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]. 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

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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.

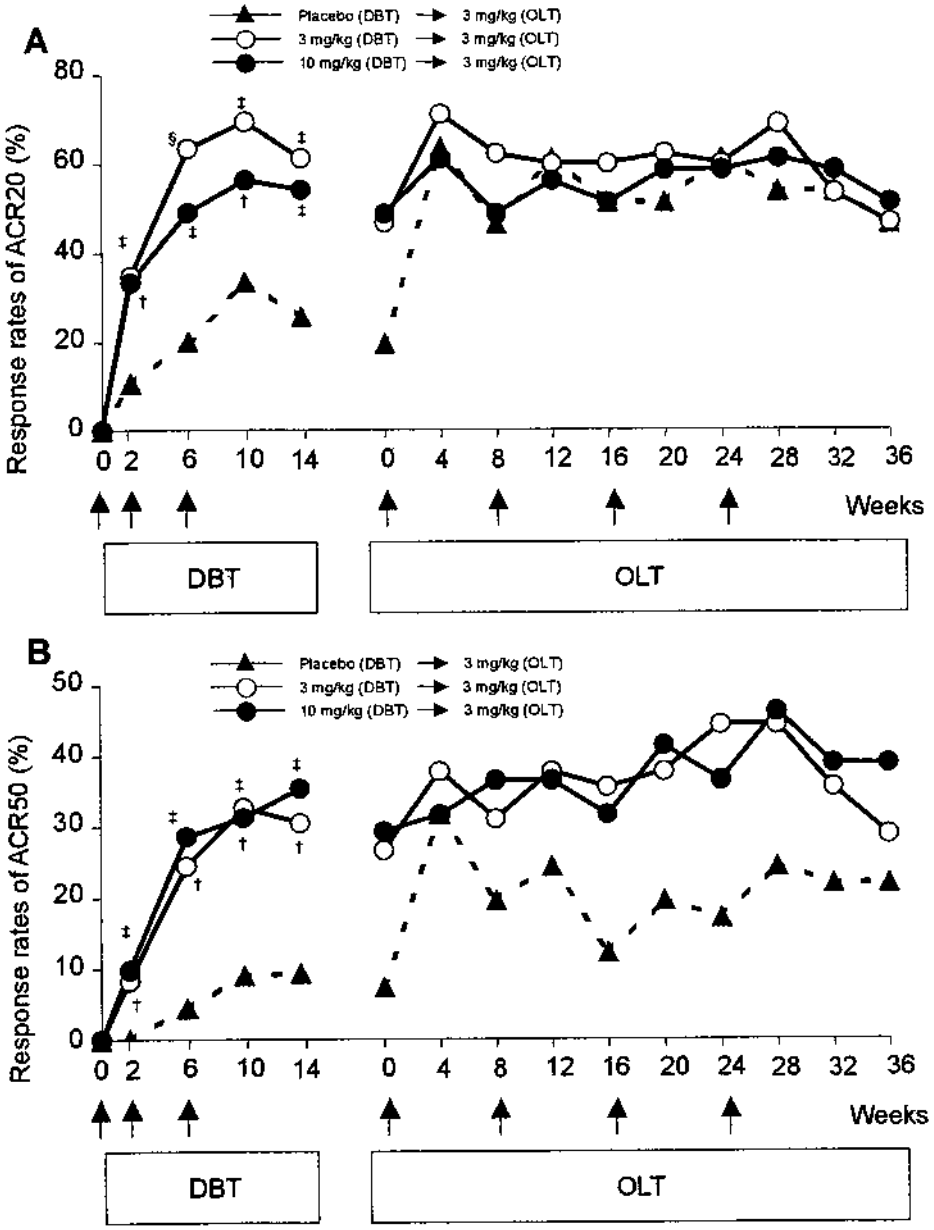

Figure 1. Response rates based on the ACR criteria in the DBT and OLT. A. 20% improvement according to the ACR criteria (ACR20). B. 50% improvement according to the ACR criteria (ACR50). Arrows indicate the time of infusions. Significance versus placebo: $^{\dagger}p < 0.05$, $^{\ddagger}p < 0.01$, $^{\S}p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

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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