Next Decade Symposium

NDS1-1

How to start and continue biologics safely'

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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 Rhuematologist', 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 Arthriyis using High Resolution Radiograph (HRR).

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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%, 69.3and 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 casettes, 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

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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

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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

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Regarding the pathogenesis of Rheumatoid arthritis (RA), several genetic susceptibility loci have been reported. *HLADRB1* 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

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There has been a rapid increase in our uderstanding of the regulatory mechanism of osteoclastic bone resorption. Expression of receptor activator of NF-kB 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 αvβ3 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 lysozomal 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. Cathepin 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

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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 (p38α-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

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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 there 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

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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

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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

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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 may joints should be examined?
In this symposium, I would like to answer these FAQs showing images 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

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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

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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.