the PPD skin test may not be suitable for critically screening TB, (3) over 4% of TB patients are resistant to isoniazid (INH), (4) prophylactic use of INH can cause liver dysfunction in at least 10% of TB patients, and (5) infliximab can mask the clinical features of TB. These problems are discussed below.

Current situation of TB in Japan and the world

According to a report issued by the World Health Organization (WHO), there were 8.8 million new cases of TB in 2002, 3.9 million of which were smear-positive.[6] The global incidence of TB is growing at a rate of approximately 1.1% per year, and the number of cases at 2.4% per year.

In Japan, the annual incidence of new TB infection in 2002 was 25.8 per 100000, or 4.6-fold higher than in the United States.[7] Although the incidence has been decreasing year by year, the proportion of the elderly population is increasing. Among 32828 newly registered TB patients in 2002, patients over 60 years of age comprise 58.4% and those over 70 years of age 41.5%, whereas the respective figures in 1996 are 53.2% and 31.7%. Fifty-three percent are positive for *M. tuberculosis* either in smear or culture. Pulmonary TB accounts for 81 and extrapulmonary for 19. There is a regional bias in the annual incidence of TB with percentages of patient increasing in urban areas: 74.4 per 100000 in Osaka city and 36.6 in Tokyo special district, but only 12.5 in Nagano Prefecture. In addition, 4.4% of isolated *M. tuberculosis* in culture is resistant to INH.

Purified protein derivative skin test

In Japan, 0.1cc of 3 tuberculin units of standardized PPD obtained from Aoyama B strain is injected intradermally into the volar surface of the forearm. Erythema, but not induration, is measured at 48h, and the diameter is recorded in millimeters. The cut-off criterion for positivity is 10mm in diameter. The size of induration, dual erythema, and presence of blisters and necrosis, if any, are also recorded. Those with diameters of more than 10mm, but not with induration or dual erythema, are evaluated to be 1+; those with induration, 2+; and those with induration, dual erythema, blisters and necrosis, 3+. The reason why erythema but not induration is measured is mainly due to the feasibility of measuring its diameter on the skin in the Japanese population. The PPD skin test has been performed in Japan at the time of entry to elementary school (6 years of age) and to junior high school (12 years of age) but this was abolished in 2003. Two-step testing is performed only in settings where tight TB screening is necessary, such as the employment of medical professionals. The PPD skin test is known to be influenced not only by exposure to TB but also by repeated PPD skin testing, which creates a booster phenomenon, and by other *Mycobacterium* infections such as *Mycobacterium avium* complex.

Bacillus Calmette-Guérin vaccination

Bacillus Calmette-Guérin vaccination has been given to those who show a negative PPD skin test in childhood. That is, the PPD skin test has been mainly used in Japan to evaluate whether BCG vaccination is necessary in childhood. Those who are negative in the PPD skin test even after BCG vaccination are subjected to revaccination. However, revaccination has not been used since 2003. Furthermore, the Japanese Government recommended that BCG vaccination should be performed to all infants by 1.5 years of age from 2004 without doing a PPD skin test. Although BCG vaccination might substantially contribute to decreasing the incidence of TB in Japan, it creates a false-positive reaction on the PPD skin test and makes it difficult to discriminate actual positivity due to TB from false positivity.

Difference in MTX dosage

The maximal dosage of MTX approved for use in Japan is 8mg/week. This dosage is based on a clinical trial conducted in Japan to determine the optimal dose, in which the efficacy of the 6 and 9mg/week groups was comparable, and was significantly better than that of the 2mg/week group.[8] Increased liver enzyme was observed at more than 9mg/week, although folic acid was not given during the trial. However, in the clinical setting, dosages of MTX in excess of 8mg/week are sometimes used if the physician deems it necessary. In such cases, informed consent is obtained from the patient.

Pneumocystis carinii pneumonia in MTX-treated RA patients

Pneumocystis carinii pneumonia (PCP) is a serious and potentially fatal infection often encountered in immunosuppressed patients such as those with acquired immunodeficiency syndrome (AIDS), cancer including hematological malignancies, and organ transplantation.[9] Patients with connective tissue diseases (CTD) are also at risk for PCP.[10] *Pneumocystis carinii* pneumonia affects 2.6%–4.3% of CTD patients with immunosuppressive treatments including corticosteroids.[11,12] Risk factors include the administration of high-dose corticosteroids or immunosuppressants, and low peripheral blood lymphocytes (PBL).[12] We have found that patients who developed PCP were significantly more intensively treated with corticosteroids and/or immunosuppressive agents and were more immunosuppressed than those who did not.[13] In our series of 124 patients who received more than 30mg/day of prednisolone, nine patients in the non-prophylaxis group (n = 82) developed PCP, whereas none in the prophylaxis group receiving one tablet of TMP/SMX (containing 80mg of trimethoprim and 400mg of sulfamethoxazole) (n = 42) developed PCP. *Pneumocystis carinii* pneumonia was diagnosed when the clinical and ra-

diographic presentation was strongly suggestive of PCP and when microbiologic confirmation of *P. carinii* in respiratory samples was made or there was a response to treatment only with agents active against *P. carinii*. All the patients diagnosed with PCP had the following four features strongly suggestive of PCP: (1) clinical manifestation including pyrexia, dry cough, and dyspnea, (2) hypoxemia ($PaO_2 < 80$ torr) and/or increased A-aDO_2 (>15 mmHg),[14] (3) diffuse alveolar infiltrates or interstitial infiltrates on chest X-ray as well as on computed tomography of the thorax, and (4) increase of serum β-D-glucan level.[15] We also found that PBL counts 4 weeks after the institution of PSL in the patients who developed PCP were significantly lower than those in the other patients (476 ± 350 vs 1229 ± 1.019, mean ± SD, $P < 0.004$). Since we occasionally but infrequently experience PCP in MTX-treated RA patients and have experienced a case of PCP during the clinical trial of infliximab in Japan, we are extremely cautious regarding the possibility of PCP developing as a complication during treatment with infliximab in combination with MTX in Japanese RA patients.

Treatment guidelines for using infliximab (Fig. 1)

We have therefore created guidelines for the use of infliximab to safely treat Japanese RA patients according to our data described above. The guidelines were initially established by the Study Group of Rheumatoid Arthritis, Ministry of Health, Labor, and Welfare, Japan (principal investigators; Nobuyuki Miyasaka, MD, Tsutomu Takeuchi, MD, and Katsumi Eguchi, MD), and were later officially approved by the Japan College of Rheumatology.

Inclusion criteria

Inclusion criteria are active RA with at least six swollen and tender joints with concomitant usage of methotrexate of over 6 mg/week. Patients must have either C-reactive protein >2.0 mg/dl or erythrocyte sedimentation rate >28 mm/h. Patients also are required to have more than 4000/mm^3 of white blood cells and more than 1000/mm^3 of peripheral blood lymphocytes in addition to negative β-D-glucan in sera, to avoid possible opportunistic infections including TB and *P. carinii*.

Exclusion criteria

Patients having concurrent infection or histories of serious infection for the last 6 months are excluded from the study. Patients who have chest X-ray findings indicative of old TB (pleural thickening, fibrotic scarring shadows, calcified shadows of more than 5 mm in diameter), a history of TB, extrapulmonary TB and PCP, congestive heart failure, malignancy, and demyelinating disease are also excluded from this study. However, if the physician thinks that the

A. Inclusion criteria

1. Disease activity
   Active RA patients with concomitant usage of methotrexate (MTX) of over 6 mg/week for more than three months who fulfill following conditions.
   1) tender joints ≧ 6
   2) swollen joints ≧ 6
   3) ESR ≧ 28 mm/hr or CRP ≧ 2.0 mg/dl
2. Laboratory data
   1) WBC ≧ 4,000/mm^3
   2) peripheral blood lymphocytes ≧ 1,000/mm^3
   3) serum β-D glucan: negative

B. Exclusion criteria

1. Ongoing infection
2. Past history of serious infection for the last six months
3. Abnormal shadows in chest radiographs suggestive of old pulmonary tuberculosis (TB) or tuberculous pleuritis (fibrotic scarring shadows, calcified shadows of more than 5 mm in diameter, pleural thickening)
4. History of pulmonary and extrapulmonary TB*
5. History of *Pneumocysits carinii* pneumonia
6. Congestive heart failure
7. Malignancy
8. Demyelinating disease

* If the physician thinks that the advantage of infliximab treatment outweighs its safety in patients with latent TB infection, prophylactic treatment of isoniazid (INH, 0.3 mg/day) is recommended.

Fig. 1. Treatment guidelines for using infliximab to rheumatoid arthritis patients in Japan

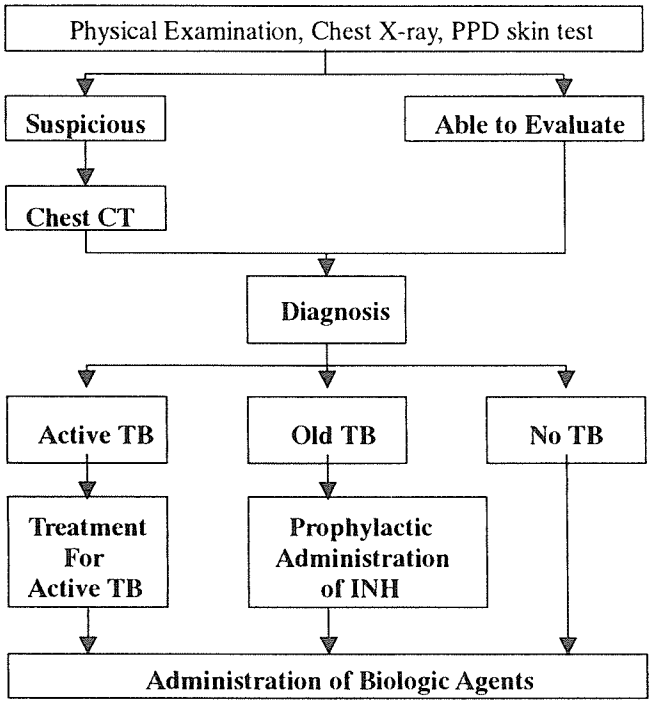

Fig. 2. Algorithm for the diagnosis and management of tuberculosis in patients with rheumatoid arthritis on biologic agents

advantage of infliximab treatment outweighs its safety in patients with latent TB infection, prophylactic treatment of INH (0.3 mg/day) is recommended.

Screening of TB (Fig. 2)

Intensive history taking and physical examination

Patients are asked whether they have had a history of TB or exposure to TB patients. They are screened for symptoms consistent with active TB, such as cough, sputum, or fever. It should be emphasized that signs and symptoms of TB can be masked by the use of infliximab, and therefore an extensive physical examination should be performed.

Purified protein derivative skin test

The PPD skin test is mandatory for all patients enrolled in this study and is performed before the initial infusion. If it is strongly positive (>2+), continuous use of INH (0.3 g/day) for 9 months, beginning one month prior to the initial infusion, is recommended.

Chest radiography and chest computed tomography (CT)

Chest radiography is also mandatory for all patients before the initiation of infliximab therapy. If the chest radiograph shows any findings suggestive of old TB, chest CT is recommended. Prophylactic use of isoniazid (INH) should be initiated in patients showing chest radiographs indicative of old pulmonary TB or tuberculous pleuritis. In the case of active TB, patients should be treated with a full course of anti-TB drugs for a sufficient period of time before starting infliximab. Physicians are simultaneously required to be capable of reading chest radiographs, evaluating them on the same day of clinical examination, and properly treating opportunistic infections including TB.

Treatment protocol

Intravenous infusion of infliximab (3 mg/kg) at weeks 0, 2, and 6 was performed, followed by subsequent infusions every 8 weeks. Intravenous infusion is initiated at a slow rate (15 ml/h) for the first 15 min and increased to 50 ml/h over a period of 2 h. The signs and symptoms of the patient are monitored throughout the infusion. Vital signs are closely monitored every 10 min during infusion with an automated manometer.

Management of infusion reactions

Physicians need to prepare for serious infusion reactions that may possibly occur during infliximab administration.[16] When mild to moderate infusion reactions occur, it is recommended to slow the infusion rate to 10 ml/h or stop infusion, if necessary. Further, p.o. or i.v. diphenhydramine (25–50 mg) and p.o. acetaminophen (650 mg) are administered. When wheezing is audible, i.v. hydrocortisone (100 mg) is given.

For severe acute reactions such as dyspnea with wheezing, significant discomfort, severe urticaria, or hypotension below 40 points of systolic blood pressure, s.c. epinephrine ([1:1000] 0.1–0.5 ml) is given and can be repeated every 5 min for three doses followed by i.v. methylprednisolone (50–100 mg) if necessary. The airway should be maintained with oxygen inhalation, and the patient should be transferred to the emergency room in case of anaphylaxis.

Assessment of the guidelines

As of July 11, 2004, 3011 cases were enrolled in this study and all of their case report forms were collected. The details of the study will be published elsewhere (Takeuchi T et al. Postmarketing survey of infliximab in 3000 cases of Japanese rheumatoid arthritis patients, in preparation). Briefly, TB was seen in nine patients, six of whom were observed in the initial 1000 cases, followed by two patients in the next 1000 cases, and one patient in the remaining 1000. Six of the cases were pulmonary and two extrapulmonary. None of the patients was under prophylactic use of INH. However, in six cases the chest radiographs turned out to be abnormal when retrospectively assessed by pulmonologists, although initial readings by attending physicians were assessed to be normal. Furthermore, three of these patients were strongly positive for the PPD skin test, and one had a history of TB. False-negative PPD skin tests were seen in two patients who had abnormal findings suggestive of old TB on chest radiographs.

Pneumocystis carinii pneumonia was observed in six patients (0.2%), none of whom was undergoing prophylactic

use of TMP/SMX. Serious infusion reactions were observed in six patients (0.3%), but all were successfully treated.

Discussion

We have established official guidelines for the use of infliximab in combination with MTX to treat Japanese RA patients and have simultaneously developed an algorithm for the diagnosis and management of TB. Approval was given by the Japan College of Rheumatology in 2003. Nine cases of TB were observed in this study, and six of them occurred during the first 1000 cases. However, if the above guidelines had been strictly followed by the treating physicians, these TB cases might have been prevented. Strict enforcement of the guidelines after the experience of the initial 1000 cases prevented the subsequent occurrence of TB at the same frequency. In this respect, Spain is in the same situation as Japan, with the incidence of TB higher than in other west European countries and the United States. However, Spain overcame this situation by establishing official guidelines and recommendations, and succeeded in dramatically reducing new cases of TB among patients receiving infliximab treatment.[17]

RA patients taking corticosteroids or MTX are often anergic, but this study had only two cases of false-negative PPD skin tests. Even though a high incidence of false-positive PPD skin tests is expected owing to BCG vaccination in childhood, the PPD skin test was useful in screening latent TB, and chest radiography combined with chest CT was effective in detecting latent TB infection in the lung.

An increased risk of TB in patients with RA has been reported in Mexico[18] but not in the United States.[5] No epidemiological studies on the risk of TB in RA patients have been carried out in Japan; however, this type of study is essential. In any event, our study again demonstrated that TNF-α is essential in host immune response to *M. tuberculosis*.[19,20]

The guidelines should be revised in the near future by more closely analyzing the upcoming results of the post-marketing survey in Japan. Enrollment of the 5000 cases initially planned for the post-marketing survey will be completed by the end of 2004.

Finally, recognition of the potential risk of opportunistic infections in RA patients treated with infliximab in combination with MTX by medical professionals is strongly required, and close monitoring of these patients for the signs and symptoms of complicated diseases such as TB and PCP will enable physicians to safely treat RA patients with infliximab.

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REVIEW ARTICLE

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Guidelines for the proper use of etanercept in Japan

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Abstract Application of biological agents targeting inflammatory cytokines such as tumor necrosis factor-α (TNF-α) dramatically caused a paradigm shift in the treatment of rheumatoid arthritis (RA). Infliximab, a chimeric anti-TNF-α monoclonal antibody, has initially been introduced to Japan in 2003 and shown to be dramatically effective in alleviating arthritis refractory to conventional treatment. However, serious adverse events such as bacterial pneumonia, tuberculosis, and *Pneumocystis jiroveci* pneumonia were reported to be in relatively high incidence; i.e., 2%, 0.3%, and 0.4%, respectively, in a strict postmarketing surveillance of an initial 4000 cases in Japan. Etancercept, a recombinant chimeric protein consisting of p75 TNF-α receptor and human IgG, was subsequently introduced to Japan in March of 2005. We therefore drew up treatment guidelines for the use of etanercept to avoid potential serous adverse events, since only approximately 150 cases have been included in the clinical study of etanercept in Japan. The guidelines were initially designed by the principal investigators (N.M, T.T., K.E.) of rheumatoid arthritis study groups of the Ministry of Health, Labor and Welfare (MHLW), Japan, and finally approved by the board of directors of the Japan College of Rheumatology. The MHLW assigned a duty to the pharmaceutical companies to perform a complete postmarketing surveillance of an initial 3000 cases to explore any adverse events, and this was performed according to the treatment guidelines shown in this article.

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Introduction

In recent years, there has been a paradigm shift in the treatment of rheumatoid arthritis (RA). It is mostly attributed to the introduction of biological agents targeting inflammatory cytokines. Biological agents have approved and marketed for the treatment of RA in Europe and the United States include anti-tumor necrosis factor-α (TNF-α) antibodies such as infliximab (Remicade) adalimumab (Humira), soluble TNF-α receptor etanercept (Enbrel), and interleukin (IL)-1 receptor antagonist anakinra (Kineret). Among these, etanercept has drawn particular attention as a highly effective and safe biological product in the treatment of RA; it was approved in January 2005 in Japan.

Efficacy and adverse events of etanercept

Etanercept is a recombinant chimeric protein consisting of two molecules of p75 and the Fc portion of human IgG1 and is produced by introducing the fusion gene into Chinese hamster ovary cells (molecular weight, approximately 150 kDa; total amino acid residues, 934). As compared with the natural-occurring soluble TNF-α receptor, etanercept showed 50-fold greater binding to TNF-α, 100- to 1000-fold greater biological activity, and 5- to 8-fold longer plasma half-life; therefore, treatment of RA with etanercept has been conducted.[1]

In a phase III study in the United States involving 234 patients with active RA who were resistant to disease-modifying antirheumatic drugs (DMARDs) including

methotrexate (MTX), treatment with etanercept 25mg showed significantly greater efficacy than etanercept 10mg or placebo.[1] Analysis of adverse events revealed that the incidence of injection-site reactions was significantly higher in the 25-mg dose group than other dose groups and that the active treatment groups had a higher incidence of infections, i.e., upper respiratory tract infections, than the placebo group.

In a double-blind study of concomitant MTX, 89 patients with active RA who had been treated with MTX for at least 6 months received either etanercept 25mg or placebo twice a week subcutaneously in addition to MTX, resulting in improvement in a 20% American College of Rheumatology (ACR 20) response in 71% of patients receiving etanercept and an ACR 50 improvement in 39% of patients receiving etanercept. Moreover, there were no significant differences in incidence of adverse events such as infections between the two groups.[2]

On the basis of these results, etanercept was approved as a treatment for RA by the Federal Drug Administration (FDA) in the United States in November 1998. More than 6 years after its approval in the United States, the drug was approved in January 2005 and has been marketed since the end of March 2005 in Japan.

The most significant benefit of etanercept is to inhibit the progression of joint destruction. Its efficacy has been demonstrated to be far superior to that of MTX, which is known to have the potent effect of slowing the progression of joint destruction.[3] The remarkable effectiveness of etanercept has been shown particularly in the recently reported TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes).[4] In this trial, 686 patients with RA who were resistant to one or more DMARDs other than MTX received one of the following three treatments for 2 years: MTX alone, etanercept alone, or etanercept plus MTX. The primary efficacy endpoint was the numeric index of the ACR response (ACR-N) area under the curve (ACR-AUC) over the first 24 weeks. The primary endpoint did not differ significantly between the MTX monotherapy group and etanercept monotherapy group; however, the etanercept plus MTX group had significantly higher ACR-AUC values than the two monotherapy groups. The proportion of patients achieving ACR 50, a clinically meaningful efficacy, at 2 years was 71% in the etanercept plus MTX group as compared with 42% in the MTX monotherapy group and 54% in the etanercept group, indicating greater efficacy of the combination of etanercept and MTX. Moreover, the change in total Sharp Score at 1 year of treatment was −0.54 in the etanercept plus MTX group as compared with +2.8 in the MTX monotherapy group and +0.52 in the etanercept group, suggesting the possibility that the combination may inhibit the progression of joint destruction and even heal the condition.

Frequently observed adverse events include injection-site reactions, which are characterized by erythema with pruritus, swelling, or pain at the injection sites. Most reactions disappear with only topical treatments such as antihistamines.

The most careful attention should be given to monitoring for infections. Among the more than 1100 patients receiving long-term treatment for at least 6 months, 50 experienced serious infections such as pyelonephritis, bronchitis, septic arthritis, and abscess formation, which were caused by various types of organisms including bacteria, fungi, and *Pneumocystis jiroveci*. Etanercept may mask clinical symptoms characteristic of infections, such as fever and chills, and inhibit the production of acute inflammatory proteins, thereby causing the problem of difficulty in detecting infections at an early stage.

In addition, occurrence of tuberculosis has recently been of particular concern, although etanercept appears to be rarely associated with tuberculosis as compared with infliximab.[5,6] However, caution should be exercised when etanercept is used in Japan, where tuberculosis frequently occurs,[7] because BCG vaccinations in Japan preclude the use of the tuberculin skin test for screening at the start of drug treatment, and there are not a few patients with drug-resistant *Mycobacterium tuberculosis*.[8,9]

Although the occurrence of malignancies was the most serious among possible complications, the incidence in the more than 1100 patients was not significantly different from the expected incidence in the general population. Also, patients with active RA have been shown to have a slightly higher incidence of malignant lymphoma. In March 2003, the FDA reported that the standardized incidence ratio (SIR) for malignant lymphoma ranged from 2.3 to 3.5 in patients receiving etanercept with no statistically significant difference.[10]

Because etanercept is known to exacerbate congestive heart failure, caution should be made when etanercept is administered to patients with heart failure. Initially, clinical trials were conducted with infliximab or etanercept as a therapeutic agent for congestive heart failure because TNF-α was believed to be involved in the pathophysiology of congestive heart failure. However, individual clinical trials showed treatment failures and even worsening cases of congestive heart failure, leading to termination of these trials.[11]

In addition, rare cases of pancytopenia have been reported. Although demyelinating diseases in the central nervous system have also been reported, a causal relationship to the treatment remains uncertain. In some patients with multiple sclerosis, an increase in disease activity has been found after the treatment.[12] A recent report showed that etanercept treatment in early RA patients was well tolerated for up to 5 years.[13]

In Japan, 147 patients who were refractory to conventional DMARDs were enrolled in phase II clinical study. Patients were randomly divided into three groups, i.e., placebo group, 10mg twice-weekly group, and 25mg twice-weekly group, and treated for 12 weeks. Consequently, both the 10mg group and 25mg group yielded an almost identical ACR20 response, significantly better than the placebo group (64.0%, 65.3% vs. 6.3%, respectively). This trend was similar in both ACR50 and ACR70 response. There was no significant difference observed in severe adverse effects between the etanercept and placebo groups.

Table 1. Treatment guidelines for the use of etanercept

A. Inclusion criteria
Patients with active rheumatoid arthritis still presenting the following despite the use of one or more MHLW recommendation-level-A-DMARDs[a] (methotrexate, bucillamine, or sulfasalazine) at a normal dose for more than 3 months:
(1) Tender joints ≥6
(2) Swollen joints ≥6
(3) ESR ≥28 mm/h or CRP ≥2.0 mg/dl
Also, the patients must meet the following as having low risk for opportunistic infections:
(1) WBC ≥4000/mm^3
(2) Peripheral blood lymphocytes ≥1000/mm^3
(3) Serum β-D-glucan: negative

B. Usage
The dose of etanercept is 10–25 mg administered twice weekly as a subcutaneous injection. A patient can self-inject etanercept only after the ability to self-inject is carefully assessed and appropriate training is provided by a health professional.

C. Contraindication
1. Ongoing infection
2. Past history of serious infections in the last 6 months
3. Abnormal shadows on chest radiographs suggestive of old pulmonary tuberculosis (TB) or tuberculosis pleuritis
4. History of extra pulmonary TB or *Pneumocystis carinii* pneumonia
5. Congestive heart failure
6. Malignancy or demyelinating disease

D. Caution
1. From the point of view of screening for infection (especially TB and opportunistic infections) as well as prevention of side effects, etanercept is recommended for clinical use at medical institutes where:
   (1) Chest X-rays can be obtained on the same day, and the X-ray can be interpreted by a pulmonologist, TB specialist, or radiologist
   (2) Opportunistic infections can be treated
2. Comprehensive TB screening should be conducted including an in-depth patient history, chest radiographs (chest CT whenever possible) and a PPD skin test. In patients with suspected TB, based on medical history, abnormal shadows on chest radiographs suggestive of old pulmonary TB, or with a PPD skin test positive (as evidenced by redness of at least 20 mm in diameter or the presence of induration), the treatment with etanercept may be considered in addition to anti-tuberculosis drugs only if the potential benefits outweigh the potential risks.

MHLW, Ministry of Health, Labor and Welfare; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; WBC, white blood cells; TB, tuberculosis; CT, computed tomography; PPD, purified protein derivative
[a]Cited in the Diagnostic Manual and Evidence-based Treatment Guidelines

Treatment guidelines for the use of etanercept (Table 1)[14]

For the safe use of etanercept in Japan, which produces such high efficacy and potential adverse events, the internal medicine rheumatology study group of the Ministry of Health, Labor and Welfare, Japan (led by N.M., T.T., and K.E.) has developed the guidelines for treatment with etanercept, which provide indications, contraindications, and tuberculosis risk assessment, which was based on the guidelines for the use of infliximab for RA patients in Japan[9] (Fig. 1). The guidelines were approved by the board of directors of Japan College of Rheumatology.

Etanercept is indicated in patients with active RA at or above a certain level. Specifically, etanercept may be used in patients who have inadequately been controlled despite treatment of at least 3 months with the usual doses of one of the DMARDs (methotrexate, bucillamine, or sulfasalazine), which are rated as "recommendation A level" in the Diagnostic Manual and Evidence-based Treatment Guidelines[15] developed by the study group of the Ministry of Health, Labor and Welfare. Leflunomide, another DMARD rated as recommendation A, is not included in the present guidelines because of the adverse event of serious interstitial pneumonia observed in Japan.[16] Inadequate response to previous treatment is defined by the presence of at least six tender joints and swollen joints and either C-reactive protein levels of at least 2.0 mg/dl or erythrocyte sedimentation rate (ESR) of at least 28 mm/h.

To avoid potential opportunistic infections, patients should have a peripheral leukocyte count of 4000/mm^3 or more, peripheral lymphocyte count of 1000/mm^3 or more, and a negative test for blood β-D-glucan. These criteria are based on the findings that cellular immunity plays an important role in opportunistic infections caused by *Mycobacterium tuberculosis* or fungi such as *Pneumocystis jiroveci*, and that these infections are likely to occur in patients with decreased peripheral lymphocyte counts.[17] A test for blood β-D-glucan has been included because β-D-glucan, a component of fungi, may be diagnostic of fungal infections, especially infections with *Pneumocystis jiroveci.*

The recommended dosage and administration of etanercept in Japan is 10–25 mg given once daily and twice weekly as a subcutaneous injection. In this aspect, once-weekly administration of 50 mg etanercept in patients with active RA patients has been approved in the United States, and this dosing regimen was shown to be equivalent to 25 mg etanercept twice weekly in terms of safety, efficacy, and pharmacokinetics.[18] Patients will switch to self-injection

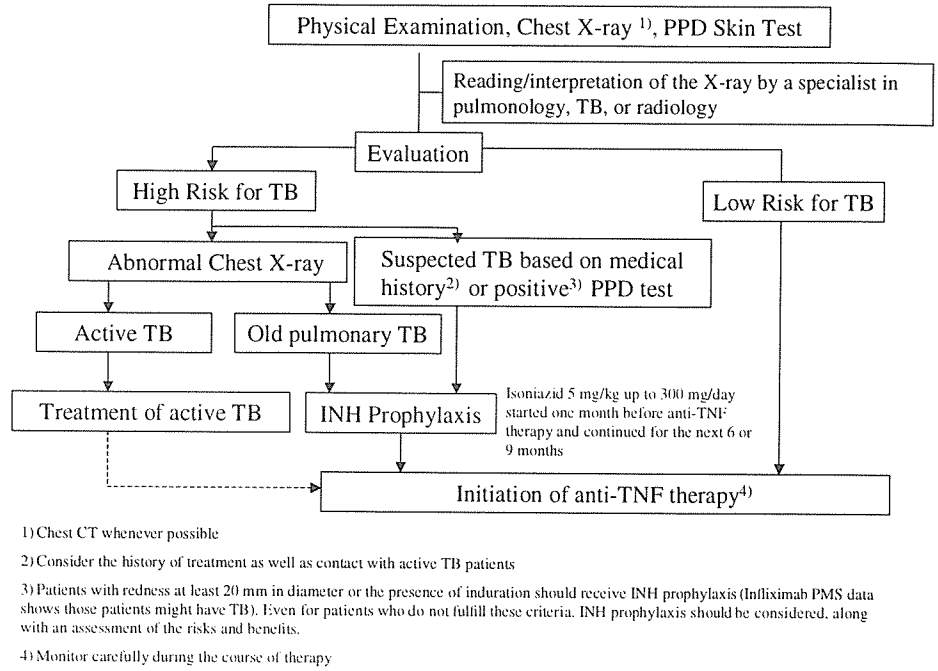

Fig. 1. Tuberculosis risk evaluation chart of the use of anti-TNF therapy. *TNF*, tumor necrosis factor; *INH*, isoniazid; *PMS*, postmarketing survery

after they are assessed as capable of conducting self-injections and receive adequate instructions. Etanercept may be used as monotherapy as the drug was administered so in clinical trials in Japan. In Europe and the United States, however, etanercept in combination with MTX has been demonstrated to provide greater efficacy in TEMPO.[4] Thus, the combination of etanercept with MTX should be considered in patients with highly active disease in Japan.

Etanercept is contraindicated in patients with active infections or a history of serious infections within the previous 6 months. In addition, careful assessment of the risk of tuberculosis should be made. Specifically, the following three examinations should be performed before treatment initiation: interview with respect to family and past history of tuberculosis, chest radiography, and purified protein derivative (PPD) skin test (Fig. 1). Chest radiographs should preferably be interpreted by a specialist in pulmonology, tuberculosis, or radiology. When abnormalities are suspected on chest radiography, computed tomography of the chest should be performed. Etanercept is contraindicated in patients with abnormalities in chest radiographs such as linear opacities, calcification ≥5 mm, and pleural thickening suggesting old pulmonary tuberculosis, and individuals infected with pulmonary or extrapulmonary tuberculosis. However, treatment with etanercept may be considered with antituberculous agents only if the potential benefits outweigh the potential risks. In patients with a positive PPD skin test (as evidenced by erythema of at least 20 mm in diameter or the presence of induration) or opacities suggesting old pulmonary tuberculosis on chest radiographs, treatment with isoniazid 0.3 g/day should be initiated at least 1 month prior to administration of etanercept and continued for the subsequent 9 months. However, no definite guidelines are available that address how to deal with isoniazid-induced hepatic impairment and isoniazid-resistant *Mycobacterium tuberculosis*, as well as how long isoniazid treatment should be given. Etanercept is also contraindicated in patients with previous *Pneumocystis jiroveci* pneumonia, congestive heart failure, malignancies, or demyelinating disease.

To sum up, in this article we focused on the guidelines for the use of etanercept that have been introduced in Japan since spring 2005. In Japan, because only about 100 patients received etanercept in clinical trials, it remains uncertain whether etanercept yields clinical benefit and adverse events with a similar frequency as observed in Europe and the United States. Nonetheless, we will conduct an all-cases postmarketing surveillance using the above-mentioned treatment guidelines, review the results, and revise the guidelines as needed.

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A Multicenter, Double-Blind, Randomized, Placebo Controlled Trial of Infliximab Combined with Low Dose Methotrexate in Japanese Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** A placebo controlled, double-blind trial (DBT) was conducted for Japanese patients with active rheumatoid arthritis (RA) despite treatment with low dose methotrexate (MTX) to evaluate the efficacy and safety of infliximab. Extended treatment with infliximab was conducted in an open-label trial (OLT).

Methods. In the DBT, 147 patients were randomly assigned and treated with a placebo or 3 mg/kg or 10 mg/kg infliximab at Weeks 0, 2 and 6, combined with MTX. In the OLT, 129 patients from the DBT received 3 mg/kg infliximab every 8 weeks.

Results. The mean dose of MTX was 7.2 ± 2.0 mg/week. Significantly more patients receiving 3 mg/kg (61.2%) and 10 mg/kg (52.9%)infliximab achieved a 20% improvement according to the American College of Rheumatology (ACR) criteria at Week 14, compared to placebo (23.4%) ($p < 0.001$). There was no significant difference in incidence of adverse events among the treatment groups. In patients receiving infliximab in the DBT, 11.6% of patients with serum infliximab just before the OLT developed antibodies to infliximab (ATI) in the OLT, whereas 62.2% of patients without serum infliximab did. In patients receiving placebo in the DBT, 43.9% developed ATI.

Conclusion. The efficacy and safety of infliximab combined with low dose MTX were similar to those of the ATTRACT study. The data from the DBT and OLT also supported the importance of an induction treatment of infliximab, followed by a maintenance treatment without a long interval, giving stable serum concentrations in order to prevent formation of ATI. (J Rheumatol 2006;33:37–44)

Key Indexing Terms:
INFLIXIMAB RHEUMATOID ARTHRITIS RANDOMIZED CONTROLLED TRIAL
JAPAN ANTI-TUMOR NECROSIS FACTOR-α

There has been great progress in the medical treatment of rheumatoid arthritis (RA) in recent years. Several reports state that early treatment with single or combined disease modifying antirheumatic drugs (DMARD) has prevented structural damage and improved functional disability[1-8].

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Methotrexate (MTX), widely used in the US and EU as a first-line DMARD, was approved in Japan in 1999 for patients with RA with inadequate response to more than one other DMARD. While MTX has produced favorable response in a growing number of Japanese patients with RA, it is still difficult to control disease activity in a substantial number of patients.

Several biological drugs that target tumor necrosis factor-α (TNF-α), a cytokine closely involved in the pathogenesis of RA, have been developed and have been found to have significant and profound efficacy in patients with active RA[9-15]. A chimeric monoclonal antibody to TNF-α, infliximab has been used worldwide for RA patients concomitantly with MTX. Infusions of infliximab in combination with MTX have been reported to be effective not only in reducing signs and symptoms, but also in inhibiting the progression of structural damage and improving physical function in patients with RA that remains active despite administration of MTX[10,11,15].

We describe a multicenter, placebo controlled, double-blind trial (DBT) of infliximab for Japanese patients with RA to evaluate efficacy, safety, and pharmacokinetics with

concomitant use of a low weekly-dose MTX. The DBT was followed by an open-label trial (OLT) for patients who agreed to continue the treatment with infliximab.

MATERIALS AND METHODS

Patients. Eligible patients were 20–75 years of age and fulfilled the diagnostic criteria for RA of the American Rheumatism Association[16] at least 6 months prior to enrollment. Patients were eligible for the DBT if they had ≥ 6 tender joints (of 68 counted) and ≥ 6 swollen joints (of 66 counted), plus at least 2 of the following: morning stiffness ≥ 45 min, erythrocyte sedimentation rate ≥ 28 mm/h, or C-reactive protein (CRP) ≥ 2 mg/dl, despite treatment with MTX for more than 3 months. The MTX dosage must have been stable 6 mg/week or more during the last 4 weeks. Patients receiving oral or suppository nonsteroidal antiinflammatory drugs (NSAID), folic acid, oral or suppository corticosteroid (10 mg/day or less prednisolone equivalent) must have been taking a stable dose for 4 weeks prior to entry. Patients were not allowed to use DMARD, immunosuppressive drugs other than MTX, intraarticular, intramuscular, intravenous or epidural corticosteroids, to have arthrocentesis and plasma exchange (for 4 wks prior to entry), or use alkylating agents (for 5 yrs prior to entry).

Patients were excluded if they had functional class IV using Steinbrocker's criteria[17], any other systemic rheumatic diseases except Sjögren's syndrome, serious infections, opportunistic infections (within the previous 3 mo), tuberculosis (within the previous 3 yrs), infections of artificial joints (within the previous 5 yrs), human immunodeficiency virus infection, malignancies (within the previous 5 yrs), a history of known allergies to human/murine chimeric antibodies, or pregnancy. Laboratory exclusion criteria were: hemoglobin < 8.5 g/dl; leukocyte count < 3500×10^6/l; neutrophil count < 1500×10^6/l; platelet count < $10 \times 10^4/\mu$l; serum creatinine level > 1.5 mg/dl; and alanine aminotransferase (ALT) levels, aspartate aminotransferase (AST) levels, and alkaline phosphatase (ALP) levels greater than twice the normal upper limit.

Patients who completed all scheduled infusions and evaluations in the DBT and desired extended treatment with infliximab were enrolled in the OLT. Permitted concomitant drugs were the same as those in the DBT.

Written informed consent was obtained from all patients for each trial. Each trial was reviewed and approved by the institutional review board of each hospital.

Protocol design and trial drugs. Patients were reviewed for entry requirements after giving informed consent, and enrolled into the DBT within 2 weeks after the initial review. One hundred fifty-one patients were enrolled from April 19, 2000, to October 27, 2000. Patients were randomly assigned to the placebo, 3 mg/kg, or 10 mg/kg groups. The first infusion (Week 0) was given within 4 weeks after enrollment, followed by additional infusions at Weeks 2 and 6.

In the OLT, patients received 4 infusions of 3 mg/kg every 8 weeks, with the first infusion in the OLT carried out within 14 weeks after the last infusion of the DBT. Patients were given 3 doses including placebo in the DBT and almost all of them entered the OLT, so that placebo infusions could be as minimal as possible, and patients who were given placebo could receive infliximab in the OLT.

Infusions of study drugs were given intravenously over 2 hours or more. All study drugs were manufactured by Centocor, Inc., Malvern, PA, USA, and supplied by Tanabe Seiyaku Co., Ltd., Osaka, Japan.

Efficacy and safety assessment. The primary endpoint of the DBT was a response rate of a 20% improvement according to the ACR criteria (ACR20)[18] at Week 14. Evaluations were made in terms of improvement of 20%, 50%, and 70% according to the ACR response (ACR20, ACR50 and ACR70) and individual measurements of the ACR core set at Weeks 0, 2, 6, 10, and 14 in the DBT and every 4 weeks from Weeks 0 to 36 in the OLT.

In the DBT, patients were monitored for safety until just before the first infusion of the OLT. Patients who did not enter the OLT were assessed until 20 weeks after the last infusion. In the OLT, safety assessments were performed until 36 weeks. An infusion reaction was defined as any adverse event occurring during or within 2 hours after the completion of each infusion. Vital signs including body temperature, blood pressure, and pulse rate were recorded every 30 min during and for 2 hours after the completion of each infusion.

Laboratory tests. Laboratory measurements included a complete blood cell count, white blood cells with differential, AST, ALT, ALP, lactate dehydrogenase (LDH), γ-glutamyl transpeptidase (γ-GTP), total protein, total cholesterol, total bilirubin, blood urea nitrogen, serum creatinine, sodium, potassium, chlorine, and urinalysis. CRP was measured by the central laboratory, and the results were not open in the DBT to maintain a strict blind. Immunoserological tests included antinuclear antibodies and anti-double-stranded DNA.

Pharmacokinetic assessment and immuno-response. Serum concentrations of infliximab were evaluated prior to and 1 hour after the completion of each infusion, and at Weeks 10 and 14 in the DBT and at Weeks 28, 32, and 36 in the OLT. In the DBT, antibodies to infliximab (ATI) was evaluated prior to the first infusion, at Week 14, and 20 weeks after the last infusion. In the OLT, ATI was evaluated prior to the first infusion and at Weeks 32 and 36. Pharmacokinetics of infliximab and ATI measurements were done at Tanabe Seiyaku Co., Ltd. using ELISA as described[9] with reagents provided by Centocor Inc.

Statistical analysis. The analysis set of demographics and efficacy was the full analysis set. The analysis set for safety consisted of patients who received at least one infusion of the study drug. In the DBT, patients who discontinued treatment before Week 14 received assessments at discontinuation as the primary endpoint. For other efficacy values, assessments up to discontinuation were adopted, but assessments after discontinuation were removed. For the efficacy values of patients discontinuing the OLT, assessments up to discontinuation were adopted and assessments at discontinuation were carried as those after discontinuation.

Demographics across treatment groups were analyzed using the chi-square test for categorical data, the Kruskal-Wallis test for ordered categorical data, and ANOVA for quantitative data. Response rates between treatment groups, based on the ACR criteria, were analyzed using logistic regression. Multiplicity of tests was not adjusted for the primary endpoint because the primary analysis was a comparison of ACR20 response rates between the placebo and the combined infliximab groups at Week 14, and the other analyses were secondary. Changes from baseline in individual measurements of the ACR core set between treatment groups were analyzed using ANOVA. Incidences of adverse events among treatment groups were analyzed using logistic regression. The significance level for demographic analysis was 15% (2-sided). The significance level for efficacy and safety analyses was 5% (2-sided).

RESULTS

Patients' demographics. Out of 151 patients enrolled in the DBT, 147 received at least one infusion of study drugs (47, 49, and 51 patients in the placebo, 3 mg/kg, and 10 mg/kg groups, respectively). Five patients receiving the placebo discontinued treatment, including 3 due to lack of efficacy, one due to an adverse event, and one due to a protocol violation. Five patients receiving infliximab discontinued treatment due to adverse events. Baseline demographics were comparable among the 3 groups, with the exception of body weight (Table 1). The difference had no influence on the result of the primary endpoint using covariance adjustment. The mean dose of MTX was 7.2 ± 2.0 mg/week. The doses of MTX among the treatment groups were well balanced. A large number of patients were treated with NSAID and corticosteroid concomitantly.

Table 1. Baseline characteristics of patients in the double-blind trial.

Patients	Placebo, n = 47	Infliximab 3 mg/kg, n = 49	Infliximab 10 mg/kg, n = 51
Female, n (%)	35 (74.5)	40 (81.6)	40 (78.4)
Age, years, mean ± SD	55.1 ± 7.6	55.2 ± 10.9	56.8 ± 10.5
Body weight, kg, mean ± SD	55.8 ± 8.3	51.9 ± 8.0	50.3 ± 7.8
Duration of disease, yrs, mean ± SD	7.5 ± 5.0	9.1 ± 7.4	7.1 ± 5.1
Steinbrocker disease stage, n (%)			
I	1 (2.1)	2 (4.1)	5 (9.8)
II	13 (27.7)	10 (20.4)	12 (23.5)
III	18 (38.3)	19 (38.8)	18 (35.3)
IV	15 (31.9)	18 (36.7)	16 (31.4)
Steinbrocker disease class, n (%)			
I	2 (4.3)	5 (10.2)	4 (7.8)
II	33 (70.2)	36 (73.5)	30 (58.8)
III	12 (25.5)	8 (16.3)	17 (33.3)
Tender joint count, mean ± SD	17.8 ± 8.7	19.0 ± 11.8	18.7 ± 12.3
Swollen joint count, mean ± SD	13.5 ± 7.6	15.1 ± 9.0	13.2 ± 6.2
CRP, mg/dl, mean ± SD	4.1 ± 2.4	4.2 ± 3.1	3.6 ± 3.2
Dose of MTX, mg/week, mean ± SD	7.4 ± 2.2	7.1 ± 1.9	7.1 ± 1.8
Corticosteroid therapy, no. (%)	42 (89.4)	42 (85.7)	47 (92.2)
Oral or suppository NSAID therapy, no. (%)	45 (95.7)	44 (89.8)	48 (94.1)
Concomitant use of folic acid, no. (%)	13 (27.7)	11 (22.4)	13 (25.5)

There was no significant difference among the 3 treatment groups, except body weight (p = 0.003). CRP: C-reactive protein, MTX: methotrexate, NSAID: nonsteroidal antiinflammatory drugs.

Efficacy. ACR20 response rates at Week 14, the primary endpoint of the DBT, were 23.4%, 61.2%, and 52.9% in the placebo, 3 mg/kg, and 10 mg/kg groups, respectively (Table 2), showing significantly higher response in the combined infliximab groups than in the placebo group ($p < 0.001$). A significantly higher percentage of patients receiving infliximab also achieved ACR50 and ACR70 improvement at Week 14 than those receiving the placebo ($p = 0.003$, $p = 0.001$). ACR response rates were not significantly different in the 2 infliximab groups. A significantly greater percentage of patients in both infliximab groups than in the placebo group achieved improvement of ACR20 and ACR50 at all evaluation points in the DBT (Figure 1).

Safety. There was no significant difference in incidence of adverse events among the treatment groups in the DBT (Table 3). Most frequent adverse events in the infliximab groups included cold, fever, diarrhea, and cough (Table 3), which were similar to those observed in previous studies. Serious adverse events were observed in 6 patients receiving 10 mg/kg and in one patient receiving placebo. All patients were assessed for tuberculosis by chest radiograph. Patients with a history of latent tuberculosis were then assessed by chest radiograph at least every 3 months. No patient experienced any new or recurrent tuberculosis.

Two patients died during the DBT. One, a 68-year-old man, had received 3 infusions of 10 mg/kg. At 58 days after the last infusion, he complained of shortness of breath and fever. He was diagnosed with pneumonia and hospitalized the next day. *Pseudomonas* and fungi were detected in the sputum culture. He died on the sixth day of hospitalization. The other patient, a 66-year-old man, had received 3 infusions of 10 mg/kg. During the last infusion, chest discomfort appeared and he was diagnosed with pulmonary edema. On the following day, the complication of pneumonia was suspected and he was transferred to the intensive care unit. Since sputum culture for tuberculosis was negative, and he

Table 2. Response rate of American College of Rheumatology (ACR) criteria at 14 weeks in the double-blind trial.

	Placebo, n = 47	Infliximab 3 mg/kg, n = 49	Infliximab 10 mg/kg, n = 51	p
ACR20, % (no.)	23.4 (11)	61.2 (30)	52.9 (27)	< 0.001
ACR50, % (no.)	8.5 (4)	30.6 (15)	35.3 (18)	0.003
ACR70, % (no.)	0 (0)	10.2 (5)	15.7 (8)	0.001

P values are comparison between placebo group and combined infliximab groups.

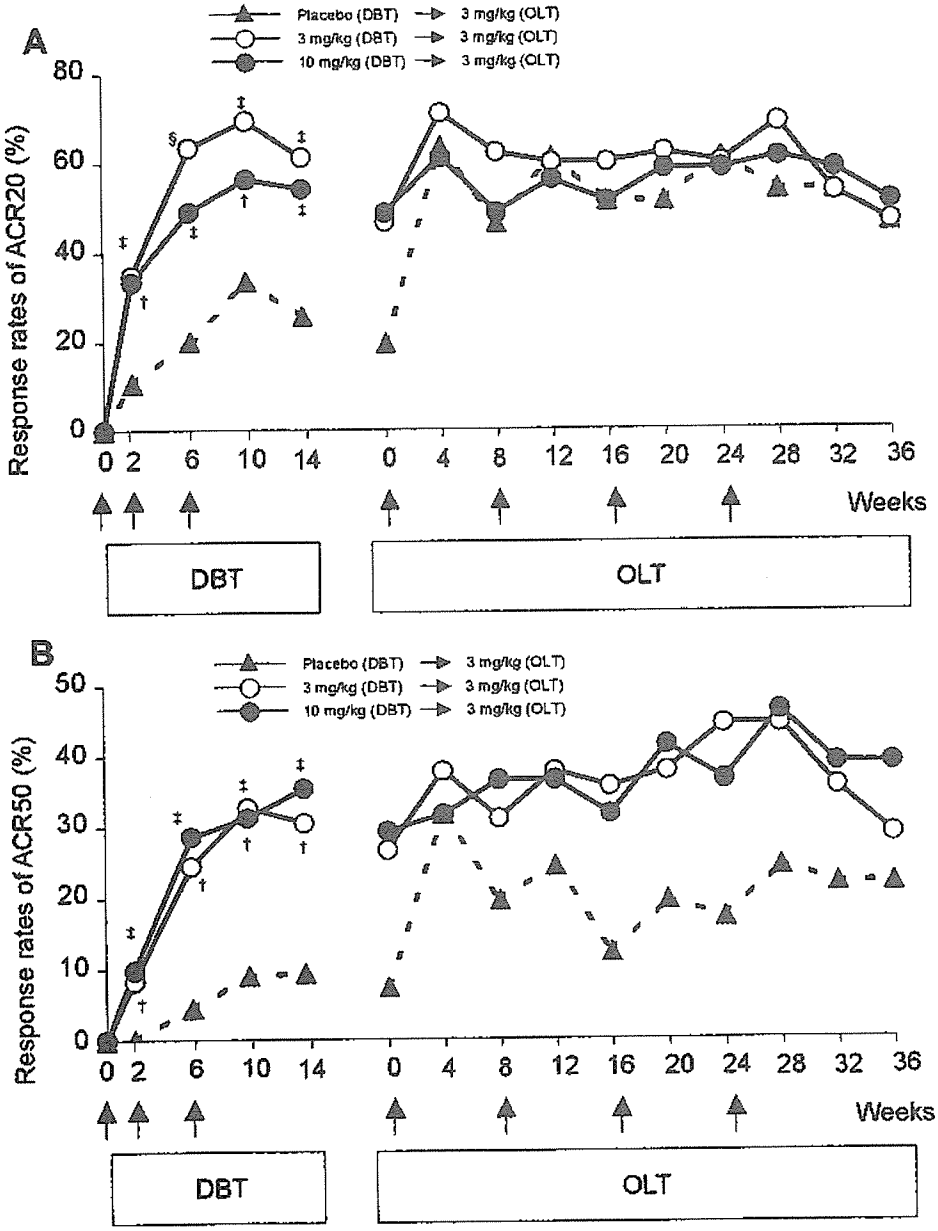

Figure 1. Response rates based on the ACR criteria in the DBT and OLT. A. 20% improvement according to the ACR criteria (ACR20). B. 50% improvement according to the ACR criteria (ACR50). Arrows indicate the time of infusions. Significance versus placebo: $^{\dagger}p < 0.05$, $^{\ddagger}p < 0.01$, $^{\S}p < 0.001$.

recovered with steroid pulse therapy without antibiotics, a diagnosis of noninfectious interstitial pneumonia was made. In spite of the transient improvement, the interstitial pneumonia again became aggravated and he died 62 days after the onset of symptoms.

Two (4.1%) and 4 (8.0%) patients in the 3 mg/kg and 10 mg/kg groups, respectively, developed ATI.

Longterm observations. In the OLT, 129 patients from the DBT received at least one infusion of 3 mg/kg infliximab (41, 45, and 43 of the patients from the placebo, 3 mg/kg, and 10 mg/kg groups in the DBT, respectively). A total of 39 patients discontinued treatment, because of adverse events in 19, lack of efficacy in 14, and other reasons in 6.

Patients who had received infliximab in the DBT experienced sustained ACR20 and ACR50 response rates (Figure 1). In patients who had received placebo in the DBT, ACR20 response rates in the OLT increased to the same level as observed in patients treated with infliximab in the DBT. However, ACR50 response rates in those patients were lower than in patients treated with infliximab in the DBT.

The most frequent adverse events throughout the DBT and OLT included colds, fever, cough, diarrhea, headache,

and sputum (Table 4), which were similar to those observed in previous studies. A total of 21 patients (14.9%) experienced serious adverse events during these trials. No patient died in the OLT.

In the OLT (n = 129), 51 patients (39.5%) developed ATI. Incidences of ATI formation were 43.9%, 42.2%, and 32.6% in the placebo, 3 mg/kg, and 10 mg/kg groups, respectively, of the previous DBT. In patients who received infliximab in the DBT and entered the OLT (n = 88), 45 (51.1%) had no detectable level of infliximab and 43 (48.9%) had detectable levels just before the first infusion of the OLT. ATI was found in only 5 patients (11.6%) with detectable levels of infliximab, whereas it was found in 28 patients (62.2%) without inflximab in their sera. The incidence of infusion reactions in ATI-positive patients was 45.1%, which was a little higher than the 38.5% for the non-positive patients. There was no serious infusion reaction in a patient in the OLT.

DISCUSSION

In our double-blind trial, Japanese patients with active RA despite treatment with low dose of MTX received infusions of placebo or 3 mg/kg or 10 mg/kg of infliximab at Weeks 0, 2, and 6, concomitant with MTX. Significantly more patients receiving infliximab achieved a rapid improvement than those receiving the placebo, which was similar to the results of the Anti-TNF Trial in the Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) study[10,11,15]. In addition, although the ACR20 response rate of the placebo group at Week 14 was almost identical to that of the ATTRACT study, the response rate of the 3 mg/kg group appeared higher in our DBT. The efficacy of infliximab observed in the DBT was also sustained throughout the OLT.

Since there was no significant difference in efficacy between the groups receiving 3 mg/kg and 10 mg/kg infliximab, 3 mg/kg infliximab was determined as an optimal dose. Although the median serum infliximab concentration was dose-dependent (data not shown), the ACR20 response rate was a little higher in the 3 mg/kg group than in the 10 mg/kg group. However, more patients receiving 10 mg/kg achieved ACR50 and ACR70 improvement than those receiving 3 mg/kg (Table 2), suggesting that a higher dose is preferable to achieve a higher level of improvement, as previously reported[19]. For patients who are unable to obtain sufficient response even with a regimen of 3 mg/kg infliximab every 8 weeks, we expect that a better clinical response can be obtained by increasing the dosage or through more frequent infusions, as reported[20].

On the other hand, it should be noted that the incidence of antibodies to infliximab at the end of the OLT was 39.5%, which was higher than that of the ATTRACT study[15]. There may be 2 possible explanations for the elevated ATI findings. The first is that the interval of infusions between the DBT and OLT was longer than 8 weeks. Patients receiving infliximab in the DBT started treatment every 8 weeks after

Table 3. Incidences of adverse events during the double-blind trial.

	Placebo, n = 47	Infliximab 3mg/kg, n = 49	Infliximab 10mg/kg, n = 51	p
Cold, no. (%)	4 (8.5)	9 (18.4)	13 (25.5)	
Fever, no. (%)	9 (19.1)	9 (18.4)	8 (15.7)	
Diarrhea, no. (%)	2 (4.3)	6 (12.2)	7 (13.7)	
Cough, no. (%)	5 (10.6)	3 (6.1)	7 (13.7)	
Headache, no. (%)	6 (12.8)	7 (14.3)	3 (5.9)	
Sputum, no. (%)	4 (8.5)	3 (6.1)	3 (5.9)	
Rash, no. (%)	0 (0.0)	4 (8.2)	3 (5.9)	
Pneumonia, no. (%)	0 (0.0)	1 (2.0)	3 (5.9)	
Hot flushes, facial, no. (%)	1 (2.1)	0 0.0)	3 (5.9)	
Pruritus, no. (%)	0 (0.0)	3 (6.1)	2 (3.9)	
Pain, pharynx, no. (%)	3 (6.4)	3 (6.1)	1 (2.0)	
Stomatitis, no. (%)	3 (6.4)	4 (8.2)	0 (0.0)	
Epigastralgia, no (%)	0 (0.0)	3 (6.1)	0 (0.0)	
Any adverse event with subjective symptoms, no. (%)	32 (68.1)	36 (73.5)	37 (72.5)	0.538
Any adverse event that resulted in discontinuation, no (%)	1 (2.1)	1 (2.0)	4 (7.8)	0.244
Any serious adverse event, no (%)*	1 (2.1)	0 (0.0)	6 (11.8)	0.607
Any infections, no. (%)	17 (36.2)	22 (44.9)	25 (49.0)	0.220
Any infusion reactions, no. (%)	17 (36.2)	23 (46.9)	19 (37.3)	0.501

* Serious adverse events included pneumonia (n = 2), interstitial pneumonia and pulmonary edema (n = 1), herpes zoster (n = 1), bacterial pneumonia (n = 1), vaginal prolapse (n = 1) in the 10 mg/kg group; and bronchopneumonia, increased AST, increased ALT, increased lactate dehydrogenase, increased γ-GTP, increased ALP, and headache (n = 1) in the placebo group. P values are for comparison between placebo group and combined infliximab groups.

Table 4. Incidences of adverse events in patients who received at least one infusion of infliximab during the double-blind trial (DBT) and open-label trial. (OLT).

	Placebo, 3 mg/kg, n = 41	Infliximab 3mg/kg, 3 mg/kg, n = 49	Infliximab 10mg/kg, 3 mg/kg, n = 51	Total n = 141
Average weeks of followup	32.2	50.0	46.2	43.5
Adverse events				
Cold, no. (%)	11 (26.8)	14 (28.6)	21 (41.2)	46 (32.6)
Fever, no. (%)	7 (17.1)	15 (30.6)	15 (29.4)	37 (26.2)
Cough, no. (%)	5 (12.2)	9 (18.4)	12 (23.5)	26 (18.4)
Diarrhea, no. (%)	6 (14.6)	7 (14.3)	9 (17.6)	22 (15.6)
Headache, no. (%)	2 (4.9)	7 (14.3)	7 (13.7)	16 (11.3)
Sputum, no. (%)	2 (4.9)	8 (16.3)	5 (9.8)	15 (10.6)
Any adverse event with subjective symptoms, no. (%)	32 (78.0)	44 (89.8)	47 (92.2)	123 (87.2)
Any adverse event that resulted in discontinuation, no. (%)	9 (22.0)	4 (8.2)	11 (21.6)	24 (17.0)
Any serious adverse event, no. (%)*	6 (14.6)	2 (4.1)	13 (25.5)	21 (14.9)
Any infections, no. (%)	22 (53.7)	31 (63.3)	31 (60.8)	84 (59.6)
Any infusion reactions, no. (%)	17 (41.5)	33 (67.3)	25 (49.0)	75 (53.2)

* Serious adverse events in the OLT included pneumonia (n = 2), *Pneumocystis carinii* Pneumonia and phlegmon (n = 1), transitory deafness (n = 1), sinusitis (n = 1), herpes zoster (n = 1), venous thrombophlebitis (n = 1), dizziness and vomiting (n = 1), bacterial enteritis (n = 1), diarrhea, nausea, urinary tract infection, swaying feeling, urine retention, pyrexia, ascites, pleural effusion, decreased sodium, and decreased partial O_2 pressure (n = 1), femur fracture (n = 1), goiter and papillary thyroid cancer (n = 1), bronchitis (n = 1), polyps (n = 1), pain in a joint involving the lower leg, ileus and arterial thrombosis of the leg (n = 1). Serious adverse events in the DBT are shown in Table 3.

a mean interval of 12 ± 1 weeks (range 10–14 wks) from the first 3 infusions at Weeks 0, 2, and 6 as the induction treatment. This interval was determined in order to complete evaluations under blind conditions prior to commencing the OLT. At the end of the interval, the serum level of infliximab was undetectable in 38% of patients whose concentrations had been observed 8 weeks after the induction treatment. At the end of the OLT, formation of ATI occurred in 11.6% of patients who had had detectable levels of serum infliximab at the end of the interval, whereas ATI formation occurred in 62.2% of patients without detectable levels. These results suggest that disappearance of infliximab, particularly after a long interval, may lead to ATI production with higher incidence after readministration of infliximab. In addition, patients receiving the placebo in the DBT started treatment with infliximab every 8 weeks without the induction regimen, and showed an incidence of ATI of 43.9%, while the incidence among patients who had induction with 3 mg/kg was 42.9%. These results may indicate why formation of ATI was higher in Japanese subjects taking part in this clinical trial.

The second explanation is that the mean dose of MTX was 7.2 ± 2.0 mg/week, which was less than half that in the ATTRACT study[10] (range 16–17 mg/week). Eighty-five percent of patients were treated with doses ≤ 8 mg/week, for the reason that the maximum dosage approved in Japan was 8 mg/week. This dose was determined by a dose-finding trial comparing 2 mg/week, 6 mg/week, and 9 mg/week conducted in Japan[21]. The efficacy of the 6 mg/week and 9 mg/week groups was comparable, and significantly higher than the 2 mg/week group. On the other hand, the incidences of liver enzyme abnormalities, elevations of ALT and AST, were significantly higher in the 9 mg/week group (21.7%, p = 0.007, and 21.7%, p = 0.005, respectively), but not in the 6 mg/week group (14.5%, p = 0.144, and 11.3%, p = 0.342), compared to the 2 mg/week group (3.2% and 3.2%). In addition, thrombocytopenia and leukocytopenia were observed only in the group receiving 9 mg/week (1.7% and 5.0%, respectively).

Since average body weights of Japanese patients with RA were around 50–56 kg, somewhat lower than those in the US and EU, body weight should be taken into account when considering the differences of doses of MTX. In addition, most patients were treated with folic acid in the ATTRACT study, whereas only 25% of patients were given folic acid in the trials in Japan. Considering these factors, the difference in the effect of MTX on RA patients might not be as large as that expected from the difference in the dose of MTX used between the Japanese trials and the ATTRACT study. Nevertheless, the dose of MTX in our study was indeed lower than doses recently used in the US and EU.

The question arises whether a low dose of MTX might prevent the formation of ATI. The rate of ATI formation in the DBT (6.1%) was comparable to that observed at the end

of the ATTRACT study (8%), suggesting that concomitant treatment with low-dose MTX successfully prevented ATI formation during short-term infliximab treatment. However, because of the longer interval of infusions, it was difficult to conclude whether a low dose of MTX was sufficient to prevent ATI formation during longterm infliximab treatment.

A previous report suggests the presence of ATI might reduce serum levels of infliximab promptly[22]. It was also reported that higher trough levels of infliximab might be beneficial for treatment of some patients with RA[19]. In the OLT, ATI-positive patients showed lower clinical response rates than patients not positive for ATI (data not shown). The data from our trials in Japan support the importance of an induction treatment of infliximab, followed without a long interval by maintenance treatment giving stable serum concentrations, in order to prevent ATI formation and sustain clinical response.

On the other hand, it was reported that infusion reactions are more frequent in ATI-positive patients. In our OLT, the incidence of infusion reactions was a little higher in ATI-positive patients than in non-positive patients (45.1% and 38.5%, respectively). Most infusion reactions observed in our trials were mild and moderate. Although the rate of ATI formation was higher in our study than that in the ATTRACT study, the occurrence of serious infusion reaction in our patients was rare (one of 141 patients), and similar to that in the ATTRACT study (one of 340 patients).

Infliximab was well tolerated throughout the DBT and OLT. There was no significant difference in incidence of adverse events among the treatment groups in the DBT. Most frequent adverse events in patients who received at least one infusion of infliximab during the trials were similar to those observed in previous studies[10,11,15]. The incidence of serious events in those patients was 14.9% (21 of 141 patients), comparable to the incidence over the 54 weeks of the ATTRACT study (16.7%)[11]. In 11 of these 21 patients, the serious adverse events were infectious. It has been reported that infliximab has the possibility of increasing susceptibility to infections, and serious infections, including tuberculosis and opportunistic infections, have occurred in previous clinical trials and post-marketing[23].

Close attention should be paid to serious infections during infliximab treatment. Since most Japanese people have been vaccinated with bacillus Calmette-Guerin (BCG), a PPD skin test should be positive in response to the BCG. This was why PPD skin test was not set for screening in this clinical trial. However, considering the prevalence of latent tuberculosis in Japan, and in order to evaluate tuberculosis as strictly as possible, tuberculosis should be assessed in all patients prior to treatment with infliximab using appropriate measures including chest radiograph, chest computed tomography scan, and PPD skin test. Infusion reactions were more frequent in ATI-positive patients in our trials, whereas the occurrence of serious infusion reaction was rare independent of the presence of ATI. However, the ELISA method has limited usefulness as a tool for measurement of ATI because the presence of serum infliximab can interfere with the detection or interpretation of the presence of ATI. Therefore, precautions should be taken to prevent infusion reactions irrespective of ATI development.

We conducted the first double-blind, placebo controlled trial of infliximab for Japanese patients with RA. In the DBT, the efficacy and safety of infliximab combined with low dose MTX were similar to those of the ATTRACT study. The data from these trials in Japan also supported the importance of an induction treatment of infliximab, followed by maintenance treatment without a long interval, giving stable serum concentrations in order to prevent formation of antibodies to infliximab.

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ORIGINAL ARTICLE

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Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan (RECONFIRM)

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Abstract This study aims to reconfirm the clinical efficacy and related factors of infliximab therapy, the first biological agent introduced to Japanese patients with rheumatoid arthritis (RA). Data of 351 RA patients with infliximab were collected retrospectively from three major centers for management of rheumatic diseases in Japan. Infliximab was infused according to the approved method, and the clinical response was evaluated following 22 weeks of infliximab therapy in 258 patients using the European League Against Rheumatism (EULAR) response criteria. DAS28-CRP (Disease Activity Score including a 28-joint count/C-reactive protein) with a threshold of 4.1 or 2.7 for the high or low disease activity cut-off was also used. A total of 90.3% of patients exhibited high disease activity before infliximab therapy. After 22 weeks of infliximab therapy, the proportions of patients exhibiting high activity, moderate activity, low activity, or in clinical remission were 27.9%, 33.3%, 10.9%, or 27.9%, respectively, thereby indicating good overall efficacy of infliximab therapy. A good or moderate overall response to therapy was achieved in 84.5% of patients. Male sex, rheumatoid factor (RF) negativity, low CRP, lower swollen joint count and a low prednisolone dose were significantly related to the clinical response. Furthermore, male sex, older age, and a high tender joint count had a significant correlation with treatment discontinuation as a result of adverse reactions. In conclusion, we have reconfirmed the effectiveness of infliximab in Japanese patients with RA by using DAS28-CRP and EULAR response criteria. These data will facilitate more efficacious use of this expensive biological agent in the daily practice of rheumatology in Japan.

Key words EULAR response · Infliximab · Retrospective study · Rheumatoid arthritis

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Introduction

After prolonged efforts, the therapeutic strategy underlying the management of rheumatoid arthritis (RA) has been dramatically improved in the last 10 years.[1] A number of new therapeutic agents have been introduced including anti-cytokine therapy using biological agents. These therapies target key molecules involved in the disease process and have had a striking impact on RA therapy, as they are clinically efficacious in the suppression of the disease activity.[2,3] In particular, inhibition of the progression of structural damage and improvement of physical function and quality of life in active RA patients is a hallmark of anti-tumor necrosis factor (TNF) biological agents and was not achieved by conventional disease modifying anti-rheumatic agents (DMARD).[4]

Infliximab is a chimeric anti-TNF alpha monoclonal antibody[5–7] and was first used in 2003 to treat Japanese patients with RA, 5 years after it was first approved in the United States for RA patients. By June 2006, approximately 13000 patients with RA had received the infusion of infliximab in Japan. Although relatively small clinical studies have reported the efficacy and safety of infliximab therapy in Japan, there is no well-established firm evidence of the efficacy of this agent in Japan. We therefore designed this retrospective clinical study to examine the efficacy of infliximab therapy and related factors in several major rheumatology centers in Japan.

Patients and methods

Data and information on RA patients fulfilling the diagnostic criteria of the American College of Rheumatology were collected from three major rheumatology centers in Japan, including the Institute of Rheumatology, Tokyo Women's Medical University; the First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health Japan, Kitakyushu; and the Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Saitama Medical Center, Saitama Medical University, Saitama. All patients receiving infliximab treatment in each institution by December 2005 were registered in this retrospective study.

Demographic data including disease duration and concomitant therapy were collected from medical charts. The following parameters were evaluated before and at 22 weeks after the initial infliximab infusion: tender joint count (TJC) 28, swollen joint count (SJC) 28, patient's assessment of pain on a visual analog scale (patient's pain VAS), patient's global assessment of disease activity (patient's global VAS), physician's global assessment of disease activity (physician's global VAS), and C-reactive protein (CRP). Data were statistically analyzed using Wilcoxon's signed rank test.

Infliximab therapy

Infliximab was infused to patients at 0, 2, and 6 weeks followed by every 8 weeks at a dose of 3 mg/kg according to the drug labeling and the guidelines of the infliximab study group in the Ministry of Health, Welfare and Labor in Japan.[8] Concomitant use of methotrexate was instituted in all cases although the dose of methotrexate was determined by each attending physician.

Therapeutic response

Disease activity was assessed by Disease Activity Score including a 28-joint count (DAS28)-CRP that was calculated according to the authorized formula (http://das-score.nl/). The value of DAS28-CRP is reported to be less than the original DAS28 using the erythrocyte sedimentation rate (ESR), and we used a threshold of 4.1 instead of the original 5.1 as the cut-off for high activity and 2.7 instead of 3.2 as the cut-off for low activity. Thus, we defined a value of DAS28-CRP >4.1 as high activity, 2.7–4.1 as moderate activity, <2.7 as low activity with <2.3 being defined as remission.[9] The response to infliximab therapy at 22 weeks was evaluated by the European League Against Arthritis (EULAR) response criteria using 4.1 and 2.7 as the thresholds for the high and low disease activities, respectively.[10]

Discontinued subjects

Cases in which infliximab therapy was discontinued were further analyzed and the causes of discontinuation were evaluated. In order to determine which patient's characteristic was related to the cause of cessation, a stratified Cox regression was performed to correct for the differences between participating institutes.

Statistical analysis

Sex, age, duration of disease, stage (Steinbrocker), class (Steinbrocker), rheumatoid factor (RF) positive/negative, concomitant methotrexate dose, concomitant prednisolone dose and the initial levels of CRP/TJC/SJC/GH were used for the explanatory variables for the logistic regression and Cox regression.

Results

Demographic data of patients from three institutes

Table 1 shows the demographic data of 351 patients receiving infliximab therapy from three institutes for rheumatology in Japan. Age, sex, and disease duration were comparable among these three institutes, although the %user and dose of methotrexate or prednisolone were significantly divergent and the disease activity assessed by TJC, SJC, GH, and DAS28 was also different. Thus, the efficacy of infliximab was investigated thereafter within individual institutions.

Efficacy of infliximab therapy

Clinical efficacy was evaluated by DAS28-CRP. The changes of DAS28-CRP before and after 22 weeks of infliximab therapy in 258 patients with available data are shown in Fig. 1. The average DAS28-CRP significantly decreased from 5.58 ± 1.10 to 5.25 ± 1.38 ($P < 1 \times 10^{-10}$) indicating the effectiveness of infliximab therapy.

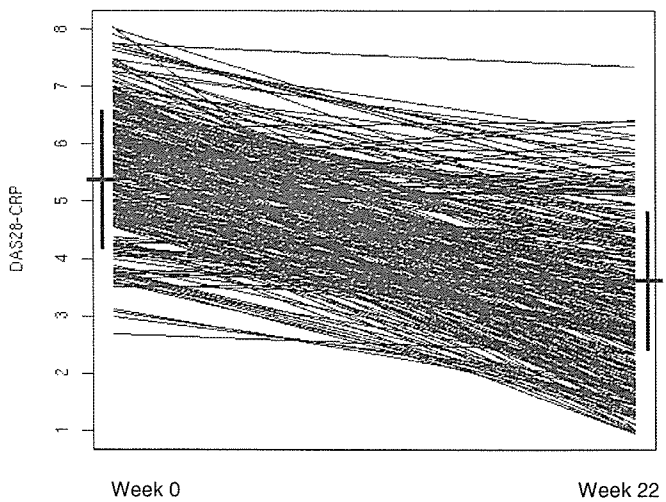

Fig. 1. Trends of DAS28-CRP (Disease Activity Score including a 28-joint count/C-reactive protein) before and after 22 weeks of the introduction of infliximab infusion. DAS28-CRP significantly decreased from 5.58 ± 1.10 to 5.25 ± 1.38 ($P < 1 \times 10^{-10}$)

Table 1. Baseline characteristics of patients in three institutions of rheumatology in Japan

Variables	Institution 1		Institution 2		Institution 3		Total	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Female (%)	0.84	–	0.91	–	0.89	–	0.89	–
Age (years)	49.7	13.0	54.4	12.8	54.0	11.5	53.1	12.6
Duration (months)	132.2	113.	112.8	110.0	104.2	101.2	115.5	108.8
Stage	3.22	0.84	2.77	0.95	3.07	1.03	2.96	0.96
Class	2.10	0.61	2.08	0.36	2.52	0.66	2.20	0.55
RF positive(%)	88.4	–	87.3	–	84.9	–	87.0	–
Methotrexate user (%)	100.0		100.0		100.0		100.0	
Methotrexate dose (mg/week)	7.84	1.19	7.02	1.07	8.92	2.76	7.74	1.88
Prednisolone user (%)	79.2	–	59.5	–	78.7	–	69.4	–
Prednisolone (mg/day)	4.85	3.41	2.84	3.14	4.91	3.55	3.89	3.46
CRP	3.48	2.56	2.99	2.88	3.71	2.61	3.33	2.73
GH	55.8	18.74	73.2	19.3	56.8	22.3	63.9	21.8
TJC28	9.3	8.6	12.0	6.9	10.6	7.3	10.9	7.5
SJC28	8.7	5.6	11.0	5.7	12.8	6.6	11.0	6.1
TJC68	13.3	12.4	16.0	9.2	15.8	10.1	15.4	10.3
SJC68	10.7	6.5	13.9	7.6	16.9	9.5	14.2	8.3
DAS28-CRP	5.17	1.12	5.78	1.03	5.63	1.12	5.58	1.11

RF, rheumatoid factor; CRP, C-reactive protein; GH, general health; TJC, tender joint count; SJC, swallen joint count; DAS, disease activity score

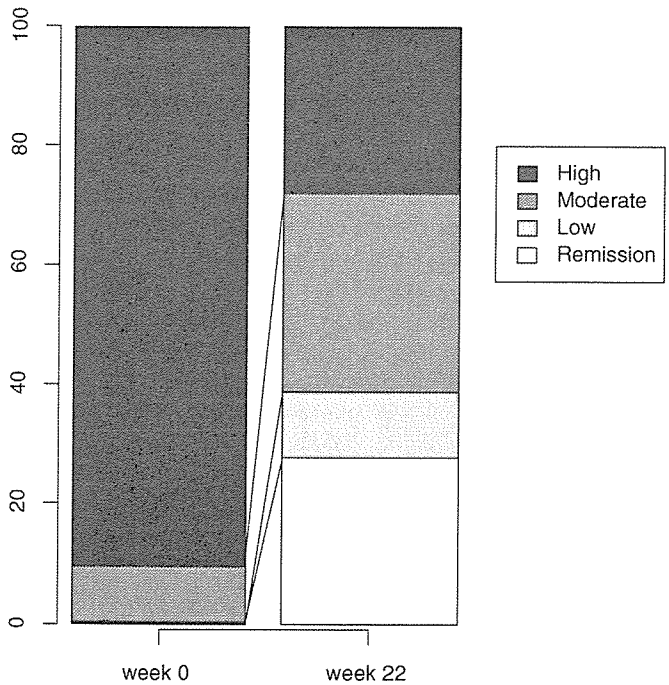

Fig. 2. Disease activity state before and after 22 weeks of the introduction of infliximab infusion. A total of 90.3% of patients were in a high activity state before the infliximab infusion. However, most patients responded to the infliximab therapy, and the percentages of patients exhibiting high activity, moderate activity, low activity or in clinical remission were 27.9%, 33.3%, 10.8%, and 27.9%, respectively, after 22 weeks of infliximab treatment

Also, the categorized disease activity is shown in Fig. 2. A total of 90.3% of patients exhibited a high disease activity before the infliximab therapy. At 22 weeks after infliximab therapy, the proportion of patients exhibiting high activity, moderate activity, low activity, or in clinical remission were 27.9%, 33.3%, 10.9%, or 27.9%, respectively, thereby indicating the overall efficacy of infliximab therapy.

Table 2. Clinical response to infliximab therapy based on EULAR criteria

	Institution 1[a]	Institution 2[b]	Institution 3[c]	Total
Good	18 (24.0)	56 (53.3)	24 (30.8)	96 (38.0)
Moderate	34 (45.3)	43 (41.0)	43 (55.1)	120 (46.5)
None	23 (30.7)	6 (5.7)	11 (14.1)	40 (15.5)
Total	75	105	78	258 (100)

EULAR, European League Against Arthritis
[a]Institute of Rheumatology, Tokyo Women's Medical University
[b]The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan
[c]Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Saitama Medical Center, Saitama Medical University

Table 3. Discontinuation of infliximab therapy and its cause

	Institution 1[a]	Institution 2[b]	Institution 3[c]	Total
Lack of efficacy	15	12	5	32
Adverse events	15	11	9	35
Other reasons	6	13	6	25
Total	36	36	20	92

[a]Institute of Rheumatology, Tokyo Women's Medical University
[b]The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan
[c]Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Saitama Medical Center, Saitama Medical University

The clinical response using the EULAR response criteria is shown in Tables 2 and 3. Although the response rate was quite diverse between the three institutions, a good or moderate overall response to therapy was achieved in 84.5% of patients.