Arthrodesis: Arthrodesis produces stability. It is indicated for the unstable wrist, thumb IP joint, ankle, and other joints.

Total joint arthroplasty: The pain relief after total shoulder arthroplasty (TSA) is excellent, but the better result are obtained when rotator cuff is preserved at the time of operation. Total elbow arthroplasty (TEA) is a well-established procedure for the RA elbows with intractable pain or limited motion. Total hip arthroplasty (THA) and total knee arthroplasty (TKA) achieves early functional recovery of the patient and has long term durability. The delay of the timing of the operation becomes the cause of the contracture, muscular atrophy, and the bone atrophy and poor functional outcome as a result.

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Tokyo 105-0001, Japan
Tel. +81-3-5251-5353, Fax. +81-3-5251-5354
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