a modified scoring method on digitized and original radiographs. Arthritis Rheum 1998;41:1583–90.

10 Bruynesteyn K, Boers M, Kostense P, van der Linden S, van der Heijde D. Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. Ann Rheum Dis 2005;64: 179–82.

11 Peluso G, Michelutti A, Bosello S, Gremese E, Tolusso B, Ferraccioli G. Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis. Ann Rheum Dis 2011;70: 172–5.

12 Brown AK, Quinn MA, Karim Z *et al.* Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. Arthritis Rheum 2006;54: 3761–73.

13 Filippucci E, Iagnocco A, Meenagh G *et al.* Ultrasound imaging for the rheumatologist VII. Ultrasound imaging in rheumatoid arthritis. Clin Exp Rheumatol 2007; 25:5–10.

14 Brown AK, Conaghan PG, Karim Z *et al.* An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum 2008;58:2958–67

15 Saleem B, Brown AK, Keen H *et al.* Should imaging be a component of rheumatoid arthritis remission criteria? A comparison between traditional and modified composite remission scores and imaging assessments. Ann Rheum Dis 2011;70:792–8.

16 Dougados M, Devauchelle-Pensec V, Ferlet JF *et al.* The ability of synovitis to predict structural damage in rheumatoid arthritis: a comparative study between clinical examination and ultrasound. Ann Rheum Dis 2012. Advance Access published on 7 June 2012, doi:10.1136/annrheumdis-2012-201469.

17 Schirmer M, Duftner C, Schmidt WA, Dejaco C. Ultrasonography in inflammatory rheumatic disease: an overview. Nat Rev Rheumatol 2011;7:479–88.

18 Lainer-Carr D, Brahn E. Angiogenesis inhibition as a therapeutic approach for inflammatory synovitis. Nat Clin Pract Rheumatol 2007;3:434–42.

19 Naredo E, Collado P, Cruz A *et al.* Longitudinal power Doppler ultrasonographic assessment of joint inflammatory activity in early rheumatoid arthritis: predictive value in disease activity and radiologic progression. Arthritis Rheum 2007;57:116–24.

Mod Rheumatol
DOI 10.1007/s10165-012-0782-y

ORIGINAL ARTICLE

Monitoring C-reactive protein levels to predict favourable clinical outcomes from tocilizumab treatment in patients with rheumatoid arthritis

Toshihisa Kojima · Yuichiro Yabe · Atsushi Kaneko · Yuji Hirano · Hisato Ishikawa · Masatoshi Hayashi · Hiroyuki Miyake · Hideki Takagi · Takefumi Kato · Kenya Terabe · Tsuyoshi Wanatabe · Hiroki Tsuchiya · Daihei Kida · Tomone Shioura · Koji Funahashi · Daizo Kato · Hiroyuki Matsubara · Nobunori Takahashi · Yosuke Hattori · Nobuyuki Asai · Naoki Ishiguro

Received: 3 July 2012 / Accepted: 4 October 2012

Abstract
Objectives The inflammatory cytokine interleukin-6 (IL-6) directly stimulates C-reactive protein (CRP) expression. The present study aimed to examine how clinical treatment outcomes of rheumatoid arthritis (RA) with tocilizumab (TCZ), a humanised monoclonal anti-IL-6 receptor antibody, are related to CRP levels monitored for 52 weeks.
Methods One hundred and twenty-two RA patients who underwent TCZ treatment between May 2008 and September 2009 were registered in the Tsurumai Biologics Communication Registry. Data were collected at initiation of treatment (baseline) and over 52 weeks for Disease Activity Score 28-ESR (DAS28-ESR), Boolean core measurements, serum CRP levels and matrix metalloproteinase-3 levels. To compare clinical results, patients were divided into three groups based on treatment time required to achieve normal CRP levels.
Results Multivariate analysis using the Cox proportional-hazards regression model found that higher CRP levels at baseline was a significant and independent factor in predicting normal CRP levels over 52 weeks (hazard ratio 0.86 per 1 mg/dL). In contrast, disease duration, concomitant methotrexate use and previous tumour necrosis factor inhibitor failure were not significant factors. Patients with

T. Kojima (✉) · K. Terabe · K. Funahashi · D. Kato · H. Matsubara · N. Takahashi · Y. Hattori · N. Ishiguro
Department of Orthopaedic Surgery and Rheumatology, Nagoya University Hospital, Nagoya University School of Medicine, 65 Tsurumai, Showa, Nagoya, Japan
e-mail: toshik@med.nagoya-u.ac.jp

Y. Yabe
Department of Rheumatology, Tokyo Kosei Nenkin Hospital, Tokyo, Japan

A. Kaneko · H. Ishikawa · D. Kida
Department of Orthopaedic Surgery, Nagoya Medical Centre, Nagoya, Japan

Y. Hirano
Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan

M. Hayashi
Department of Rheumatology, Nagano Red Cross Hospital, Nagano, Japan

H. Miyake
Department of Orthopaedic Surgery, Ichinomiya Municipal Hospital, Ichinomiya, Japan

H. Takagi · H. Tsuchiya
Department of Orthopaedic Surgery, Nagoya Kyoritsu Hospital, Nagoya, Japan

T. Kato
Kato Orthopaedic Clinic, Okazaki, Japan

K. Terabe
Department of Orthopaedic Surgery, Fukuroi Municipal Hospital, Fukuroi, Japan

T. Wanatabe
Department of Orthopaedic Surgery, Kariya-Toyota General Hospital, Kariya, Japan

T. Shioura
Department of Orthopaedic Surgery, Shizuoka Kosei Hospital, Shizuoka, Japan

N. Asai · N. Ishiguro
Department of Orthopaedic Surgery, Nagoya University, Faculty and Graduate School of Medicine, Nagoya, Japan

Published online: 26 October 2012

normal CRP levels at 12 weeks of TCZ treatment achieved better clinical outcomes, including remission based on DAS28-ESR criteria, compared to patients with elevated CRP levels at 12 weeks.

Conclusions Adequate suppression of pathological IL-6 signalling during TCZ treatment improves clinical outcomes and can be monitored with serum CRP levels, a readily available biomarker in clinical practice.

Keywords Rheumatoid arthritis · Tocilizumab · C-reactive protein · Interleukin-6

Introduction

The goal of treating rheumatoid arthritis (RA) is remission [1]. Clinical trials have reported that early intervention is associated with better outcomes for patients treated with biologics [2–4]. Early intervention is also recommended by the European League Against Rheumatism and the American College of Rheumatology (ACR) [5, 6]. It is therefore important to predict and track the effectiveness of biologics in each patient using a variety of baseline characteristics found in clinical practice.

Because biological agents tend to have a specific target, maximum treatment efficacy should be achieved if the treatment can more adequately inhibit the pathological effect of target cytokines such as tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6). The biologic infliximab, an antibody against TNF-α with a dosage range of 3–10 mg/kg, could have its precise treatment amount determined by serum TNF-α levels in the patient [7]. In addition, biologic trough levels could be associated with clinical response [8] and the development of anti-drug antibodies during treatment with infliximab and adalimumab [9]. The ability to measure cytokines and trough levels is not available in daily clinical practice, however, which makes it difficult to know whether administered biologics are adequately inhibiting their targets.

Tocilizumab (TCZ), a humanised monoclonal antibody against the IL-6 receptor, was approved in 2008 for clinical practice in Japan. The efficacy of TCZ for RA was demonstrated in several clinical trials [10–13] and in practice [14–16].

C-reactive protein (CRP) is a major acute-phase protein expressed in acute and chronic inflammatory diseases. In inflammation due to RA, various cytokines, including TNF-α, IL-6, and IL-1 and others, are expressed and construct a complex network with each other. IL-6 is a pivotal cytokine for inducing CRP in hepatocytes [17]. A recent study demonstrated that transcriptional complex formation of signal transducer and activator of transcription 3 (STAT3), cFos, and hepatocyte nuclear factor-1α (HNF-1α) is needed for full induction of CRP gene expression by IL-1 and IL-6 [18]. Based on these results, TCZ is expected to inhibit the interaction between IL-6 and other cytokines, which normalizes the expression level of CRP.

Importantly, TCZ trough levels should correlate with serum CRP level [19], the latter of which is a convenient and readily accessible marker used in daily clinical practice. Thus, by monitoring CRP expression, one could also easily track TCZ trough levels during RA treatment.

The present study focussed on the association between TCZ treatment outcomes for RA and CRP levels, and aimed to determine the time required to achieve normal serum CRP levels.

Patients and methods

Patient selection and data collection

All eligible patients were registered in and followed by the Tsurumai Biologics Communication Registry Study Group (TBCR), an RA research consortium started in 2008 that consists of Nagoya University Hospital and 12 affiliated institutes [20]. Briefly, TBCR was initiated in October 2008 to study long-term efficacy and safety of treatment involving biological agents in RA patients. Data were collected retrospectively from 2003 to 2008 and prospectively after 2008. Patient data for characteristics and disease activity are registered and available for all RA patients treated with biological agents commercially available in Japan who are treated at institutes that have joined the TBCR. Registered data are updated once per year and contain a great deal of information, including drug continuation, reason for switching drugs, and adverse events (e.g. surgery, pregnancy) occurring during treatment with biological agents. As of September 2010, 1481 RA patients treated with biological agents have been registered with the TBCR. For this study, 134 patients were selected who underwent TCZ treatment between May 2008 and September 2009. The present study was approved by the Ethics Committee at the Nagoya University School of Medicine. Patient anonymity was maintained during data collection, and the security of personal information was strictly controlled.

All patients met the 1987 ACR classification criteria for RA. TCZ (8 mg/kg) was infused every four weeks according to the drug label and Japan College of Rheumatology guidelines. Demographic data were recorded at the initiation of treatment (baseline), and included disease duration, concomitant treatments [methotrexate (MTX) and prednisolone], previous biologics use, joint damage (Steinbrocker stages) and daily dysfunction (Steinbrocker classifications).

Table 1 Patient characteristics at baseline according to the time required for normalisation of CRP levels

Variables	Total (n = 122)		4w(−) (n = 78)		4w(+)12w(−) (n = 28)		12w(+) (n = 16)		P value
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	
Age (years)	59	47–66	59	49.8–66	58	41–63.5	61.5	54.3–67.8	0.32
Female/male	96/27		64/14		20/8		11/5		0.33
Disease duration (years)	7.9	3.3–14.0	7.6	3.4–14.9	8.1	1.8–13.4	8.6	5.7–12.8	0.90
Stage (I/II/III/IV)	19/29/28/47		16/20/12/30		2/7/7/12		1/2/8/5		0.06
Class (1/2/3/4)	18/59/46/0		15/39/24/0		1/13/14/0		2/6/8/0		0.15
Previous anti-TNF-α use (%)	60.7		50		82.1		75		0.005#
MTX use (%)	39		39		39		38		0.99
MTX dose (mg/week)	8	6–8	6	6–8	8	7.5–10	8	6–8	0.05
PSL use (%)	70		65		79		75		0.38
PSL dose (mg/day)	5	3–5	5	3–5	5	3.6–5.3	5	3–9.4	0.51
Tender joint count (/28)	6	4–12.3	6	4–25.1	4.5	2.3–14.5	8.5	5–23.5	0.12
Swollen joint count (/28)	6	3–10	5	3–9	6	3.25–8	11.5	5.3–17.8	0.015*
General health (mm)	52	35–75	52	32.5–74.5	49.5	35.5–78.8	64.5	45.5–84	0.43
ESR (mm/1 h)	66	41.5–93.5	48	32.5–81	71.5	59.8–94.5	102.5	75.5–115.8	0.0001*
CRP (mg/dL)	2.3	0.9–4.6	3.1	1.5–5.3	4	1.9–5.5	5.1	3.6–6.3	<0.0001*
DAS28-ESR(4)	5.6	5.0–6.6	5.39	4.8–6.4	5.7	5.1–7.0	6.6	5.7–8	0.003*
MMP-3 (ng/mL)	280.9	143–441.2	282.6	141.4–441.6	304.3	143.7–470.6	241.2	147.6–351.7	0.78

4w(−) normal CRP levels at 4 weeks, *4w(+)12w(−)* normal CRP levels at 8–12 weeks, *12w(+)* positive CRP levels at 12 weeks

IQR interquartile range, *TNF* tumour necrosis factor, *MTX* methotrexate, *PSL* prednisolone, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *DAS28-ESR* Disease Activity Score 28-ESR, *MMP-3* matrix metalloproteinase-3

Statistically significant P values (<0.05) were determined by the * Kruskal–Wallis test or # chi-squared test

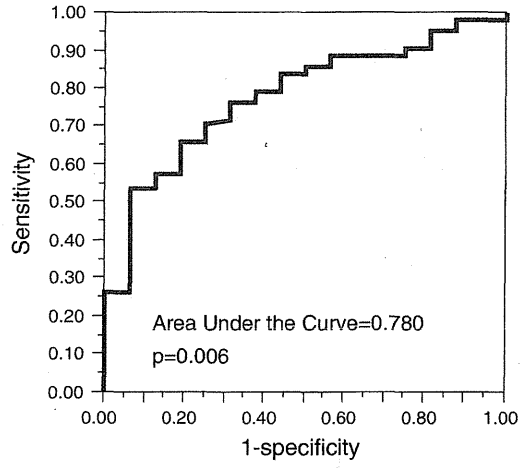

Fig. 1 Predicting baseline CRP levels to achieve normal CRP levels in 12 weeks. A receiver operating characteristic (ROC) curve was prepared

The following clinical outcome parameters were recorded at baseline, 24 and 52 weeks: tender joint count on 28 joints (TJC28), swollen joint count on 28 joints (SJC28), patient global assessment of disease activity (GH-VAS), erythrocyte sedimentation rate (ESR) and serum matrix metalloproteinase-3 (MMP-3) levels. Serum CRP levels were also recorded at baseline, 4, 8, 12, 24 and 52 weeks.

CRP measurements were performed at each TBCR institute, with the normal range for each institute used. MMP-3 measurements were performed at each institute or outsourced to clinical laboratories using the same ELISA kit (Panaclear MMP Latex, Sekisui Medical Co. Ltd., Tokyo, Japan). The normal MMP-3 range was based on data from the manufacturer: 17.3–59.7 ng/mL for females and 36.9–121 ng/mL for males. Remission rates at 24 and 52 weeks were evaluated based on the Boolean approach and Disease Activity Score 28-ESR (DAS28-ESR).

Statistical analyses

Continuous variables are expressed as the median and interquartile range, while categorical variables are expressed as percentages. Patients were categorised into the following groups based on treatment time for CRP reduction to normal levels: normalised at 4 weeks [group 4w(−)], normalised at 8–12 weeks [group 4w(+)12w(−)] and positive CRP levels at 12 weeks [group 12w(+)]. Differences in patient characteristics were evaluated among the three groups using the Kruskal–Wallis test for continuous variables and the chi-squared test for categorical variables.

Clinical responses from baseline were evaluated using the Wilcoxon signed-rank test.

A receiver operating characteristic (ROC) curve was prepared to estimate whether baseline CRP levels can predict their normalisation at 12 weeks. The impact of baseline CRP levels, concomitant MTX use, previous use of TNF-α inhibitors and disease duration on normalisation of CRP levels over 52 weeks was analysed using a Cox proportional-hazards regression model.

Drug survival rate over 52 weeks was determined by the Kaplan–Meier method.

Drop-out rates are often informative, as the population of patients that dropped out is different from that which completed the study. In cases where TCZ therapy was discontinued before 24 weeks and 52 weeks, the data at last observation were used to assess discontinuation (the last-observation-carried-forward method), rather than excluding those data.

All statistical data were analysed using JMP version 8.0 (SAS Institute Japan, Tokyo, Japan), and $P < 0.05$ was considered statistically significant.

Results

Of the 134 patients selected for this study, 11 were excluded from analysis because they moved during TCZ therapy and final treatment status could not be determined; an additional patient was excluded due to lost data.

Baseline characteristics of all included patients are shown in Table 1 and are categorised by treatment time required to reduce CRP to normal levels.

Nineteen patients discontinued treatment but were included in the analysis using the last-observation-carried-forward method. Of the patients who discontinued TCZ therapy, 11 were in group 4w(−) (adverse events, $n = 6$; inadequate response, $n = 3$; patient convenience, $n = 2$), two were in group 4w(+)12w(−) (adverse events, $n = 1$; inadequate response, $n = 1$) and six were in group 12w(+) (adverse events, $n = 5$; inadequate response, $n = 1$).

Of the 122 patients included in the present study, 106 (86.9 %) achieved normal CRP levels at 12 weeks. Seventy-eight of the 106 cases (73.6 %) achieved normal CRP levels after only 4 weeks.

Of the three groups, group 4w(−) had the highest proportion of anti-TNF-α biologics-naïve patients. The proportion of concomitant MTX patients (39 %) was relatively low, with no significant differences among the groups.

DAS28-ESR, as well as its components SJC28 and ESR, significantly increased with the time required to achieve normal CRP levels. CRP levels also significantly increased with normalisation time. MMP-3 levels remained about the same between groups.

The ROC curve for baseline CRP was able to significantly predict normalised CRP levels at 12 weeks (area under the curve 0.780, $P = 0.006$, Fig. 1). The baseline CRP cut-off to predict normalisation at 12 weeks was 2.13 mg/dL, with 93.7 % specificity and 53.8 % sensitivity.

Only 37.5 % of the patients in group 12w(+) achieved normal CRP levels at 52 weeks. Using Cox's proportional-hazards regression model, univariate analysis found that the higher disease activity (CRP per 1 mg/mL, ESR per 1 mm/h, swollen joint count, DAS28-ESR per 1 point) had a significant impact on normalisation of CRP levels over 52 weeks. For multivariate analysis, CRP was used as a measure of disease activity. We found that higher CRP levels significantly impacted the time required to achieve normalisation of CRP levels over 52 weeks (HR per 1 mg/dL, 0.86; 95 % CI 0.78–0.95) (Table 2). In contrast, other factors such as concomitant MTX use, previous TNF-α inhibitor use and disease duration were not found to be significant to this end (Table 2).

Table 2 Impact of baseline clinical variables on achievement of normal CRP levels for 52 weeks

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95 %CI)	*P* value	Hazard ratio (95 %CI)	*P* value
Age (years)	1.001 (0.99–1.02)	0.85	0.999 (0.98–1.01)	0.89
Disease duration (years)	1.000 (0.98–1.02)	1.00	1.003 (0.978–1.03)	0.79
Gender (male)	0.856 (0.54–1.31)	0.48	0.948 (0.58–1.50)	0.83
CRP (mg/mL)	0.852 (0.78–0.93)	0.0001	0.860 (0.78–0.945)	0.001
Use of anti-TNF agents	0.682 (0.48–1.01)	0.05	0.944 (0.64–1.39)	0.35
Concomitant MTX	0.962 (0.66–1.39)	0.84	0.945 (0.64–1.39)	0.77
Concomitant PSL	0.915 (0.62–1.39)	0.67	1.001 (0.67–1.54)	0.99

Statistically significant *P* values (<0.05) were determined by the Cox proportional-hazards regression model

CI confidence interval, *TNF* tumour necrosis factor, *MTX* methotrexate, *PSL* prednisolone, *CRP* C-reactive protein

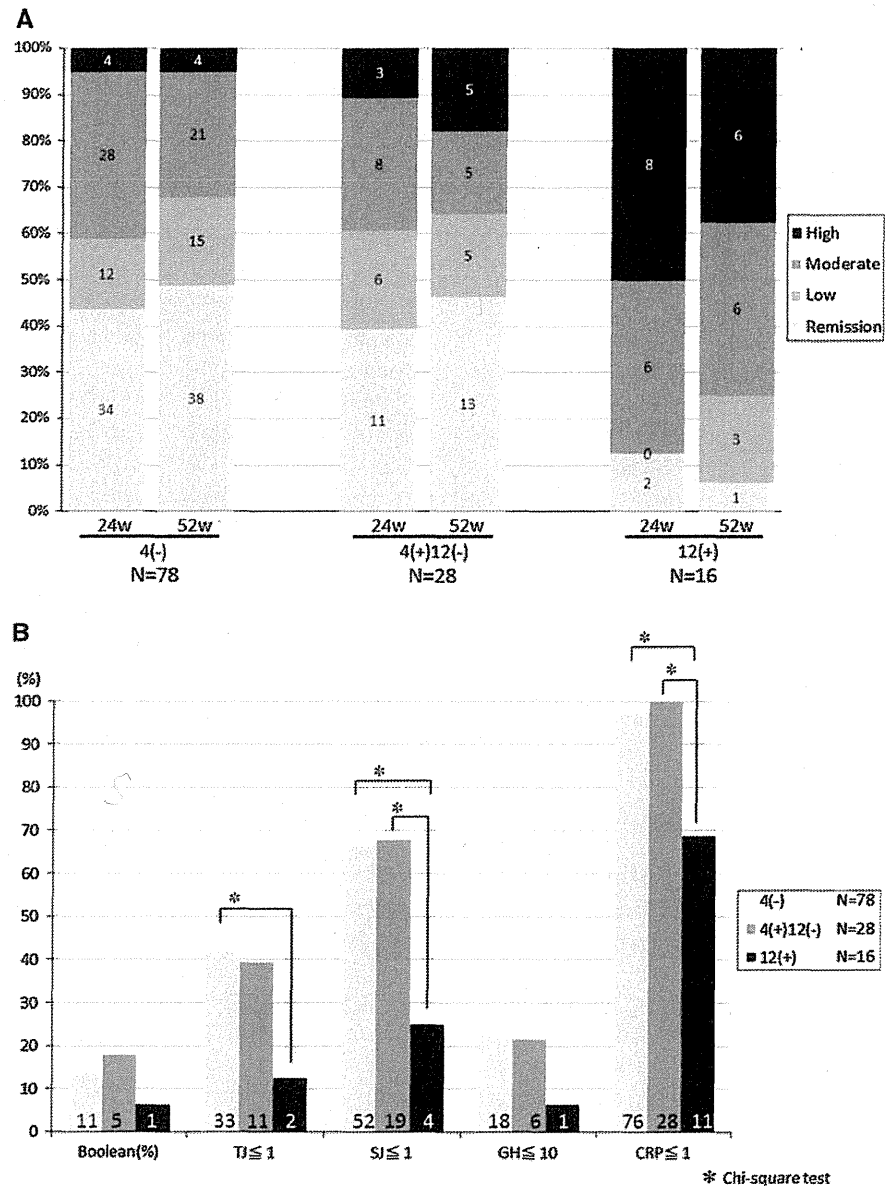

Fig. 2 Differences in tocilizumab efficacy based on DAS28-ESR criteria and Boolean core set measurements categorised by time (weeks) required to achieve normal CRP levels. **a** Remission rates based on DAS28-ESR criteria were compared among patients categorised by the time required to reduce CRP levels to normal. **b** Evaluation based on Boolean core set measurements at 52 weeks. *4w(−)* normal at 4 weeks, *4w(+)12w(−)* normal at 8–12 weeks, *12w(+)* positive at 12 weeks. Numbers of patients are indicated by the *bars*

Patients in group 4w(−) and group 4w(+)12w(−) had a significantly higher remission rate based on DAS28-ESR criteria than patients in group 12w(+) at 24 and 52 weeks. Remission rates did not differ significantly between group 4w(−) and group 4w(+)12w(−) (Fig. 2a). Remission rates for the three groups did not differ when defined by the Boolean core set measurement, although group 4w(−) achieved SJC28 ≤1 and/or TJC28 ≤1 more often than patients in group 4w(+)12w(−). None of the core set components differed significantly between group 4w(−) and group 4w(+)12w(−) (Fig. 2b). Furthermore, the drug survival rate over 52 weeks while receiving TCZ treatment was significantly higher in group 12w(−) than group 12w(+) (log-rank test, $P = 0.006$, Fig. 3).

Clinical responses to TCZ treatment at 24 and 52 weeks, including DAS28-ESR components, are summarised in Fig. 1. SJC28, TJC28, ESR and CRP improved significantly from baseline to 24 and 52 weeks in all three

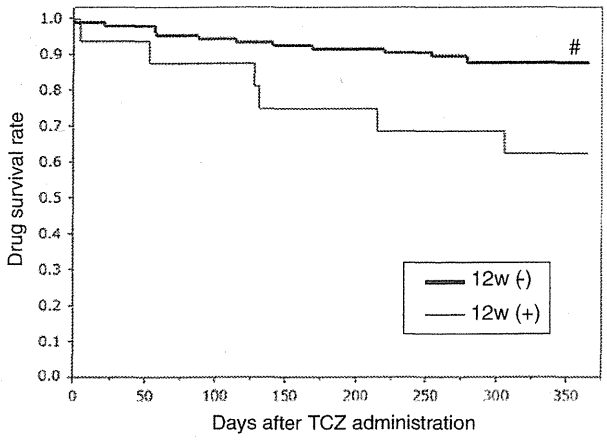

Fig. 3 Differences in drug survival rate following tocilizumab treatment according to time required to achieve normal CRP levels. Survival curves were determined by the Kaplan–Meier method. $^{\#}P = 0.006$, log-rank test

groups. Interestingly, GH-VAS and MMP-3 showed significant improvements in group 4w(−) and group 4w(+)12w(−) (Fig. 4).The proportion of patients with normal MMP-3 levels at 52 weeks was significantly higher in group 4w(−) and group 4w(+)12w(−) (46.6 and 50 %, respectively) than in group 12w(+) (0 %) (Fig. 5).

Discussion

The present study results suggest that a favourable clinical response to TCZ treatment was related to achieving normal CRP levels only 12 weeks after treatment.

TCZ administration should provide adequate treatment for patients with lower CRP levels, as the latter should imply less pathological IL-6 signalling. Multivariate analysis revealed that lower baseline CRP levels were more critical than disease duration, concomitant MTX treatment and previous TNF-α inhibitor use for reaching normal CRP levels over 52 weeks. The less targeted signalling of cytokines should be critical for achieving adequate inhibition of pathological signalling using biologics.

Sensitivity for the cut-off of baseline CRP (2.13 mg/dL) was relatively low at 53.8 %. The percentage indicates that half of the patients capable of achieving normalisation after 12 weeks of treatment had CRP levels over 2.13 mg/dL. Actually, 87 % of our patients reached normal CRP levels at 12 weeks, with maximum baseline CRP levels (17.7 mg/dL) normalised at 4 weeks, although group 12w(+) had a higher mean CRP level and a greater history of TNF-α inhibitor failure than the other groups.

Patients with lower CRP levels (e.g. lower than 2.13 mg/dL) could have the viable option of changing to TCZ as a second biologics option after treatment with TNF-α inhibitors, especially in those for whom concomitant MTX use may not be a viable option for whatever reason.

Interestingly, we found that some patients did not achieve normal CRP levels at 12 weeks, but showed significant changes in clinical responses through decreases in CRP as well as in SJC28 and TJC28. Partial inhibition of IL-6 signalling by TCZ could influence clinical response based on the number of receptors blocked. We surmise that targeting the IL-6 receptor rather than the cytokine itself may more effectively inhibit the signalling process.

A discrepancy has been reported between inflammation biomarkers (ESR and CRP) and components used to evaluate DAS28-ESR [21]. We reported that GH-VAS was more critical in achieving remission based on Boolean criteria than CRP, SJC28 or TJC28 during TCZ treatment. Non-inflammatory factors such as disease duration, joint damage and depression have a strong influence on GH-VAS [21, 22]. However, we found that insufficient TCZ efficacy for GH-VAS was also associated with MMP-3 levels in group 12w(+). MMP-3 is believed to be a good biomarker for evaluating RA synovitis [23] and gauging the effectiveness of TCZ treatments [24, 25]. MMP-3 expression, when associated with GH-VAS, could help indicate tight control, even if other indices of disease activity show some clinical response during TCZ therapy.

The effectiveness of biologics is difficult to compare in clinical practice. It is currently unclear how the other biologics, including anti-TNF-α reagents and abatacept, achieve normal CRP levels based on clinical practice in Japan. Data from daily practice in Japan have yielded remission rates for biologics as follows: infliximab (DAS28-CRP <2.3), 27.9 % at 22 weeks, Yamanaka et al. [26] and 27.6 % at 54 weeks, Tanaka et al. [27]; adalimumab (DAS28-ESR <2.6), 23.0 % at 24 weeks, Kaneko et al. [28] and 38.3 % at 52 weeks, Takeuchi et al. [29]; TCZ (DAS28-ESR <2.6): 40.7 % at 24 weeks, Yamanaka et al. [15] and 43.1 % at 52 weeks, Kojima et al. [21]; ABT (DAS28-ESR <2.6), 26.6 % at 24 weeks, Takahashi et al. [30]. As shown in the present study, normalization of CRP and ESR (outcomes distinct to TCZ treatment) could yield relatively high rates of remission for TCZ compared to other biologics.

The number of cases in group 12w(+) was relatively low at 16 (13 %), indicating that additional TBCR patients are needed to gather detailed information on those slow to reach normal CRP levels. These difficult TCZ cases can provide valuable information in predicting clinical outcomes. Further studies should also explore whether intervention in normalising CRP levels through TCZ dose escalation or shortened administration intervals achieves favourable clinical results in patients with positive CRP levels after 12 weeks. This aggressive protocol could prove effective by monitoring CRP levels to adjust TCZ

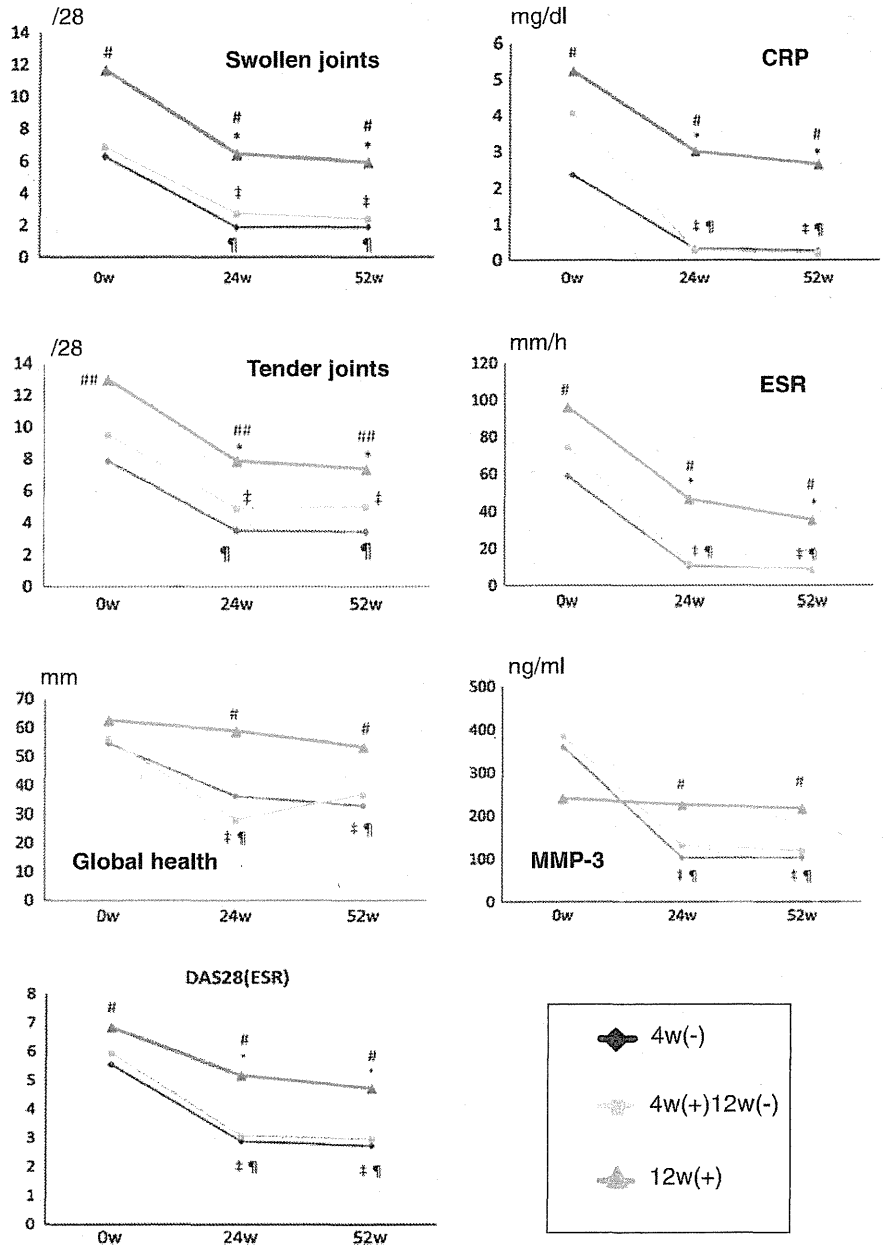

Fig. 4 Changes in DAS28-ESR, its components and matrix metalloproteinase-3 during tocilizumab treatment for 52 weeks. Changes in DAS28-ESR and its components—number of swollen and tender joints of 28 joints, patient global health, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and matrix metalloproteinase-3 (MMP-3)—were compared among patients categorised by extent of CRP reduction to normal levels. *4w(−)* normal at 4 weeks, *4w(+)12w(−)* normal at 8–12 weeks, *12w(+)* positive at 12 weeks. $^{¶}P < 0.05$: versus group 4w(−) 0w; $^{‡}P < 0.05$: versus group 4w(+)12w(−) 0w; $^{*}P < 0.05$: versus group 12w(+) 0w; $^{\#}P < 0.05$: group 4w(−) versus group 4w(+)12w(−) versus group 12w(+); $^{\#\#}P < 0.05$: group 4w(−) versus group 12w(+). *, ‡, ¶Wilcoxon signed-rank test; $^{\#}$, $^{\#\#}$Mann–Whitney *U* test

treatment, but prospective clinical trials would be needed to confirm this hypothesis. As a possible complication, it should be noted that reducing CRP to normal levels during TCZ therapy could mask physiological reactions if a serious infection occurred.

Because this study is retrospective, the number of patients and follow-up periods are limited. Further studies will be needed to determine the long-term clinical outcome of TCZ treatment.

From this study, we suggest that, from a clinical perspective, CRP is a biomarker potentially associated with TCZ trough levels. Given that Takeuchi et al. [31] reported that IL-6 concentrations and trough levels of infliximab were associated with remission, future investigations should examine how TCZ changes concentrations of IL-6 and other cytokines such as TNF-α in relation to clinical outcome. It will also be important to examine the relationship between MMP-3 and cytokines such as IL-6 and TNF-α.

In conclusion, adequate suppression of IL-6 signalling is important in achieving a favourable clinical outcome during TCZ therapy for RA. Monitoring of CRP levels, which are readily available biomarkers indicative of adequate inhibition of targeting molecules by TCZ in daily clinical practice, can help to predict the clinical outcomes for TCZ treatment.

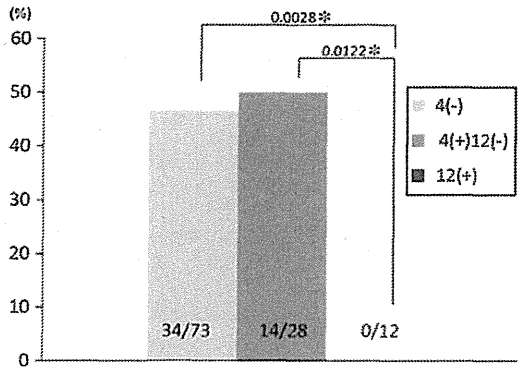

Fig. 5 Efficacy of tocilizumab based on rate of achievement of normal matrix metalloproteinase-3 levels at 52 weeks. The proportion of cases with normal matrix metalloproteinase-3 (MMP-3) levels was compared among patients categorised by extent of CRP reduction to normal levels. *4w(−)* normal at 4 weeks; *4w(+)12w(−)* normal at 8–12 weeks, *12w(+)* positive at 12 weeks. *Chi-squared test

Acknowledgments We thank Dr. Toshihisa Kanamono (Department of Orthopaedic Surgery, Nagano Red Cross Hospital, Nagano, Japan), Dr. Yukiyoshi Oh-ishi (Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan), Dr. Yoshito Etoh (Department of Orthopaedic Surgery, Higashi Nagoya National Hospital, Nagoya, Japan), Dr. Masahiro Kobayakawa (Department of Orthopaedic Surgery, Fukuroi Municipal Hospital, Fukuroi, Japan), Dr. Naoki Fukaya (Department of Orthopaedic Surgery, Kariya-Toyota General Hospital, Kariya, Japan) and Dr. Seiji Tsuboi (Department of Orthopaedic Surgery, Shizuoka Kosei Hospital, Shizuoka, Japan) for their kind suggestions. This work was supported by a grant from Aichi D.R.G. Foundation.

Conflict of interest N. Ishiguro received lecture fees (<$10000) from Mitsubishi Tanabe Pharma Corporation, Takeda Pharma Corporation, Eisai Pharma Corporation, Chugai Pharma Corporation, Abbott Japan Co. Ltd., Bristol-Myers Squibb and Pfizer. T. Kojima received lecture fees (<$5000) from Mitsubishi Tanabe Pharma Corporation, Takeda Pharma Corporation, Eisai Pharma Corporation, Chugai Pharma Corporation, Abbott Japan Co. Ltd., Bristol-Myers Squibb Janssen Pharma Corporation and Pfizer. A. Kaneko received lecture fees (<$5000) from Abbott Japan Co. Ltd., Eisai Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Janssen Pharma Corporation, Pfizer Co. Ltd., Chugai Pharmaceutical Co. Ltd., and Bristol-Myers Squibb Co. Ltd. Y. Yabe received lecture fees (<$1000) from Abbott Japan Co. Ltd., Chugai Pharma Corporation. The other authors declare no conflicts of interest.

References

1. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2010;69:631–7.
2. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum. 2005;52:3381–90.
3. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006;54:26–37.
4. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet. 2008;372:375–82.
5. Bathon JM, Cohen SB. The 2008 American College of Rheumatology recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis: where the rubber meets the road. Arthritis Rheum. 2008; 59:757–9.
6. Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis. 2010; 69:964–75.
7. Takeuchi T, Miyasaka N, Tatsuki Y, Yano T, Yoshinari T, Abe T, et al. Baseline tumour necrosis factor alpha levels predict the necessity for dose escalation of infliximab therapy in patients with rheumatoid arthritis. Ann Rheum Dis. 2011;70:1208–15.
8. St Clair EW, Wagner CL, Fasanmade AA, Wang B, Schaible T, Kavanaugh A, et al. The relationship of serum infliximab concentrations to clinical improvement in rheumatoid arthritis: results from ATTRACT, a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002;46:1451–9.
9. Radstake TR, Svenson M, Eijsbouts AM, van den Hoogen FH, Enevold C, van Riel PL, et al. Formation of antibodies against infliximab and adalimumab strongly correlates with functional drug levels and clinical responses in rheumatoid arthritis. Ann Rheum Dis. 2009;68:1739–45.
10. Nishimoto N, Hashimoto J, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an X-ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis. 2007;66:1162–7.
11. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet. 2008;371:987–97.
12. Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum. 2008;58: 2968–80.
13. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol. 2009;19:12–9.
14. Nakashima Y, Kondo M, Harada H, Horiuchi T, Ishinishi T, Jojima H, et al. Clinical evaluation of tocilizumab for patients with active rheumatoid arthritis refractory to anti-TNF biologics: tocilizumab in combination with methotrexate. Mod Rheumatol. 2010;20:343–52.

15. Yamanaka H, Tanaka Y, Inoue E, Hoshi D, Momohara S, Hanami K, et al. Efficacy and tolerability of tocilizumab in rheumatoid arthritis patients seen in daily clinical practice in Japan: results from a retrospective study (REACTION study). Mod Rheumatol. 2011;21:122–33.
16. Yabe Y, Kojima T, Kaneko A, Asai N, Kobayakawa T, Ishiguro N. A review of tocilizumab treatment in 122 rheumatoid arthritis patients included in the Tsurumai Biologics Communication Registry (TBCR) Study. Mod Rheumatol. 2012 [Epub ahead of print].
17. Kishimoto T. The biology of interleukin-6. Blood. 1989;74:1–10.
18. Nishikawa T, Hagihara K, Serada S, Isobe T, Matsumura A, Song J, et al. Transcriptional complex formation of c-Fos, STAT3, and hepatocyte NF-1 alpha is essential for cytokine-driven C-reactive protein gene expression. J Immunol. 2008;180:3492–501.
19. Nishimoto N, Terao K, Mima T, Nakahara H, Takagi N, Kakehi T. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. Blood. 2008;112: 3959–64.
20. Kojima T, Kaneko A, Hirano Y, Ishikawa H, Miyake H, Oguchi T, et al. Study protocol of a multicenter registry of patients with rheumatoid arthritis starting biologic therapy in Japan: Tsurumai Biologics Communication Registry (TBCR) study. Mod Rheumatol. 2012;22:339–45.
21. Kojima T, Kaneko A, Hirano Y, Ishikawa H, Miyake H, Takagi H, et al. Early aggressive intervention with tocilizumab for rheumatoid arthritis increases remission rate defined using a Boolean approach in clinical practice. Mod Rheumatol. 2012;22: 370–5.
22. Kojima M, Kojima T, Suzuki S, Oguchi T, Oba M, Tsuchiya H, et al. Depression, inflammation, and pain in patients with rheumatoid arthritis. Arthritis Rheum. 2009;61:1018–24.
23. Yamanaka H, Matsuda Y, Tanaka M, Sendo W, Nakajima H, Taniguchi A, et al. Serum matrix metalloproteinase 3 as a predictor of the degree of joint destruction during the six months after measurement, in patients with early rheumatoid arthritis. Arthritis Rheum. 2000;43:852–8.
24. Funahashi K, Koyano S, Miura T, Hagiwara T, Okuda K, Matsubara T. Efficacy of tocilizumab and evaluation of clinical remission as determined by CDAI and MMP-3 level. Mod Rheumatol. 2009;19:507–12.
25. Kaneko A, Kida D, Saito K, Tsukamoto M, Sato T. Clinical results for tocilizumab over one year in the clinical setting as assessed by CDAI (clinical disease activity index): CRP at week 12 and MMP-3 at week 24 are predictive factors for CDAI. Rheumatol Int. 2011.
26. Yamanaka H, Tanaka Y, Sekiguchi N, Inoue E, Saito K, Kameda H, et al. Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan (RECONFIRM). Mod Rheumatol. 2007;17:28–32.
27. Tanaka Y, Takeuchi T, Inoue E, Saito K, Sekiguchi N, Sato E, et al. Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan: one-year clinical outcomes (RECONFIRM-2). Mod Rheumatol. 2008;18:146–52.
28. Kaneko A, Hirano Y, Fujibayashi T, Hattori Y, Terabe K, Kojima T, et al. Twenty-four-week clinical results of adalimumab therapy in Japanese patients with rheumatoid arthritis: retrospective analysis for the best use of adalimumab in daily practice. Mod Rheumatol. 2012 [Epub ahead of print].
29. Takeuchi T, Tanaka Y, Kaneko Y, Tanaka E, Hirata S, Kurasawa T, et al. Effectiveness and safety of adalimumab in Japanese patients with rheumatoid arthritis: retrospective analyses of data collected during the first year of adalimumab treatment in routine clinical practice (HARMONY study). Mod Rheumatol. 2012;22: 327–38.
30. Takahashi N, Kojima T, Terabe K, Kaneko A, Kida D, Hirano Y, et al. Clinical efficacy of abatacept in Japanese rheumatoid arthritis patients. Mod Rheumatol. 2012 [Epub ahead of print].
31. Takeuchi T, Miyasaka N, Tatsuki Y, Yano T, Yoshinari T, Abe T, et al. Inhibition of plasma IL-6 in addition to maintenance of an efficacious trough level of infliximab associated with clinical remission in patients with rheumatoid arthritis: analysis of the RISING Study. Ann Rheum Dis. 2012;71:1583–5.

Mod Rheumatol
DOI 10.1007/s10165-012-0760-4

ORIGINAL ARTICLE

Clinical efficacy of abatacept in Japanese rheumatoid arthritis patients

Nobunori Takahashi · Toshihisa Kojima · Kenya Terabe · Atsushi Kaneko · Daihei Kida · Yuji Hirano · Takayoshi Fujibayashi · Yuichiro Yabe · Hideki Takagi · Takeshi Oguchi · Hiroyuki Miyake · Takefumi Kato · Naoki Fukaya · Hisato Ishikawa · Masatoshi Hayashi · Seiji Tsuboi · Daizo Kato · Koji Funahashi · Hiroyuki Matsubara · Yosuke Hattori · Masahiro Hanabayashi · Shinya Hirabara · Yutaka Yoshioka · Naoki Ishiguro

Received: 24 May 2012 / Accepted: 24 August 2012

Abstract
Objectives The purpose of this study was to examine the treatment retention and efficacy of abatacept, the first member of a new class of biologic agents, in Japanese rheumatoid arthritis (RA) patients during clinical practice.
Methods A retrospective multicenter study was conducted with patients who underwent abatacept therapy for 24 weeks ($n = 143$).
Results Patients at baseline had a mean age of 63.5 years, a mean disease duration of 11.3 years, and a mean disease activity score in 28 joints (DAS28) of 4.5. Overall retention of abatacept treatment was 83.2 % at 24 weeks, when 46.2 % of patients achieved DAS28-defined low disease activity (LDA; DAS28 <3.2) and 26.6 % achieved DAS28-defined remission (DAS28 <2.6). LDA was achieved in a significantly higher proportion of patients without prior biologics therapy compared to those with prior biologics (60.9 vs. 34.2 %, $p = 0.001$). There was no significant difference between patients with or without concomitant methotrexate (MTX) therapy (45.2 vs. 47.5 %).

N. Takahashi (✉) · T. Kojima · K. Terabe · D. Kato · K. Funahashi · H. Matsubara · Y. Hattori · M. Hanabayashi · S. Hirabara · Y. Yoshioka · N. Ishiguro
Department of Orthopedic Surgery and Rheumatology, Nagoya University Hospital, Nagoya University Graduate School of Medicine, 65 Tsuruma-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan
e-mail: nobunori@med.nagoya-u.ac.jp

A. Kaneko · D. Kida · H. Ishikawa
Department of Orthopedic Surgery and Rheumatology, Nagoya Medical Center, 4-1-1 Sanno-maru, Naka-ku, Nagoya, Aichi, Japan

Y. Hirano
Department of Rheumatology, Toyohashi Municipal Hospital, 50 Hakken-nishi, Aotake-cho, Toyohashi, Japan

T. Fujibayashi
Department of Orthopedic Surgery, Konan Kosei Hospital, 137 Oomatsubara, Takaya-cho, Konan, Aichi, Japan

Y. Yabe
Department of Rheumatology, Tokyo Kosei Nenkin Hospital, 5-1 Tsukudo-cho, Shinjuku-ku, Tokyo, Japan

H. Takagi
Department of Orthopedic Surgery, Nagoya Kyoritsu Hospital, 1-172 Hokke, Nakagawa-ku, Nagoya, Japan

T. Oguchi
Department of Orthopedic Surgery, Anjo Kosei Hospital, 28 Higashihirokute, Anjo, Japan

H. Miyake
Department of Orthopedic Surgery, Ichinomiya Municipal Hospital, 2-2-22 Bunkyo, Ichinomiya, Japan

T. Kato
Kato Orthopedic Clinic, 8-4 Minami-myoudaiji-cho, Okazaki, Japan

N. Fukaya
Department of Orthopedic Surgery, Kariya-Toyota General Hospital, 5-15 Sumiyoshi-cho, Kariya, Japan

M. Hayashi
Department of Rheumatology, Nagano Red Cross Hospital, 5-22-1 Wakazato, Nagano, Japan

S. Tsuboi
Department of Orthopedic Surgery, Shizuoka Kosei Hospital, 23 Kitaban-cho, Aoi-ku, Shizuoka, Japan

Published online: 14 September 2012

Conclusions Abatacept therapy appears to be highly effective and well tolerated during clinical treatment of RA. Abatacept was particularly effective in patients with no history of biologics use, and did not appear to be dependent on concomitant MTX therapy.

Keywords Abatacept · Concomitant methotrexate · Japanese patients · Prior biologics · Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic and systemic autoimmune inflammatory disease that clinically manifests as joint pain and swelling [1]. Persistent inflammation without treatment can lead to cartilage damage, bone erosion, joint destruction, and subsequent long-term disability. Therapy to prevent these outcomes has improved dramatically with the introduction of biological treatments such as inhibitors of tumor necrosis factor-alpha (TNF-α), interleukin-6 receptor (IL-6R), and B cell-specific antigen CD20. Previous studies have demonstrated the significant and dramatic clinical efficacy of these biologics on RA patients.

RA is characterized by synovial membrane hyperplasia and infiltration by inflammatory cells such as activated T cells [2]. T cells require both an antigen-specific signal and a co-stimulatory signal for full activation [3]. One of the best-characterized co-stimulatory pathways involves the interaction of CD28 on T cells with CD80 or CD86 (CD80/86) found on antigen-presenting cells [4]. In a normal immune response, endogenous cytotoxic T-lymphocyte antigen-4 (CTLA-4) downregulates CD28-mediated T-cell activation by binding to CD80/86 with a higher affinity than CD28 [5, 6]. Abatacept is the first member of a new class of biologic agents for RA treatment to inhibit T-cell activation by binding to CD80/86 and modulating its interaction with CD28; this strategy is expected to achieve clinical efficacy in patients that either respond inadequately to or are naïve to other classes of biologics.

The efficacy and safety of abatacept has been reported in several clinical trials. The AGREE study demonstrated a greater efficacy of abatacept plus methotrexate (MTX) treatment than placebo plus MTX in MTX-naïve patients [7]. The AIM and ATTEST studies showed that additional abatacept therapy has significant efficacy in patients with an inadequate response to MTX [8–10], while the ATTAIN and ARRIVE studies demonstrated efficacy in patients with an inadequate response to anti-TNF therapy [11, 12]. The effectiveness of abatacept has also been reported in Danish clinical practice, as well as from the abovementioned trials [13]; however, abatacept has only been clinically used in Japan since 2010, so data relevant to Japanese RA patients is lacking. Racial background can affect responsiveness to some drugs, and a CTLA-4 polymorphism has been found that differs between Caucasians and Asians [14]. Thus, it remains critical to evaluate abatacept use in clinical practice for Japanese patients.

Materials and methods

Tsurumai Biologics Communication Registry (TBCR)

The TBCR was developed in 2008 to explore the long-term prognosis of biologics in clinical practice, and consisted of patients who were starting biologic treatments. Data were collected prospectively from 2008 and retrospectively for patients treated until 2008 [15, 16]. The present study included all patients ($n = 143$) who underwent abatacept treatment for 24 weeks at Nagoya University Hospital or one of 12 other institutes affiliated with the TBCR and were prospectively enrolled in the TBCR. All patients met the 1987 American College of Rheumatology classification criteria for RA and received abatacept infusions three times every two weeks followed by every four weeks according to the drug label and Japan College of Rheumatology guidelines for treatment. Patient anonymity was maintained during data collection, and the security of personal information was strictly controlled. This study was approved by the Ethics Committee of the Nagoya University Graduate School of Medicine.

Data collection

Data were retrospectively collected from the clinical records. The following demographic data were recorded at the initiation of treatment (baseline, week 0): disease duration, concomitant treatment (MTX or prednisolone), joint damage (Steinbrocker stage), and daily dysfunction (Steinbrocker class). The following disease parameters were recorded at baseline, 4, 12, and 24 weeks of treatment: tender joint count (TJC) and swollen joint count (SJC) on 28 joints, general health on a visual analog scale (GH-VAS), and serum C-reactive protein (CRP) levels. Disease activity was evaluated at each time point using the 28-joint disease activity score with CRP (DAS28-CRP), which includes data from the abovementioned disease parameters.

Statistical analysis

Demographic and disease characteristics were reported using descriptive statistics. All results are expressed as the mean ± SD or as a percentage. Student's t test was used for two-group comparisons and the chi-squared test for

categorical variables. The last observation carried forward (LOCF) method was used in each analysis. To determine predictors of clinical remission and low disease activity (LDA) at 24 weeks, we performed multivariate logistic regression analysis. All statistical tests were two-sided, and significance was defined as $p < 0.05$. All analyses were performed with SPSS version 20.0.0 software (IBM Corp., Armonk, NY, USA).

Results

Demographic data for the study population

The baseline characteristics of the 143 patients enrolled in this study who received abatacept are shown in Table 1. The mean age was 63.5 years, and the mean disease duration was 11.3 years. Ninety-nine patients (69.2 %) were categorized into the advanced Steinbrocker stages (III and IV), indicating established RA and joint damage. Disease activity was moderate, as shown by a mean DAS28-CRP score of 4.47 and a mean CRP level of 2.18 mg/dL. MTX was concomitantly used with 58.7 % of the patients, and 55.2 % had been treated previously with anti-TNF and/or anti-IL-6R biologics.

Overall clinical efficacy of abatacept treatment

As shown in Fig. 1a, the mean DAS28-CRP score significantly decreased from 4.47 ± 1.28 at baseline to 3.85 ± 1.18 at week 4, 3.63 ± 1.23 at week 12, and 3.47 ± 1.25 at week 24 ($p < 0.01$). TJC decreased from 6.8 ± 6.3 at baseline to 4.5 ± 5.5 at week 24 (Fig. 1b), SJC decreased from 5.4 ± 5.4 to 2.4 ± 3.7 (Fig. 1c), CRP decreased from 2.2 ± 2.8 to 1.3 ± 2.0 mg/dL (Fig. 1d), and GH-VAS decreased from 56.3 ± 26.9 to 41.2 ± 26.3 mm (Fig. 1e), demonstrating a significant improvement in RA with abatacept treatment ($p < 0.01$). The proportions of patients who achieved LDA and remission as defined by DAS28 are shown in Fig. 1f. LDA (DAS28 <3.2) was achieved in 28.0 % of patients at week 4, 39.9 % at week 12, and 46.2 % at week 24. Remission (DAS28 <2.6) was achieved in 14.0 % of patients at week 4, 22.4 % at week 12, and 26.6 % at week 24.

Patient retention of abatacept treatment

Over 24 weeks, 24 of the 143 patients withdrew from treatment with abatacept, while 83.2 % continued (Fig. 2). The most frequent reason for discontinuation was an inadequate response to abatacept (15 patients, 10.5 %). There were six (4.2 %) patients who stopped abatacept therapy due to adverse events (AEs). The remaining two patients discontinued abatacept therapy for personal reasons.

Safety

In total, 38 AEs were observed in 36 (25.2 %) of 143 patients. The most frequent AE was an infection (18 patients, 12.6 %). The most common infection was upper respiratory inflammation (6 patients, 4.2 %). Serious infections were reported in five (3.5 %) patients. Appendicitis was reported in one patient, leading to the discontinuation of abatacept treatment. In addition, there single cases each of pneumonia, bronchopneumonia, herpes zoster, and cellulitis. The most common laboratory abnormalities were liver function abnormality in 3 (2.1 %) patients. There were two cases of lymphoproliferative disorder, two cases of interstitial pneumonia, and one case of purpura, leading to discontinuation of further abatacept treatment.

Comparison of abatacept efficacy in patients with and without prior biologics therapy

The baseline characteristics of patients with prior biologics therapy (switch group) were compared to those of patients with no history of biologics use (naïve group), as shown in Table 1. The switch group had a significantly higher proportion of patients on regular oral steroid therapy as well as a higher mean SJC than the naïve group. Although mean disease duration was also higher in the switch group, it was not significant ($p = 0.11$). The data for previous biological DMARDs in the switch group are summarized in Table 2. The previous biologics used were anti-TNF agents in 62 (78.5 %) and tocilizumab in 17 (21.5 %) patients. The number of biologics used previously was one in 40 (50.6 %) patients, two in 27 (34.2 %), three in 8 (10.1 %), and four in 4 (5.1 %). The most frequent reason for previous biologics discontinuation was inadequate effect, which corresponded to 61 (77.2 %) patients; the other reasons were AEs in 17 (21.5 %) and the patient's wish in 1 (1.3 %). The mean interval from previous biologics discontinuation to the start of abatacept treatment is shown separately for each discontinuation reason in the table. The mean interval was approximately twice the agent dosing interval in the patients who discontinued previous biologics due to inadequate effect.

The efficacy of abatacept therapy as evaluated by the reduction in DAS28-CRP showed a significant decrease over time compared to the baseline ($p < 0.01$) in each group (Fig. 3a). The mean DAS28-CRP values were not significantly different for the naïve and switch groups at baseline (4.41 ± 1.15 and 4.52 ± 1.38, respectively); however, significance was achieved at week 4 (3.63 ± 1.02 and 4.03 ± 1.27, respectively; $p = 0.048$), and it became

Table 1 Baseline characteristics of rheumatoid arthritis patients who received abatacept

Over	Overall ($n = 143$)	Concomitant MTX			Previous biologics		
		(+) ($n = 84$)	(−) ($n = 59$)	p value	(+) ($n = 79$)	(−) ($n = 64$)	p value
Age (years)	63.5 ± 10.8	62.1 ± 11.1	65.5 ± 10.1	0.068	61.8 ± 10.1	65.6 ± 11.2	**0.036**
Gender (% female)	76.9	79.8	72.9	0.336	81.0	71.9	0.197
Disease duration (years)	11.3 ± 10.4	10.5 ± 9.4	12.5 ± 11.6	0.284	12.6 ± 10.4	9.8 ± 10.2	0.11
Stage (I/II/III/IV, %)	11.2/19.6/38.5/30.8	14.3/22.6/31.0/32.1	6.8/15.3/49.2/28.8	0.121	8.9/16.5/40.5/34.2	14.1/23.4/35.9/26.6	0.459
Class (I/II/III/IV, %)	8.4/47.6/42.7/1.4	10.7/51.2/36.9/1.2	5.1/42.4/50.8/1.7	0.318	6.3/46.8/45.6/1.3	10.9/48.4/39.1/1.6	0.732
Prior use of biologics (%)	55.2	56.0	54.2	0.839	100	–	–
RF positive (%)	87.9	92.6	81.1	0.184	87.2	88.6	0.838
MTX use (%)	58.7	100	–	–	59.5	57.8	0.839
MTX dose (mg/week)[a]	7.5	7.5	–	–	7.6	7.3	0.695
Oral steroid use (%)	58.7	64.3	50.8	0.108	65.8	50.0	0.056
Oral steroid dose (mg/day)[a]	4.3	4.0	4.9	0.916	4.3	4.4	0.212
MMP-3 (ng/mL)	230.9 ± 244.0	234.1 ± 256.9	226.3 ± 226.7	0.861	231.4 ± 263.9	230.2 ± 219.0	0.98
SJC, 0–28	5.4 ± 5.4	4.9 ± 4.7	6.1 ± 6.3	0.235	6.4 ± 6.3	4.2 ± 3.9	**0.016**
TJC, 0–28	6.8 ± 6.3	6.7 ± 5.9	7.1 ± 6.9	0.736	7.4 ± 6.7	6.2 ± 5.8	0.255
ESR (mm/h)	52.2 ± 32.9	51.2 ± 30.0	53.7 ± 39.0	0.667	48.6 ± 31.4	57.0 ± 34.4	0.137
CRP (mg/dL)	2.2 ± 2.8	2.1 ± 2.5	2.3 ± 3.2	0.678	2.3 ± 3.3	2.0 ± 2.1	0.493
GH, VAS 0–100 mm	56.3 ± 26.9	54.5 ± 27.4	58.8 ± 26.2	0.358	55.8 ± 25.6	56.9 ± 28.5	0.811
DAS28-CRP	4.5 ± 1.3	4.5 ± 1.2	4.5 ± 1.4	0.997	4.5 ± 1.4	4.4 ± 1.2	0.55
HAQ-DI	0.75 ± 0.70	0.86 ± 0.69	0.87 ± 0.71	0.954	0.91 ± 0.59	0.82 ± 0.81	0.502

Data are presented as the mean ± SD except when otherwise indicated

Stage Steinbrocker stage, *Class* Steinbrocker class, *RF* rheumatoid factor, *MTX* methotrexate, *SJC* swollen joint count, *TJC* tender joint count, *ESR* erythrocyte sedimentation rate, *MMP-3* matrix metalloproteinase-3, *CRP* C-reactive protein, *GH* general health, *VAS* visual analog scale, *DAS28* disease activity score in 28 joints, *HAQ-DI* Health Assessment Questionnaire for rheumatoid arthritis

[a] Mean among patients receiving the drug

increasingly apparent at week 12 (3.28 ± 1.06 and 3.92 ± 1.29, respectively; $p = 0.002$) and week 24 (3.06 ± 1.10 and 3.81 ± 1.26, respectively; $p < 0.0001$). The proportion of patients who achieved LDA is displayed in Fig. 3a, which shows that there was a significant difference between the naïve and switch groups at week 12 (50.0 vs. 31.6 %; $p = 0.039$) and week 24 (60.9 vs. 34.2 %; $p = 0.002$).

Comparison of abatacept efficacy in patients with and without concomitant MTX therapy

The baseline characteristics of patients with concomitant MTX therapy were compared to those without MTX and, as shown in Table 1, there was no significant difference for any of the clinical parameters. The efficacy of abatacept therapy as evaluated by the DAS28-CRP reduction showed a significant decrease over time compared to the baseline ($p < 0.01$) in each group (Fig. 3b). Mean DAS28-CRP values for patients with concomitant MTX therapy were 4.48 ± 1.18 at baseline and 3.50 ± 1.27 at week 24. Mean DAS28-CRP values for patients without MTX were 4.45 ± 1.42 at baseline and 3.43 ± 1.22 at week 24. No significant differences were observed between the two patient groups at any of these time points. Interestingly, concomitant MTX usage did not demonstrate any additional improvement in disease activity at any time point. The proportion of patients who achieved LDA is displayed in Fig. 3b, which shows that there was no significant difference between patients with concomitant MTX therapy and patients without MTX (45.2 vs. 47.5 % at week 24).

Comparison of abatacept efficacy in patients with and without prior biologics therapy and concomitant MTX therapy

Concomitant MTX usage still did not lead to any additional improvement in disease activity or the proportion of patients who achieved LDA at any time point in the switch group (Fig. 3c). In the naïve group, the mean DAS28-CRP

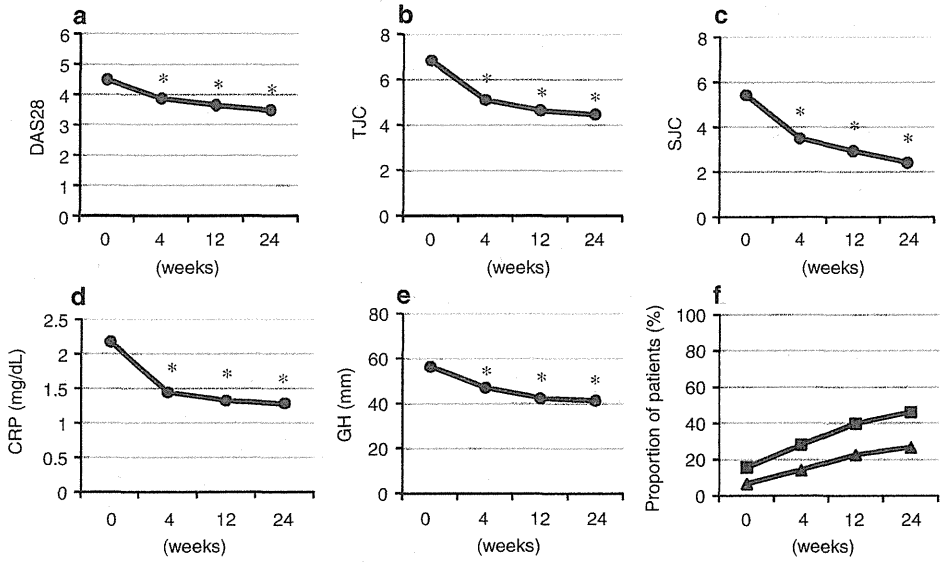

Fig. 1 Overall clinical efficacy of abatacept in rheumatoid arthritis patients. Mean values for **a** the daily activity score based on 28 joints (DAS28-CRP) and its components, **b** tender joint count (TJC), **c** swollen joint count (SJC), **d** C-reactive protein (CRP), and **e** general health on a visual analog scale (GH-VAS) are shown, while **f** displays the proportions of patients achieving low disease activity (*filled squares*) and DAS28-defined clinical remission (*filled triangles*). $*p < 0.01$, compared to week 0

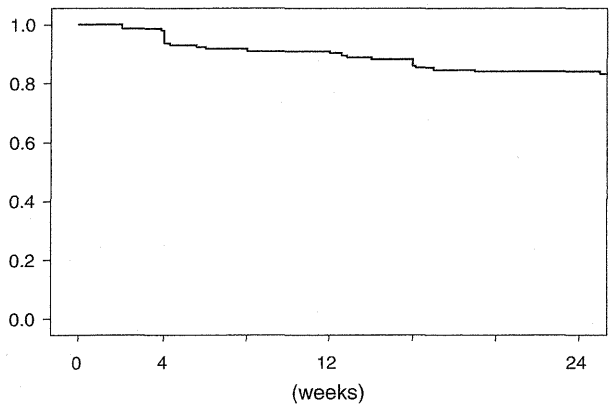

Fig. 2 Patient retention of abatacept treatment. Kaplan–Meier curve of the abatacept therapy retention rate among rheumatoid arthritis patient cases over 24 weeks of treatment ($n = 143$ at baseline)

value for patients with concomitant MTX was significantly lower than those without MTX at week 12 (2.98 ± 0.87 vs. 3.69 ± 1.17; $p = 0.007$), and the proportion of MTX patients who achieved LDA was significantly higher than it was among patients without MTX (62.2 vs. 33.3 %; $p = 0.042$) (Fig. 3c). However, there was no significant difference at week 24 between patients with concomitant MTX therapy and patients without MTX in both the mean DAS28-CRP (2.95 ± 0.99 vs. 3.21 ± 1.24) and the proportion of patients who achieved LDA (62.2 vs. 59.3 %). The baseline characteristics of patients in the naïve group with concomitant MTX therapy were compared to those without MTX. As shown in Table 3, there was no significant difference between the groups in any of the clinical parameters except for a higher SJC in the MTX (−) group. In the patients without MTX, there was no significant difference between the switch and naïve groups in both the mean DAS28-CRP and the proportion of patients who achieved LDA at any time point. The naïve group had a lower proportion of patients taking oral steroid (33.3 vs. 65.6 %; $p = 0.013$) and a lower SJC (3.7 ± 3.2 vs. 8.2 ± 7.6; $p = 0.006$) at baseline compared to the switch group.

We compared the retention rate of abatacept therapy between four groups; patients with and without prior biologics therapy and concomitant MTX therapy (Fig. 4). We found no significant difference, even between the naïve and switch groups, in the retention rate.

Since there are substantial confounding factors that may contribute to the clinical efficacy of abatacept, we next performed multivariate logistic regression to confirm the effect of previous use of biologics and concomitant MTX use on the disease activity at 24 weeks (Table 4). The odds ratios (ORs) were adjusted for the following parameters; age, gender, disease duration, stage, class, DAS-CRP at baseline, serum CRP at baseline, previous biologics use, MTX use, and PSL use. Multivariate analysis confirmed that no previous use of biologics was an independent factor for achieving clinical remission [adjusted OR 3.4, 95 % confidence interval (CI) 1.5–8.4] or LDA (adjusted OR 3.4, 95 % CI 1.5–7.4) at 24 weeks. It was also confirmed that concomitant MTX use was not an independent factor for

Table 2 Previous biological DMARDs used before abatacept, reasons for discontinuation, and interval before abatacept initiation

Previous biological DMARDs	*n* (%)	Reasons for previous biologics discontinuation	*n*	Mean intervals after discontinuation (mean ± SD) (weeks)
Infliximab	13 (16.5)	Inadequate effect	10	17.6 ± 26.4
		Adverse events	2	10.8 ± 3.9
		Other	1	265.4
Etanercept	29 (36.7)	Inadequate effect	24	2.0 ± 1.6
		Adverse events	5	71.0 ± 46.5
Adalimumab	20 (25.3)	Inadequate effect	14	5.0 ± 6.3
		Adverse events	6	8.0 ± 11.3
Tocilizumab	17 (21.5)	Inadequate effect	13	10.3 ± 13.6
		Adverse events	4	22.8 ± 25.1

Data are shown as *n* (%)

DMARDs disease-modifying anti-rheumatic drugs

achieving clinical remission (adjusted OR 1.3, 95 % CI 0.6–3.1) or LDA (adjusted OR 1.1, 95 % CI 0.5–2.4) at 24 weeks.

Discussion

The present study is the first collection of clinical practice data on Japanese RA patients using abatacept to be compiled by the TBCR. Although data from Japanese clinical trials with abatacept have been reported [17], the participants in such trials are very different from patients seen in everyday practice. Patients achieving the inclusion criteria of a clinical trial are definitively uniform in their baseline characteristics. Since, in the real world, patients have somewhat different clinical backgrounds, data derived from clinical trials are not always applicable. A multicenter registry can provide real-world, long-term data on these patients with comorbidities that are relevant to safety, efficacy, or future outcomes. Its value in accumulating and evaluating relevant data cannot be underestimated.

In this study, 48.6 % of patients achieved LDA and 27.9 % achieved clinical remission at week 24 of abatacept treatment. In the ATTEST study, with patients who responded inadequately to MTX, 20.7 % achieved LDA and 11.3 % achieved clinical remission at week 24 [9]. The ATTAIN study, with patients who responded inadequately to anti-TNF agents, demonstrated that 17.1 % achieved

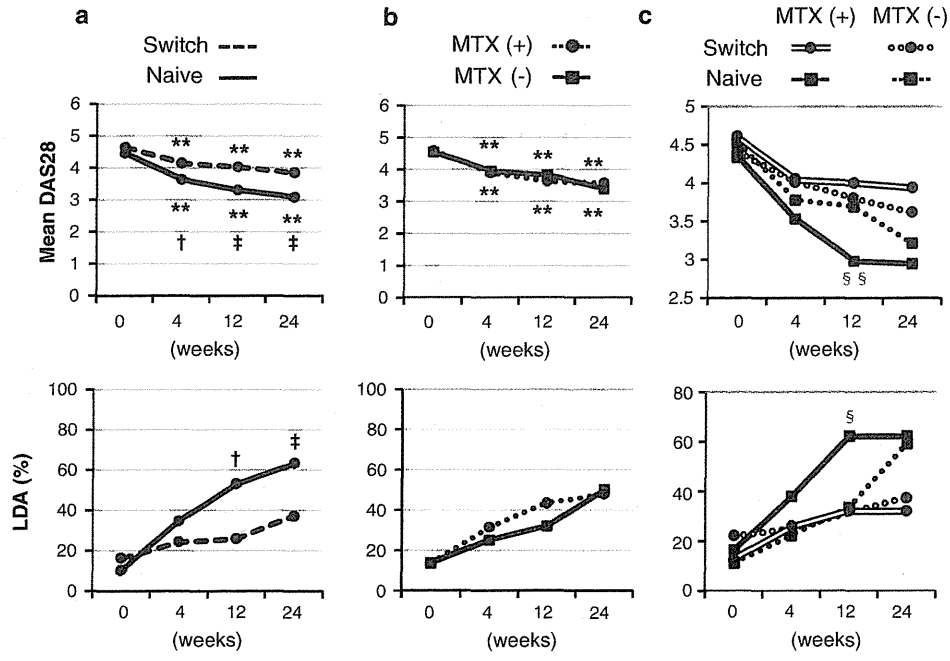

Fig. 3 Comparison of abatacept efficacy between patient groups. **a** Comparison of patient groups who concomitantly received methotrexate (MTX) treatment (*dotted line*; $n = 84$) or did not (*solid line*; $n = 59$). **b** Comparison of patients who previously received biologics therapy (switch; *dotted line*, $n = 79$) or did not (naïve; *solid line*, $n = 64$). **c** Comparison between patients with and without prior biologics treatment and concomitant MTX; switch-MTX (+) (*gray solid line*, $n = 47$), switch-MTX (−) (*gray dotted line*, $n = 32$), naïve-MTX (+) (*black solid line*, $n = 37$), and naïve-MTX (−) (*black dotted line*, $n = 27$). Mean values for the daily activity score based on 28 joints (DAS28-CRP) and the proportions of patients achieving low disease activity (LDA; DAS28-CRP <3.2) from baseline to 24 weeks after the initiation of abatacept therapy were compared between groups. $^{**}p < 0.01$, compared to week 0; $^{\dagger}p < 0.05$, $^{\ddagger}p < 0.01$, compared to switch group; $^{\S}p < 0.05$, $^{\S\S}p < 0.01$, compared to naïve-MTX (−) group

Table 3 Baseline characteristics of rheumatoid arthritis patients who received abatacept

Variables	Switch			Naïve		
	MTX (+) ($n = 47$)	MTX (−) ($n = 32$)	p value	MTX (+) ($n = 37$)	MTX (−) ($n = 27$)	p value
Age (years)	60.4 ± 10.5	63.8 ± 9.3	0.149	64.3 ± 11.5	67.4 ± 10.7	0.272
Gender (% female)	83.0	78.1	0.589	75.7	66.7	0.429
Disease duration (years)	11.0 ± 8.5	15.2 ± 12.4	0.085	10.0 ± 10.5	9.5 ± 10.0	0.865
Stage (I/II/III/IV, %)	12.8/19.1/36.2/31.9	3.1/12.5/46.9/37.5	0.359	16.2/27.0/24.3/32.4	11.1/18.5/51.9/18.5	0.158
Class (I/II/III/IV, %)	6.4/55.3/36.2/2.1	6.3/34.4/59.4/0	0.194	16.2/45.9/37.8/0	3.7/51.9/40.7/3.7	0.29
Prior use of biologics (%)	100	100	–	–	–	–
RF positive (%)	93.3	76.5	0.226	91.7	85.0	0.828
MTX use (%)	100	–	–	100	–	–
MTX dose (mg/week)[a]	7.6	–	–	7.3	–	–
Oral steroid use (%)	66.0	65.6	0.976	62.2	33.3	**0.023**
Oral steroid dose (mg/day)[a]	3.8	5.0	0.083	4.3	4.8	0.545
MMP-3 (ng/mL)	248.8 ± 308.3	206.7 ± 186.4	0.515	215.8 ± 176.5	251.0 ± 271.7	0.559
SJC, 0–28	5.2 ± 4.9	8.2 ± 7.6	**0.043**	4.6 ± 4.4	3.7 ± 3.2	0.355
TJC, 0–28	7.7 ± 6.6	7.0 ± 7.0	0.651	5.5 ± 4.8	7.1 ± 7.0	0.253
ESR (mm/h)	50.4 ± 28.1	45.9 ± 36.1	0.536	52.3 ± 28.2	63.2 ± 41.0	0.225
CRP (mg/dL)	2.3 ± 2.9	2.4 ± 3.8	0.852	1.9 ± 1.9	2.2 ± 2.4	0.602
GH, VAS 0–100 mm	55.9 ± 26.9	55.5 ± 24.1	0.948	52.8 ± 28.3	62.4 ± 28.3	0.184
DAS28-CRP	4.6 ± 1.2	4.4 ± 1.6	0.564	4.3 ± 1.1	4.5 ± 1.2	0.446
HAQ-DI	0.92 ± 0.58	0.90 ± 0.62	0.878	0.80 ± 0.81	0.85 ± 0.82	0.829

Data are presented as the mean ± SD except when otherwise indicated

Switch patient group with previous biologics treatment history, *Naïve* patient group without previous biologics treatment history, *Stage* Steinbrocker stage, *Class* Steinbrocker class, *RF* rheumatoid factor, *MTX* methotrexate, *SJC* swollen joint count, *TJC* tender joint count, *ESR* erythrocyte sedimentation rate, *MMP-3* matrix metalloproteinase-3, *CRP* C-reactive protein, *GH* general health, *VAS* visual analog scale, *DAS28* disease activity score in 28 joints, *HAQ-DI* Health Assessment Questionnaire for rheumatoid arthritis

[a] Mean among patients receiving the drug

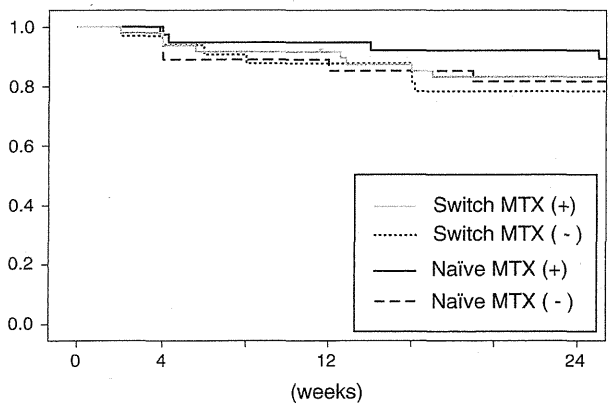

Fig. 4 Patient retention of abatacept treatment. Kaplan–Meier curve of the abatacept therapy retention rate among rheumatoid arthritis patient cases beyond 24 weeks of treatment. Comparison of patients with and without prior biologics treatment and concomitant MTX; switch-MTX (+) ($n = 47$), switch-MTX (−) ($n = 32$), naïve-MTX (+) ($n = 37$), and naïve-MTX (−) ($n = 27$)

LDA and 10.0 % achieved clinical remission [12]. Although it is difficult to compare our results to these clinical trials given the different patient backgrounds, the efficacy of abatacept in Japanese RA patients appears to be equivalent [8, 9, 11, 12]. In abatacept studies lasting over a year, patients achieved LDA and clinical remission rates of 54.3 and 41.4 %, respectively, in the AGREE study, and 42.5 and 23.8 %, respectively, in the AIM study. A longer study period would be needed to compare the clinical efficacy of abatacept in Japanese RA patients to these reports.

One important finding in this study was the efficacy of abatacept in patients with no concomitant MTX therapy. We did not find any other clinical studies that compared this efficacy with concomitant MTX use directly. In the patient group who did not receive prior biologics treatment, the patients with concomitant MTX usage demonstrated slightly higher or faster improvements in disease activity at week 12 compared to those without MTX, but we found no difference at week 24. In the ARRIVE study, 43 patients received abatacept as a monotherapy [11], and it was suggested that the resulting efficacy was comparable to that seen when using background disease-modifying antirheumatic drugs. The proportion of patients receiving background MTX was not recorded. Previous studies have emphasized that TNF inhibitors need sufficient background

Table 4 Multivariate logistic regression analysis for the achievement of clinical remission or low disease activity at 24 weeks

	Clinical remission		Low disease activity	
	Adjusted OR (95 % CI)	*p* value	Adjusted OR (95 % CI)	*p* value
No previous use of biologics	3.58 (1.52–8.44)	0.004	3.35 (1.52–7.39)	0.003
Concomitant MTX use	1.33 (0.58–3.08)	0.502	1.09 (0.50–2.39)	0.834

OR odds ratio, *CI* confidence interval, *MTX* methotrexate

MTX therapy to maximize their clinical efficacy against RA [18–23]. Our results show positive outcomes with abatacept even without concomitant MTX, although it is difficult to make direct comparisons to patients with concomitant MTX given the different backgrounds in disease history or other characteristics. Abatacept monotherapy could be a practical option for patients with risk factors that preclude MTX use, such as pulmonary or renal disorders.

The efficacy of abatacept in patients with a history of biologics use seemed inferior to its efficacy in biologics-naïve patients. The switch group had a lower proportion of patients who achieved LDA or clinical remission and a significantly higher mean DAS28 score than the naïve group at 0, 4, and 24 weeks of treatment. Although previous biologics usage was and MTX usage was not an independent factor predicting clinical remission or LDA at 24 weeks in this study, the difference in clinical improvement between the switch and naïve groups was not statistically significant in the patients without concomitant MTX treatment. We noted that, in the naïve group, the patients without MTX demonstrated a slower clinical improvement than the patients with concomitant MTX treatment. This slower response to abatacept may have decreased the effect of previous biologics usage. It is necessary for us to study the clinical efficacy of abatacept over a longer period and in more patients to confirm this hypothesis in the future. A few reports have examined the effect of previous biologics therapy on abatacept efficacy. Tanaka [24] reported that a history of biologics use was a significant indicator of decreased clinical remission, and that the remission rate was significantly lower in patients with previous biologics treatment than in those with no history at week 48 (28.3 vs. 50.4 %, respectively, $p < 0.01$). Interestingly, our results showed that abatacept significantly improved disease activity, even in patients with prior biologics treatment. Although abatacept is clearly more effective when used as the first treatment option against RA, it should still be considered after other biologics have been tried.

The main limitations of this study are that it was observational and not randomized, and that treatments were likely influenced by patient characteristics and other factors. Other than patients who took oral steroids in the comparison between switch and naïve groups, however, there were no statistically significant differences in clinical variables between patient groups (Table 1). Although we did not find a significant combined effect of abatacept and concomitant MTX, the mean dose of MTX was relatively low in this study. Thus, we have to wait for a future study in which a higher dose of MTX is used before we can draw any conclusion about a possible synergistic effect of abatacept and MTX. Additionally, we do not have radiographic data at the TBCR at this time. Since it is really important to evaluate the joint protective effect in order to demonstrate the clinical efficacy of a DMARD, it would be necessary to study the radiographic changes in patients undergoing abatacept treatment in the future.

In conclusion, this study indicates that selective co-stimulation of T cells by abatacept is highly effective and well tolerated in Japanese RA patients. Since abatacept showed significant effectiveness without concomitant MTX therapy, abatacept would also be a good treatment option for patients that cannot tolerate MTX. Finally, abatacept could still be a treatment option if other biologics fail, given its significant efficacy in patients with a history of biologics use. However, an extended study is still needed to evaluate the long-term efficacy and safety of abatacept therapy in Japanese patients.

Acknowledgments We thank Dr. Toshihisa Kanamono (Department of Orthopedic Surgery, Nagano Red Cross Hospital, Nagano, Japan), Dr. Yukiyoshi Oh-ishi (Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan), Dr. Yoshito Etoh (Department of Orthopedic Surgery, Higashi Nagoya National Hospital, Nagoya, Japan), and Dr. Masahiro Kobayakawa (Department of Orthopedic Surgery, Fukuroi Municipal Hospital, Fukuroi, Japan) for their kind suggestions. This work was supported by the Aichi D.R.G. Foundation and a grant from the Ministry of Health, Labour, and Welfare entitled "Study for mortality-based optimal management of patients with rheumatoid arthritis in the biologic era" (chaired by Prof. H. Yamanaka, Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan).

Conflict of interest N. Ishiguro, T. Kojima, Y. Hirano and A. Kaneko have received speaking fees (<$5000) from Abbott Japan Co. Ltd.; Eisai Co. Ltd.; Mitsubishi Tanabe Pharma Corporation; Pfizer Co. Ltd.; Chugai Pharmaceutical Co. Ltd.; and Bristol-Myers Squibb Co. Ltd. The other authors declare no conflicts of interest.

References

1. Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet. 2001; 358(9285):903–11.
2. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med. 2001;344(12):907–16.
3. Goronzy JJ, Weyand CM. T-cell regulation in rheumatoid arthritis. Curr Opin Rheumatol. 2004;16(3):212–7.
4. Lenschow DJ, Walunas TL, Bluestone JA. CD28/B7 system of T cell costimulation. Annu Rev Immunol. 1996;14:233–58.
5. Silver PB, Hathcock KS, Chan CC, Wiggert B, Caspi RR. Blockade of costimulation through B7/CD28 inhibits experimental autoimmune uveoretinitis, but does not induce long-term tolerance. J Immunol. 2000;165(9):5041–7.
6. Yamada A, Salama AD, Sayegh MH. The role of novel T cell costimulatory pathways in autoimmunity and transplantation. J Am Soc Nephrol. 2002;13(2):559–75.
7. Westhovens R, Robles M, Ximenes AC, Nayiager S, Wollenhaupt J, Durez P, et al. Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. Ann Rheum Dis. 2009;68(12):1870–7.
8. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2006;144(12):865–76.
9. Schiff M, Keiserman M, Codding C, Songcharoen S, Berman A, Nayiager S, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis. 2008;67(8):1096–103.
10. Kremer JM, Russell AS, Emery P, Abud-Mendoza C, Szechinski J, Westhovens R, et al. Long-term safety, efficacy and inhibition of radiographic progression with abatacept treatment in patients with rheumatoid arthritis and an inadequate response to methotrexate: 3-year results from the AIM trial. Ann Rheum Dis. 2011;70(10):1826–30.
11. Schiff M, Pritchard C, Huffstutter JE, Rodriguez-Valverde V, Durez P, Zhou X, et al. The 6-month safety and efficacy of abatacept in patients with rheumatoid arthritis who underwent a washout after anti-tumour necrosis factor therapy or were directly switched to abatacept: the ARRIVE trial. Ann Rheum Dis. 2009;68(11):1708–14.
12. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med. 2005;353(11):1114–23.
13. Leffers HC, Ostergaard M, Glintborg B, Krogh NS, Foged H, Tarp U, et al. Efficacy of abatacept and tocilizumab in patients with rheumatoid arthritis treated in clinical practice: results from the nationwide Danish DANBIO registry. Ann Rheum Dis. 2011;70(7):1216–22.
14. Danoy P, Wei M, Johanna H, Jiang L, He D, Sun L, et al. Association of variants in MMEL1 and CTLA4 with rheumatoid arthritis in the Han Chinese population. Ann Rheum Dis. 2011; 70(10):1793–7.
15. Kojima T, Kaneko A, Hirano Y, Ishikawa H, Miyake H, Takagi H, et al. Early aggressive intervention with tocilizumab for rheumatoid arthritis increases remission rate defined using a Boolean approach in clinical practice. Mod Rheumatol. 2012;22: 370–5.
16. Kojima T, Kaneko A, Hirano Y, Ishikawa H, Miyake H, Oguchi T, et al. Study protocol of a multicenter registry of patients with rheumatoid arthritis starting biologic therapy in Japan: Tsurumai Biologics Communication Registry (TBCR) Study. Mod Rheumatol. 2012;22:339–45.
17. Yasuoka Y, Goto A, Seriu T, et al. Pharmacological properties and clinical efficacy of abatacept (Orencia®) for the treatment of rheumatoid arthritis. Nihon Yakurigaku Zasshi. 2011;137(2): 87–94.
18. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al. 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.
19. Kameda H, Kanbe K, Sato E, Ueki Y, Saito K, Nagaoka S, et al. Continuation of methotrexate resulted in better clinical and radiographic outcomes than discontinuation upon starting etanercept in patients with rheumatoid arthritis: 52-week results from the JESMR study. J Rheumatol. 2011;38(8):1585–92.
20. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006;54(1):26–37.
21. Takeuchi T, Tanaka Y, Kaneko Y, Tanaka E, Hirata S, Kurasawa T, et al. Effectiveness and safety of adalimumab in Japanese patients with rheumatoid arthritis: retrospective analyses of data collected during the first year of adalimumab treatment in routine clinical practice (HARMONY study). Mod Rheumatol. 2012;22:327–38.
22. Maini RN, Taylor PC, Szechinski J, Pavelka K, Broll J, Balint G, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Arthritis Rheum. 2006;54(9):2817–29.
23. Takeuchi T, Tanaka Y, Amano K, Hoshi D, Nawata M, Nagasawa H, et al. Clinical, radiographic and functional effectiveness of tocilizumab for rheumatoid arthritis patients—REACTION 52-week study. Rheumatology (Oxford). 2011;50(10): 1908–15.
24. Tanaka Y. Abatacept demonstrated long-term safety and efficacy in active RA patients who showed inadequate response to methotrexate: an analysis of the Japanese phase III open-label, long-term extension trial. Presented at the 14th Asian Pacific League of Associations for Rheumatology (APLAR) Congress. Hong Kong, 2010. p. FP6-1.

Mod Rheumatol
DOI 10.1007/s10165-012-0648-3

ORIGINAL ARTICLE

A review of tocilizumab treatment in 122 rheumatoid arthritis patients included in the Tsurumai Biologics Communication Registry (TBCR) Study

Yuichiro Yabe · Toshihisa Kojima · Atsushi Kaneko · Nobuyuki Asai · Tomonori Kobayakawa · Naoki Ishiguro

Received: 2 December 2011 / Accepted: 23 March 2012

Abstract
Objectives Biologics have transformed the treatment of rheumatoid arthritis. Clinical remission is now the goal. We sought to verify whether the administration of tocilizumab—a biologic—can help to achieve current treatment goals.
Methods Using data from the Tsurumai Biologics Communication Registry for 122 patients treated with tocilizumab, we evaluated changes in DAS28-ESR at 12 months after initiation, and also evaluated remission rates defined using conventional and new Boolean-based remission criteria. We divided 50 patients who had received tocilizumab as a first-line treatment into two groups [disease duration at baseline of 12 months or less ($\leq$12 M) and more than 12 months (>12 M)].
Results At 12 months after initiation, there was no difference in DAS28-ESR, and remission rates based on the conventional criterion were also comparable (50 % in both groups). However, under the new criterion, remission was 50.0 % in the $\leq$12 M group against 12.5 % in the >12 M group ($p = 0.0181$). Among the individual components of the new remission criterion, the small proportion of patients in the >12 M group with a patient global assessment (PtGA) of $\leq$1 had a particularly strong influence on the remission rate for that group, but this component was not as important for the $\leq$12 M group.
Conclusions When used as a first-line biological drug for patients with early-stage RA ($\leq$12 M), tocilizumab appears to provide high rates of remission under the Boolean-based remission criterion, which were strongly affected by the PtGA.

Keywords Interleukin-6 · Multicenter study · Remission · Rheumatoid arthritis · Tocilizumab

Y. Yabe (✉)
Department of Rheumatology, Tokyo Kosei Nenkin Hospital, 5-1 Tsukudo-cho, Shinjuku-ku, Tokyo 162-8543, Japan
e-mail: y-yabe@tkn-hosp.gr.jp

T. Kojima · N. Ishiguro
Department of Orthopedic Surgery and Rheumatology, Nagoya University School of Medicine, Nagoya, Japan

A. Kaneko
Department of Orthopedic Surgery, Nagoya Medical Center, Nagoya, Japan

N. Asai
Department of Orthopedic Surgery, Nakatsugawa Municipal General Hospital, Nakatsugawa, Japan

T. Kobayakawa
Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Aichi, Japan

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease characterized by chronic and destructive inflammation of the joints. The major transformation in treatment brought about by the advent of biologics over the last few years in particular has evoked a number of responses: the European League Against Rheumatism (EULAR) has published *Recommendations for the management of RA with synthetic and biological disease-modifying anti-rheumatic drugs (DMARDs)* [1]; the American College of Rheumatology (ACR) and EULAR have jointly drawn up new classification criteria defining rheumatoid arthritis as "having at least one joint with definite clinical synovitis, with the synovitis not better explained by another disease" [2]; and the concept of

Published online: 22 April 2012