Issues in the Usages of New Anti-rheumatic Drugs in Japan

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Abstract
Rheumatoid arthritis (RA) is an inflammatory disease with its principal lesions appearing in the synovial membranes of joints. Historically, the objectives of the treatment were improvement of activity of daily living (ADL) and quality of life (QOL). However, the objective has now shifted to prevention of joint destruction due to the following reasons: 1) early diagnosis of RA has become possible; 2) early intervention with disease-modifying antirheumatic agents (DMARDs) has exhibited high efficacy; and 3) biological agents have been introduced. However, in Japan, as compared with the U.S. and Europe, there are disparities in the use of DMARDs and biological agents, and in their adverse effects. Physicians should acknowledge these disparities when providing treatment.

Key words Rheumatoid arthritis, Disease-modifying antirheumatic drugs, Biological agents, Methotrexate, Leflunomide, Interstitial pneumonitis

Introduction
Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disease with polyarthritis as the cardinal symptom. Lesions mainly preside in the synovial membranes of joints. However, when arthritis continues, it progressively destroys the cartilage and bones resulting in decline or loss of joint function. Furthermore, RA often affects other organs such as the lung. Persistence of inflammation can induce secondary amyloidosis. In addition, recent epidemiological studies showed that RA causes frequent cardiovascular complications due to atherosclerosis and the lifespan of affected patients is approximately 10 years shorter than that of healthy individuals.

The incidence of RA is approximately 1% of the population worldwide. However, due to the global increase of aged population, including Japan, RA are expected to increase in future. With this background, the World Health Organization (WHO) declared the decade beginning in 2000 the “Bone and Joint Decade,” and is taking measures to suppress bone and joint diseases including RA.

Paradigm Shift in Ultimate Goal of RA Treatment
The treatment of RA has been focused on relieving the inflammation, improving ADL, and sustaining and ameliorating QOL of RA patients. However, now that early diagnosis of RA has become possible, and therapeutic drugs with high efficacy such as methotrexate (MTX) and biological agents have been introduced, remission of the disease and delaying or inhibiting destruction of the cartilage and bones can be realized. Consequently, the main objective of current treatment has become prevention of joint destruction which can be obtained from complete remission of the disease, leading the American College of Rheumatology (ACR) to advocate positive treatment algorism to prevent joint destruction in 2002.1
The basis of traditional RA therapies was the so-called pyramid therapy. In other words, treatment began with nonsteroidal anti-inflammatory drugs (NSAIDs). When inflammation could not be controlled with NSAIDs, then antirheumatic agents (DMARDs) or corticosteroids were subsequently initiated. The concept of this therapy was based on the hypothesis that “bone destruction in RA will not occur in early stages of the disease.”

However, recent studies in the U.S. and in Europe have introduced surprising evidence that “bone destruction in RA progresses the most in 1 to 3 years after the onset of the disease.”2 As a result, treatment guidelines presented by American College of Rheumatology (ACR) in 2002 have knocked the bottom out of the traditional pyramid therapy. The characteristics of the guidelines are to establish the diagnosis as early as possible, to assess the disease activity and presence of radiographic damage, and to promptly initiate proper treatment including DMARDs, NSAIDs, and corticosteroids. Initiation of DMARDs treatment is suggested to begin within 3 months of diagnosis when the disease is not yet controlled. After 3 months, the efficacy of the initial treatment needs to be reevaluated. If the treatment is found to be ineffective, it is recommended to administer stronger DMARDs, mainly MTX, by rheumatologists. If the efficacy of MTX is not sufficient, other DMARDs such as leflunomide will be used instead, or combination therapy of MTX and other DMARDs are advised. Furthermore, if the situation allows, biological agents will be considered. This positive treatment algorithm has become the world trend.

Issues of MTX in Japan

In the U.S. and Europe, MTX is a first-line agent for severe, active RA. Not only is MTX effective in controlling or retarding joint destruction, but it is also proven to improve the lifespan of RA patients. In addition, prolonged administration of other DMARDs often cause progressive reduction or lack of efficacy (escape phenomenon), and is a reason for discontinuation of the remedies. However, with MTX, escape phenomenon is rare.3

The dosing regimen of MTX significantly differs between the Western countries and Japan. In the U.S. and Europe, it starts at 7.5 mg/week with gradual increase to the maximum of 20 to 25 mg/week. On the other hand, in Japan, it starts at 4 to 6 mg/week with maximum of 8 mg/week. However, remission is often observed only after the administration of more than 8 mg even among Japanese patients. For this reason many rheumatologists advocate that the legal dosage of MTX should be increased. In addition, in Japan, MTX cannot be used as the first-line drug because of the drug package insert stating that MTX can be used “only when at least more than 1 kind of DMARDs is ineffective.” However, patients with rapid progression should be treated with sufficient doses of MTX from the early stages to prevent further joint damage. The dosing regimen and indication of MTX should therefore be reconsidered in Japan.

Issues of Leflunomide in Japan

Leflunomide is a pyrimidine synthesis inhibitor. Due to its strong inhibitory effects of controlling the disease and halting joint destruction, it was approved and put on the market in the U.S. in 1998, in European countries in 1999, and in Japan in September 2003. However, in Japan, in January 2004, fatal cases of interstitial pneumonitis were reported. Interstitial pneumonitis was complicated between 2 weeks to a couple of months after institution of leflunomide. Postmarketing surveillance disclosed that preexisting lung lesions, the elderly over 60, and hypoalbuminemia were identified as risk factors. In addition, there was no correlation between the occurrence of interstitial pneumonitis and the dosage of leflunomide, thus assuming an allergenic mechanism may be implicated in the pathogenesis. However, it is still possible that opportunistic infections such as Pneumocystis jiroveci might be included in some of these cases. Exacerbation of interstitial pneumonitis with leflunomide is generally rapid and progressive. In particular, chest X-rays which are compatible with diffuse alveolar damage (DAD) have a poor prognosis.4 Incidence of interstitial pneumonitis with leflunomide is generally rapid and progressive. In particular, chest X-rays which are compatible with diffuse alveolar damage (DAD) have a poor prognosis.4 Incidence of interstitial pneumonitis with leflunomide is approximately 1%, while the mortality rate is high as approximately 30%. This incidence is approximately 80 to 100 times higher when compared with that of Western countries. However, it remains to be
clarified why interstitial pneumonitis is complicated in such a high frequency and mortality with the use of leflunomide in Japan. Detailed investigations including genetic polymorphism will shed a light on its pathogenesis.

**Issues of Biological Agents in Japan**

Two types of biological agents are currently approved in Japan: infliximab, which is a chimeric monoclonal antibody against TNF-α, and etanercept, which is a soluble TNF receptor. Both have inhibitory effects against TNF-α which is a known inflammatory cytokine. The most significant benefit of these TNF-α inhibitors is to inhibit the progression of joint destruction. Among these, infliximab is used in more than 10,000 cases in Japan, and the results of a post-marketing surveillance study are being released. On the other hand, there are not yet sufficient results of post-marketing surveillance for etanercept is provided because of its late appearance in the market.

In Japan, infliximab must be used in combination with MTX in cases in which disease activity is not controlled with more than 6 mg/week of MTX alone. Physician’s global assessment with the use of infliximab indicated a marked response in about 30% of the patients and moderate response in more than 50% suggesting its dramatic efficacy. In addition, rapid and sustained response are of characteristic profiles of infliximab.

One of the issues using infliximab in Japan is the association of infectious diseases. Especially, pneumonia is observed in approximately 2% of the cases with administration of infliximab. Risk factors such as diabetes, advanced age, and preexisting lung diseases are identified in postmarketing surveillance. Infliximab tends to be used in advanced and longstanding cases of RA with multiple organ involvement in Japan, and this may explain high frequency of pneumonia.

Globally, Japan is a country with high prevalence of tuberculosis (TB), leading to increased frequency of complicated cases of TB with infliximab, i.e. 0.3%. Since the occurrence of TB is more frequent within the 3rd administration from the onset of the treatment, an exacerbation of previous TB rather than a new TB infection can be speculated. Prior to start infliximab, all patients should be screened for TB by examining previous history of or exposure to TB, tuberculin reaction, and chest radiograph. Patients with an abnormal chest radiograph and/or strongly positive tuberculin test should receive isoniazid (INH) 0.3 g/day one month prior to the onset of the infliximab administration for 6 to 9 months as a prophylactic measure.

Pneumocystis pneumonia is seen in about 0.4% of the cases with administration of infliximab, a much higher frequency than in the U.S. or Europe. Reasons for this are still unknown. However, in Japan, there is a risk of Pneumocystis pneumonia even in cases with MTX, which may suggest that racial and environmental differences are involved in its pathogenesis.

**Conclusion**

The ultimate goal of RA treatment has shifted to prevention of joint destruction. However, in Japan, MTX cannot be used as a first-line drug and its dosage is limited. In addition, leflunomide is not an alternative for MTX at present because of frequent and fatal complication of interstitial pneumonitis. Furthermore, although biological agents have shown remarkable efficacy compared with cases in the U.S. and Europe, opportunistic infections such as pneumonia, TB and Pneumocystis pneumonia are observed in higher incidence than in the U.S. or Europe. Consequently, it is vital to periodically monitor adverse effects and to detect them at early stages in the course of treatment. In addition, physicians are required to have sufficient clinical knowledge to undergo proper risk management upon complication of adverse effects.

**References**


