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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 13 000 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.

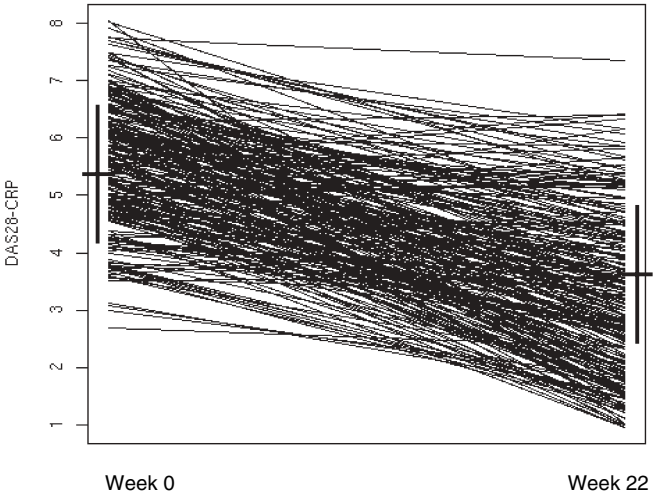

Fig. 1. Trends of DAS28-CRP (Disease Activity Score including a 28-joint count/C-reactive protein) before and after 22 weeks of the introduction of infliximab infusion. DAS28-CRP significantly decreased from 5.58 ± 1.10 to 5.25 ± 1.38 ($P < 1 \times 10^{-10}$)

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

	Institution 1		Institution 2		Institution 3		Total	
Variables	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

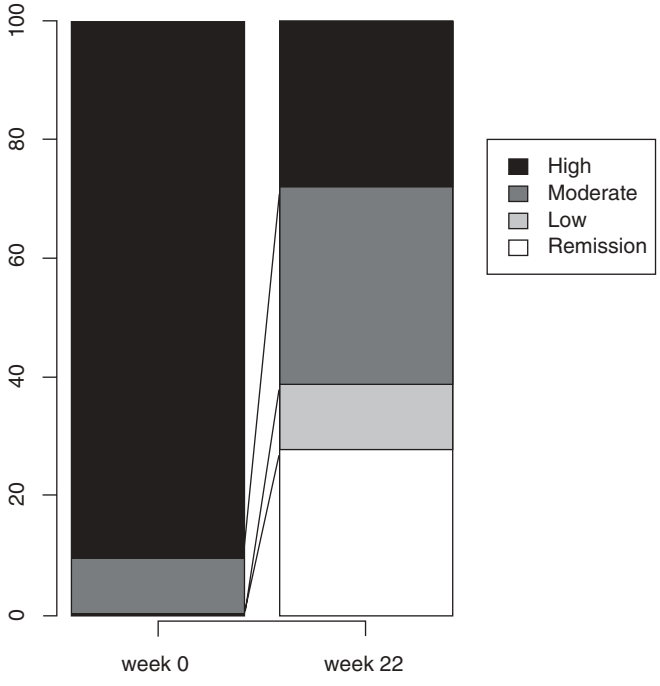

Fig. 2. Disease activity state before and after 22 weeks of the introduction of infliximab infusion. A total of 90.3% of patients were in a high activity state before the infliximab infusion. However, most patients responded to the infliximab therapy, and the percentages of patients exhibiting high activity, 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.

Table 4. Logistic regression analysis to predict good (vs. moderate + none) response to infliximab therapy

$n = 224$	Coefficient	OR	Std. error	z value	Pr(>|z|)
(Intercept)	1.1980	3.3134	0.7610	1.5742	0.1154
Institution 2	1.0406	2.8310	0.4778	2.1779	0.0294
Institution 3	1.5813	4.8613	0.4445	3.5575	0.0004
CRP	–0.1393	0.8700	0.0625	–2.2281	0.0259
SJC	–0.0429	0.9580	0.0203	–2.1125	0.0346
RF positive	–0.7751	0.4607	0.4197	–1.8465	0.0648
Female	–0.8973	0.4077	0.5037	–1.7815	0.0748
Prednisolone	–0.0700	0.9324	0.0481	–1.4543	0.1459

Table 5. Logistic regression analysis to predict good + moderate (vs. none) response to infliximab therapy

$n = 224$	Coefficient	OR	Std. error	z value	Pr(>|z|)
(Intercept)	–0.1806	0.8348	0.3998	–0.4517	0.6515
Institution 2	1.3029	3.6799	0.4856	2.6829	0.0073
Institution 3	2.0559	7.8139	0.5190	3.9616	0.0001
TJC	0.0603	1.0622	0.0235	2.5700	0.0102

Table 6. Stratified Cox regression analysis to predict the discontinuation of infliximab therapy as a result of adverse events

$n = 303$	Coefficient	RR	Std. error	z value	Pr(>|z|)
Female	–1.3791	0.2518	0.4955	–2.7831	0.0054
Age	0.0662	1.0684	0.0238	2.7836	0.0054
TJC	0.0559	1.0575	0.0178	3.1349	0.0017

Discontinuation of infliximab therapy

Infliximab was discontinued in 92 cases (26.2%) among 351 patients at 52 weeks and included 35 cases (10%) with adverse reactions and 32 cases (9.1%) with a lack of efficacy (Tables 4–6). Adverse events included seven cases of infusion reactions, four cases of pneumonia, four cases of interstitial pneumonitis, two cases of *Pneumocystis* pneumonia, and three cases of malignancies.

Demographic factors related to the clinical efficacy of infliximab therapy

Because the demographic data as well as clinical response were diverse among the three institutions, we performed a multivariate analysis using a logistic regression with stepwise selection after the correction of institutional differences (Tables 4–6). Comparison of good ($n = 98$) versus moderate or no response ($n = 160$), analysis showed that male sex, RF negativity, a low CRP, lower SJC, and a lower prednisolone dose were significantly related to the clinical response (Table 4). However, a comparison of good and moderate responses ($n = 218$) versus no response ($n = 40$) showed that a higher TJC was related to clinical response (Table 5).

Demographic factors related to the discontinuation of infliximab therapy

In 92 cases who terminated infliximab treatment, the time and the cause of discontinuation were evaluated. A stratified Cox regression was performed to analyze the causative factor resulting in discontinuation of the infusion. There was no significant factor responsible for the discontinuation of infliximab due to the lack of efficacy on the one hand. On the other hand, male sex, older age, and a higher TJC had a significant correlation with the discontinuation of infliximab due to adverse reactions.

Discussion

This study was conducted to determine the efficacy and related factors of infliximab therapy in Japanese RA patients receiving treatment in a university hospital outpatient setting at three institutions for rheumatic diseases.

The safety profile of infliximab therapy was extensively investigated in Japan using an all-case registered post-marketing surveillance system (PMS) that was conducted by Tanabe Pharmaceutical Co. (Osaka, Japan) under the auspices of the regulatory authority of the Japanese government, with effective suggestions from the subcommittee of the Japan College of Rheumatology. A total of 5000 cases were registered from July 2003 to January 2005 and were extensively investigated for toxicity for 6 months after starting infliximab therapy. As a result, the entire profile of adverse events related to infliximab therapy was clearly identified and the information from this PMS study was incorporated in the daily practice of rheumatology clinics in Japan.[11] Efficacy data were also investigated in this PMS study as one of the secondary measures. The assessment of efficacy, however, was based only on the physician's general evaluation and not on quantitative measures such as American College of Rheumatology (ACR) improvement of EULAR criteria.

Thus, this study was planned to show the efficacy of infliximab using scientifically validated measures. In particular, since we aimed to show the predictive factors for the efficacy and toxicity of infliximab therapy, we named this study "RECONFIRM" (Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group).

DAS28-CRP was used for the evaluation of disease activity, because all three institutes measured CRP level on a regular basis. Because DSA28-CRP is noted to be less than the original DAS28 measured with ESR, a newly proposed threshold of 4.1 and 2.7 was used for the threshold of high and low disease activity state (Inoue et al, unpublished).

Patients received the approved dose of 3 mg/kg of infliximab in combination with methotrexate. As with any other previous reports, infliximab showed high efficacy in reducing disease activity. The baseline characteristics of patients in this study showed that the disease activity of these patients was quite high and corresponded to the disease activity of the ATTRACT,[6] ASPIRE[12] and TEMPO[13] trials. Even in these highly active patients, the approved dose of 3 mg/kg of infliximab with methotrexate showed a clinical response in a total of 84.5% of patients based on EULAR

criteria, and 27.9% of patients entered clinical remission (DAS28-CRP < 2.3). Infusion of infliximab every 8 weeks after the initial dose is the approved method in Japan and thus the clinical response may decline after 30 weeks. Actually, there are several reports indicating a decline of the clinical response to infliximab after the interval of infusion becomes 8 weeks. Presumably, the clinical response at 22 weeks of infliximab therapy shown in this study might be a maximum level of efficacy. Based on the physician's evaluation in the above-mentioned all-case PMS study, 91.4% of patients responded and 34% of patients entered clinical remission by the infliximab infusion. Thus, this RECONFIRM study reconfirmed the clinical efficacy of infliximab infusion in Japan using the verified, quantitative measures of DAS28-CRP.

Because biological agents are quite expensive, and serious adverse events are likely to be expected in a certain proportion, the prediction of efficacy and safety of biologics is quite beneficial to both patients and physicians. We tried to identify these predisposing factors from the demographic characteristics of RA patients. Sex, age, duration of disease, stage (Steinbrocker), class (Steinbrocker), RF positivity/negativity, 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. Because there was a significant divergence in the baseline data and clinical response in these three institutions, a careful correction of the data was conducted before the regression analysis. Our data indicated that male sex, RF negativity, a low CRP, lower SJC, and lower prednisolone dose were significant predictive factors for the EULAR good response, whereas male sex, older age and higher TJC were significant predictors for the discontinuation of treatment as a result of adverse reactions. We should take these factors into consideration when infliximab therapy is administered to our patients. It is intriguing that male sex is predictive of both good response and discontinuation as a result of adverse events.

Although it has been said that patients at an earlier stage of the disease are sensitive to anti-rheumatic treatments,[14] the duration of disease was not related to the EULAR response in this study. This study was performed as a retrospective analysis of data collected in daily practice and thus there are many confounding factors that might affect the data. Further analysis is required on this issue.

The limitations of this study include the retrospective nature of the study design. Because all patients who had infliximab therapy by December 2005 in each institution were included, there is no substantial bias on patient selection. However, we have not provided any limitations on the concomitant drugs such as methotrexate and prednisolone or on the previous treatment just before the introduction of infliximab, and these might therefore result in a wide diversity of baseline characteristics of patients.

In conclusion, this RECONFIRM study reconfirmed the effectiveness of infliximab in Japanese patients with RA by using DAS28-CRP and EULAR response criteria. Among 258 patients with active disease, 84.5% of patients had a clinical response at 22 weeks of infliximab therapy. Several demographic factors including male sex, RF negativity, a low CRP, fewer SJC, and a lower prednisolone dose were significant predictive factors for EULAR good response. Male sex, older age, and a higher TJC were significant predictors for the discontinuation of infliximab as a result of adverse reactions. The promising effectiveness of infliximab to improve measures of disease activity and prevent progression of this disabling disease in RA patients has allowed this therapy to become one of the critical advances in the management of RA. Our data will facilitate more efficacious use of this expensive biological agent in the daily practice of rheumatology in Japan.

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