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.

Acknowledgments The authors thank all medical staff in the three institutions for providing the data.

References

1. Firestein GS. Evolving concepts of rheumatoid arthritis. Nature 2003;423:356–61.
2. Kalden JR. Expanding role of biologic agents in rheumatoid arthritis. J Rheumatol Suppl 2002;66:27–37.
3. Weaver AL. Efficacy and safety of the anti-TNF biologic agents. Modern Rheum 2004;14(2):101–12.
4. Ostor AJ. Beyond methotrexate: biologic therapy in rheumatoid arthritis. Clin Med 2005;5(3):222–6.
5. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumor necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomized phase III trial. Lancet 1999;354:1932–9.
6. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med 2000;343:1594–602.
7. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Furst D, Weisman MH, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. Arthritis Rheum 2004;50:1051–65.
8. Miyasaka N, Takeuchi T, Eguchi K. Official Japanese Guidelines for the use of infliximab for rheumatoid arthritis. Modern Rheum 2005;15(1):4–8.
9. Inoue E, Yamanaka H, Hara M, Tomatsu T, Kamatani N. Comparison of DAS28-ESR and DAS28-CRP on threshold values. Ann Rheum Dis 2006;in press [Epub ahead of print].
10. van Riel PL, van Gestel AM, van de Putte LB. Development and validation of response criteria in rheumatoid arthritis: steps towards an international consensus on prognostic markers. Br. J Rheumatol 1996;35(Suppl 2):4–7.
11. Takeuchi T, Togo M, Etoh A, Suzuki T, Callegari PA, Gilmer KE. Safety of infliximab therapy in 4,475 Japanese patients with rheumatoid arthritis: results from post marketing surveillance study (Abstract). Ann Rheum Dis 2006;65(Suppl II):503.
12. St Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 2004;50:3432–43.
13. Klareskog L, van der Heijde D, de Jager JP, et al. TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363(9410):675–81.
14. Anderson JJ, Wells G, Verhoeven AC, Felson DT. Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. Arthritis Rheum 2000;43(1):22–9.