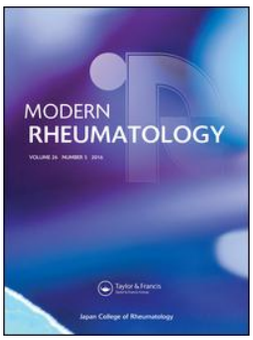

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ORIGINAL ARTICLE

Clinical and structural remission rates increased annually and radiographic progression was continuously inhibited during a 3-year administration of tocilizumab in patients with rheumatoid arthritis: A multi-center, prospective cohort study by the Michinoku Tocilizumab Study Group

Yasuhiko Hirabayashi[1], Yasuhiko Munakata[2], Masayuki Miyata[3], Yukitomo Urata[4], Koichi Saito[5], Hiroshi Okuno[6], Masaaki Yoshida[7], Takao Kodera[8], Ryu Watanabe[9], Seiya Miyamoto[10], Tomonori Ishii[9], Shigeshi Nakazawa[11], Hiromitsu Takemori[12], Takanobu Ando[13], Takashi Kanno[14], Masataka Komagamine[15], Ichiro Kato[16], Yuichi Takahashi[17], Atsushi Komatsuda[18], Kojiro Endo[19], Chihiro Murai[20], Yuya Takakubo[21], Takao Miura[22], Yukio Sato[23], Kazunobu Ichikawa[24], Tsuneo Konta[24], Noriyuki Chiba[25], Tai Muryoi[26], Hiroko Kobayashi[27], Hiroshi Fujii[9], Yukio Sekiguchi[28], Akira Hatakeyama[16], Ken Ogura[29], Hirotake Sakuraba[30], Tomoyuki Asano[27], Hiroshi Kanazawa[12], Eiji Suzuki[14], Satoshi Takasaki[24], Kenichi Asakura[31], Kota Sugisaki[32], Yoko Suzuki[33], Michiaki Takagi[21], Takahiro Nakayama[34], Hiroshi Watanabe[27], Keiki Miura[35], Yu Mori[6], and for the Michinoku Tocilizumab Study Group

[1]Department of Rheumatology, Hikarigaoka Spellman Hospital, Sendai, Japan, [2]Munakata Yasuhiko Clinic, Sendai, Japan, [3]Department of Internal Medicine, Fukushima Red Cross Hospital, Fukushima, Japan, [4]Department of Rheumatology, Tsugaru General Hospital, Gosyogawara, Japan, [5]Suminoya Rheumatism & Orthopedics Clinic, Iwaki, Japan, [6]Department of Orthopaedic Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan, [7]Yoshida Orthopaedic Surgery and Rheumatology Clinic, Morioka, Japan, [8]Center for Arthritis and Rheumatic Diseases, Tohoku Pharmaceutical University Hospital, Sendai, Japan, [9]Department of Hematology and Rheumatology, Tohoku University Graduate School of Medicine, Sendai, Japan, [10]Department of Orthopaedic Surgery, Nakadori General Hospital, Akita, Japan, [11]Nakazawa Sports Clinic, Hachinohe, Japan, [12]Department of Rheumatology, Aomori Prefectural Central Hospital, Aomori, Japan, [13]School of Medicine Department of Orthopaedic Surgery, Iwate Medical University, Morioka, Japan, [14]Department of Rheumatology, Ohta Nishinouchi Hospital, Koriyama, Japan, [15]Komagamine Orthopedic and Rheumatology Clinic, Morioka, Japan, [16]Department of Arthritis and Rheumatic Diseases, Tohoku Rosai Hospital, Sendai, Japan, [17]Yu Family Clinic, Sendai, Japan, [18]Department of Hematology, Nephrology, and Rheumatology, Akita University Hospital, Akita, Japan, [19]Department of Rheumatology and Department of Orthopaedic Surgery, Hoshi General Hospital, Koriyama, Japan, [20]Murai Clinic, Hachinohe, Japan, [21]Department of Orthopaedic Surgery, Yamagata University Faculty of Medicine, Yamagata, Japan, [22]Department of Orthopaedic Surgery, Hirosaki Memorial Hospital, Hirosaki, Japan, [23]Sendai Taihaku Hospital, Sendai, Japan, [24]Department of Cardiology, Pulmonology, and Nephrology, Yamagata University Faculty of Medicine, Yamagata, Japan, [25]Department of Internal Medicine, Morioka National Hospital, Morioka, Japan, [26]Muryoi Clinic, Shiogama, Japan, [27]Department of Gastroenterology and Rheumatology, Fukushima Medical University Hospital, Fukushima, Japan, [28]NTT East Tohoku Hospital, Sendai, Japan, [29]Department of Orthopaedic Surgery, Yonezawa City Hospital, Yonezawa, Japan, [30]Department of Gastroenterology and Hematology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan, [31]Department of Internal Medicine, Yuri Kumiai General Hospital, Yurihonjo, Japan, [32]Department of Internal Medicine, Mito Red Cross Hospital, Mito, Japan, [33]Izumi Himawari Clinic, Sendai, Japan, [34]Department of Internal Medicine, Nihonkai General Hospital, Sakata, Japan, and [35]Department of Orthopaedic Surgery, Tome Citizen Hospital, Miyagi, Japan

Abstract

Objective: To evaluate the clinical and structural efficacy of tocilizumab (TCZ) during its long-term administration in patients with rheumatoid arthritis (RA).

Methods: In total, 693 patients with RA who started TCZ therapy were followed for 3 years. Clinical efficacy was evaluated by DAS28-ESR and Boolean remission rates in 544 patients. Joint damage was assessed by calculating the modified total Sharp score (mTSS) in 50 patients.

Results: When the reason for discontinuation was limited to inadequate response or adverse events, the 1-, 2-, and 3-year continuation rates were 84.0%, 76.8%, and 72.2%, respectively. The mean DAS28-ESR was initially 5.1 and decreased to 2.5 at 6 months and to 2.2 at 36 months. The Boolean remission rate was initially 0.9% and increased to 21.7% at 6 months and to 32.2% at 36 months. The structural remission rates (ΔmTSS/year $\leq$ 0.5) were 68.8%, 78.6%, and 88.9% within the first, second, and third years, respectively. The structural remission rate at 3 years (ΔmTSS $\leq$ 1.5) was 66.0%, and earlier achievement of swollen joint count (SJC) of 1 or less resulted in better outcomes.

Conclusions: TCZ was highly efficacious, and bone destruction was strongly prevented. SJC was an easy-to-use indicator of joint destruction.

Keywords

Joint destruction, Long-term administration, Real clinical practice, Rheumatoid arthritis, Tocilizumab

History

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Correspondence to: Yasuhiko Hirabayashi, MD, PhD, Department of Rheumatology, Hikarigaoka Spellman Hospital, 6-7-1 Higashisendai, Miyagino-ku, Sendai, Miyagi, 983-0833, Japan. Tel: +81 22 257 0231. Fax: +81 22 257 0201. E-mail: mr.hirabayashi@gmail.com

Introduction

Tocilizumab (TCZ), which was originally developed in Japan, is a humanized monoclonal antibody against the interleukin (IL)-6 receptor that functions by inhibiting the interaction between IL-6 and the IL-6 receptor [1]. Clinical trials evaluating the use of TCZ for rheumatoid arthritis (RA) were initiated in 1999. In the SATORI study, TCZ was shown to yield significantly higher improvement rates than methotrexate (MTX) [2]. Additionally, in the OPTION study, clinical efficacy was found to be higher with combined MTX plus TCZ than with MTX alone [3]. In the SAMURAI study, TCZ was shown to be effective as monotherapy for controlling the progression of bone and joint destruction [4]. Furthermore, the STREAM study showed that TCZ was highly efficacious and provided continuity of response as a long-term monotherapy [5].

Based on these trials, TCZ was approved for treatment of RA in Japan on April 16, 2008, which was its first approval worldwide. The Ministry of Health, Labour, and Welfare of Japan required that Chugai Pharmaceutical Company Limited conduct postmarketing surveillance (PMS) to investigate the safety and efficacy of TCZ in real-world settings [6]. All patients who started treatment with TCZ between April 2008 and August 2010 were enrolled; thus, patients who were the first to receive TCZ in the real-world setting were included. However, the observation period was only 6 months.

In this study, we extended this observation period to 3 years and evaluated the efficacy of TCZ, including structural efficacy, during long-term administration.

Patients and methods

Study protocol

This study was a multicenter prospective observational cohort study, termed the Michinoku Tocilizumab Study. The study was approved by the Ethics Committee of Tohoku University and was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (#UMIN000011584). The patients were observed for 3 years after receiving TCZ in real clinical practice. Tender joint count (TJC), swollen joint count (SJC), patient global assessment-visual analog scale (PGA-VAS), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were assessed every 3 months after the first TCZ dose to calculate the remission rates under the 28-joint disease activity score using ESR (DAS28-ESR < 2.6) and under the new 2011 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) Boolean-based remission criteria (TJC ≤ 1, SJC ≤ 1, PGA-VAS ≤ 1 cm, and CRP ≤ 1 mg/dL) [7,8]. Posteroanterior radiographs of hands and anteroposterior radiographs of feet were obtained at baseline and at the end of years 1–3. Radiographs were randomly evaluated using the van der Heijde-modified total Sharp score (mTSS) by two independent, blinded readers (H.O. and R.W.) who were trained at the Department of Rheumatology, Leiden University Medical Center. Yearly progression of mTSS of ≤ 0.5 was considered structural remission [9]. Comorbidities were classified according to the International Classification of Diseases ver. 10 (ICD-10).

Patients

The subjects of this analysis were patients meeting the 1987 revised RA classification criteria from the ACR who received TCZ following its marketing approval in Japan for use in patients with RA. In total, 724 patients from 34 institutions in the Tohoku area were registered between April 1, 2008 and December 31, 2010 by the Michinoku Tocilizumab Study Group (MTSG), and 693 patients were followed up. To reduce adverse events (AEs), patients were screened according to the guidelines of the Japan College of Rheumatology, and we worked to treat or control all comorbidities as well as possible before giving TCZ. The patients received TCZ at 8 mg/kg intravenously every 4 weeks. The clinical efficacy was evaluated by DAS28-ESR and Boolean remission rate in 544 patients. Joint damage was assessed by calculating mTSS in 50 patients.

Statistical analysis

The cumulative treatment continuation rate was assessed by the Kaplan–Meier method. The baseline data were analyzed by the Mann–Whitney *U*-test, Welch's *t* test, or a test for the difference in the population proportions. For comparison of more than two groups, an analysis of variance (ANOVA) was used. Chi-squared or Fisher's exact tests were used for univariate comparison. Trends were assessed using the Cochran–Armitage trend test. $p < 0.05$ was considered statistically significant. The significance level was adjusted by the Bonferroni method in the analysis of sequential data.

Results

Patient characteristics

The demographics and baseline characteristics of patients at baseline are summarized in Table 1. In total, 693 patients were followed up, and 384 patients had completed 3 years of treatment (Figure 1a). The 1-, 2-, and 3-year overall continuation rates were 80.0%, 66.1%, and 57.7%, respectively, and 168 patients withdrew for reasons other than inadequate response (IR) or AEs. Among the remaining 525 patients, 146 withdrew due to IR or AEs. When the reason for discontinuation was limited to IR or AEs, the 1-, 2-, and 3-year continuation rates were 84.0%, 76.8%, and 72.2%, respectively.

Clinical efficacy

The mean DAS28-ESR score was initially 5.1 ± 1.4 (arithmetic mean $\pm$ standard deviation (SD); this format is used hereafter) and then decreased to 2.4 ± 1.3 at 6 months, meeting the DAS28-ESR remission criteria. The mean DAS28-ESR scores were 2.2 ± 1.2, 2.1 ± 1.3, and 2.0 ± 1.1 at 12, 24, and 36 months, respectively (Figure 1b). The percentage of patients with high disease activity (DAS28-ESR > 5.1) was 49.4% at baseline, rapidly falling to 4.1% at 3 months (Figure 1c). The percentage of patients in DAS28-ESR remission was 3.1% at baseline, rapidly increasing to 43.4% at 3 months and to 65.0% at 36 months.

Figure 1(d) shows the time courses for the percentages of patients with CRP ≤ 1 mg/dL, TJC ≤ 1, SJC ≤ 1, PGA-VAS ≤ 1 cm, Boolean remission, and DAS28-ESR remission. The percentage of patients with CRP ≤ 1 mg/dL was initially 40% and then increased to approximately 90% from 6 months onward. The percentages of patients with TJC ≤ 1, SJC ≤ 1, and PGA-VAS ≤ 1 cm also increased. The Boolean remission rate was initially 0.9% and increased to 21.7% at 6 months and 32.2% at 36 months.

Next, we investigated differences in the therapeutic efficacy of TCZ according to the patients' background characteristics. First, the factors influencing Boolean remission at 12 and 36 months were analyzed (Table 2). For the multivariate logistic regression analysis, we included the factors found to be significant ($p < 0.05$) in the univariate logistic regression analyses as well as four fixed factors (age, disease duration, SJC, and history of TNFi use). Multivariate analyses indicated that stage 3 + 4, PGA-VAS, and history of TNFi use were significant factors at both 12 and 36 months. At 36 months, the TNFi-naive patients were 2.4-fold more likely to achieve remission than were the TNFi-treated patients. As a result, the Boolean remission rate of the TNFi-naive group was

Table 1. Baseline characteristics of the patients.

	Group		
	I	II	III
Number of patients	693	544 (264: 280)	50 (32: 18)
Age (years)	59.5 ± 13.4	59.4 ± 13.0 (60.1 ± 13.2: 58.8 ± 12.8)	58.0 ± 11.9 (59.7 ± 2.2: 54.8 ± 2.3)
Female (%)	82.1	82.5 (83.7: 81.4)	88.0 (90.6: 83.3)
Disease duration (years)	9.5 ± 8.9	9.6 ± 8.7 (10.0 ± 9.2: 9.2 ± 8.2)	10.9 ± 9.9 (11.2 ± 1.8: 10.8 ± 2.5)
Stage 1/2/3/4 (%)	14/25/30/32	14/24/28/34 (18/20/23/39: 10/28/34/29)	17/12/17/44 (22/19/19/41: 22/17/22/39)
Class 1/2/3/4 (%)	22/56/21/1	25/56/18/1 (30/59/11/0: 20/54/25/1)[a]	30/60/10/0 (47/53/0/0: 22/67/11/0)[a]
CRP (mg/dL)	2.6 ± 2.9	2.5 ± 2.7 (1.9 ± 2.3: 3.0 ± 2.9)[b]	2.0 ± 2.1 (1.7 ± 0.4: 2.5 ± 0.5)
ESR (mm/1 h)	49.3 ± 33.1	49.0 ± 33.2 (44.0 ± 30.0: 53.6 ± 35.1)[b]	40.5 ± 29.1 (34.2 ± 4.4: 52.1 ± 8.1)
TJC [0–28 joints]	6.1 ± 6.0	6.1 ± 6.1 (5.2 ± 5.3: 7.0 ± 6.6)[b]	5.3 ± 4.7 (5.1 ± 0.9: 5.7 ± 1.0)
SJC [0–28 joints]	5.4 ± 5.1	5.5 ± 5.2 (4.9 ± 4.5: 6.0 ± 5.7)[b]	5.0 ± 3.8 (4.3 ± 0.6: 6.3 ± 1.0)
VAS (mm)	55.1 ± 25.7	55.2 ± 25.9 (52.4 ± 25.3: 57.8 ± 26.2)[b]	49.1 ± 23.5 (49.2 ± 4.1: 48.8 ± 5.9)
DAS28-ESR	–	5.1 ± 1.4 (4.8 ± 1.3: 5.3 ± 1.4)[b]	4.8 ± 1.2 (4.6 ± 0.2: 5.1 ± 0.3)
History of TNFi use (%)	54.4	51.4 (0: 100)[c]	18.0 (9.4: 33.3)[c]
Baseline MTX use (%)	56.9	55.7 (52.3: 59.3)	34.0 (34.3: 38.9)
Baseline PSL use (%)	67.1	66.0 (58.3: 73.6)[c]	67.3 (65.6: 70.6)

Group I: entire cohort; Group II: patients for whom clinical efficacy was evaluated by DAS28ESR and Boolean remission rates; Group III: patients for whom joint damage was assessed by mTSS. In group II, data for patients who did not receive TNFi appear to the left of the colon in parentheses, and data for patients who had previously received TNFi appear to the right. In group III, data for patients whose ΔmTSS score during the 3-year study ≤ 1.5 appear to the left of the colon in parentheses, and data for patients whose ΔmTSS during the 3-year study > 1.5 appear on the right. Statistically significant differences ($p < 0.05$) were observed by [a]the Mann–Whitney *U*-test, [b]Welch's *t* test, or [c]a test for the difference in the population proportions. Values are mean ± standard deviation (SD). Stage, Steinbrocker stage; Class, Steinbrocker class; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; TJC, tender joint count; SJC, swollen joint count; DAS28-ESR, the 28-joint disease activity score using ESR; TNFi, tumor necrosis factor inhibitor; MTX, methotrexate; PSL, prednisolone.

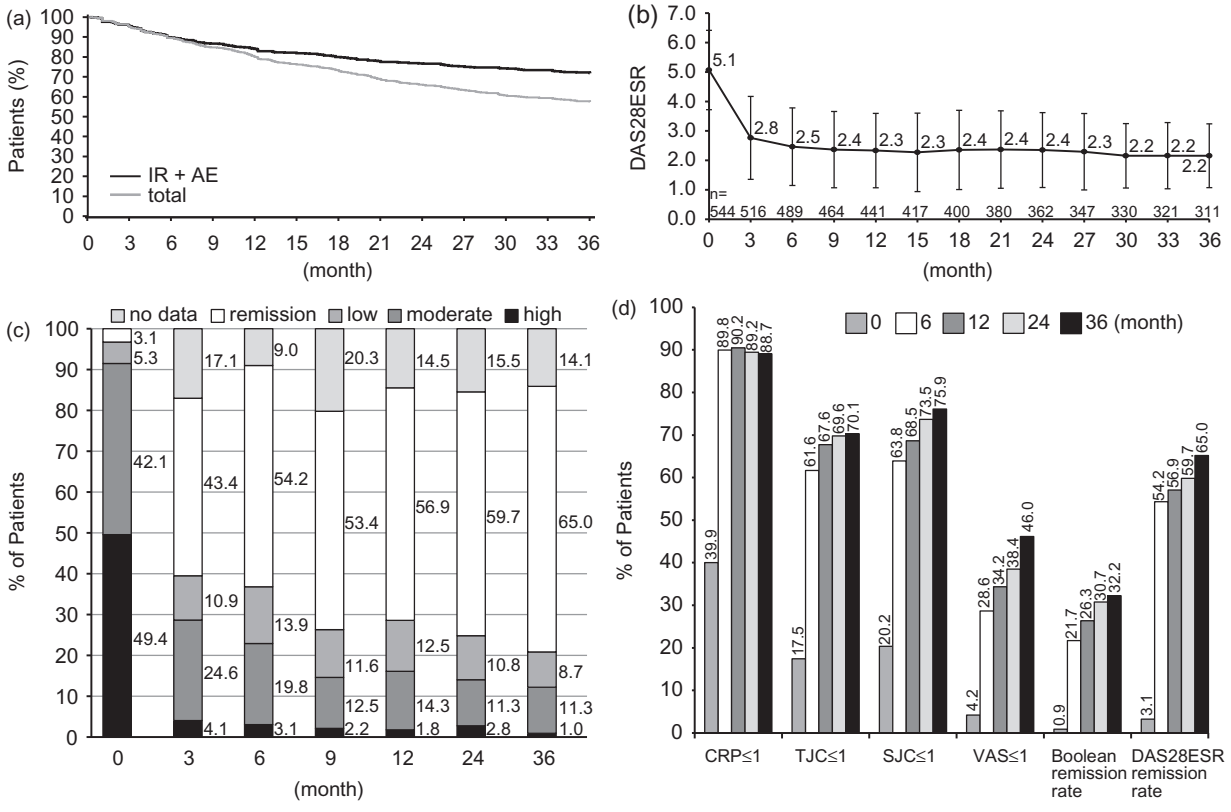

Figure 1. (a) Kaplan–Meier estimate of the probability of continuing treatment with TCZ. The upper black line indicates the continuation rate when the reason for discontinuation was limited to inadequate response (IR) or adverse events (AEs). The lower gray line indicates the total continuation rate. (b) Changes in DAS28-ESR in all patients. Mean values are shown. Bars indicate standard deviation (SD). (c) Disease activity over time. The categories are based on the DAS28-ESR (<2.6: remission, ≥2.6 and <3.2: low disease activity, 3.2–5.1: moderate disease activity, and <5.1: high disease activity). (d) Percentage of patients achieving each component of the Boolean-based remission criteria or achieving remission at 0, 6, 12, 24, and 36 months.

40.5% while that of the TNFi-treated group was 23.0% ($p < 0.01$ by the Chi-squared test). The baseline characteristics of the TNFi-naive patients and the TNFi-treated patients are summarized in Table 1. Although the mean DAS28-ESR score of the TNFi-treated group (2.3 ± 1.1) was significantly higher than that of the TNFi-naive group (1.8 ± 1.1) even at 36 months ($p < 0.01$ by Welch's *t* test), both scores remained below the remission threshold from 9 months onward (Figure 2a). At 36 months, the

Table 2. Factors influencing Boolean remission.

	12 months Odds ratio (95% CI)	*p* value	36 months Odds ratio (95% CI)	*p* value
Univariate analysis for achieving Boolean remission				
Age	0.98 (0.96–1.00)	<0.05	0.98 (0.96–1.00)	<0.05
Disease duration	0.96 (0.93–0.99)	<0.01	1.00 (0.97–1.03)	0.74
Stage 3 + 4 vs 1 + 2	0.43 (0.27–0.68)	<0.01	0.57 (0.34–0.95)	<0.05
Class 3 + 4 vs 1 + 2	0.19 (0.08–0.45)	<0.01	0.76 (0.37–1.56)	0.46
CRP	0.98 (0.90–1.06)	0.59	0.99 (0.90–1.09)	0.81
ESR	0.99 (0.98–1.00)	<0.05	1.00 (0.99–1.01)	0.85
TJC	0.90 (0.86–0.95)	<0.01	0.93 (0.88–0.97)	<0.01
SJC	0.93 (0.88–0.97)	<0.01	0.94 (0.89–0.99)	<0.05
PGA-VAS	0.98 (0.97–0.99)	<0.01	0.99 (0.98–1.00)	<0.01
DAS28ESR	0.66 (0.55–0.79)	<0.01	0.73 (0.61–0.88)	<0.01
History of TNFi use	0.48 (0.30–0.76)	<0.01	0.44 (0.26–0.73)	<0.01
Baseline MTX use	0.96 (0.62–1.50)	0.87	0.70 (0.42–1.16)	0.16
Baseline PSL use	0.73 (0.45–1.16)	0.18	0.76 (0.44–1.30)	0.31
Multivariate analysis for achieving Boolean remission				
Age	0.99 (0.97–1.01)	0.19	0.98 (0.96–1.00)	0.07
Disease duration	0.98 (0.94–1.01)	0.27	0.97 (0.94–1.01)	0.16
Stage 3 + 4 vs 1 + 2	0.52 (0.59–0.92)	<0.05	0.51 (0.29–0.90)	<0.05
Class 3 + 4 vs 1 + 2	0.38 (0.15–0.96)	<0.05		
ESR	0.99 (0.98–1.01)	0.26		
TJC	0.91 (0.83–1.00)	0.06	0.94 (0.87–1.02)	0.11
SJC	0.94 (0.96–1.02)	0.13	0.96 (0.90–1.04)	0.33
PGA-VAS	0.98 (0.96–0.99)	<0.01	0.98 (0.97–0.99)	<0.01
DAS28ESR	1.50 (0.79–2.85)	0.22	1.08 (0.73–1.58)	0.71
History of TNFi use	0.49 (0.29–0.82)	<0.01	0.43 (0.26–0.71)	<0.01

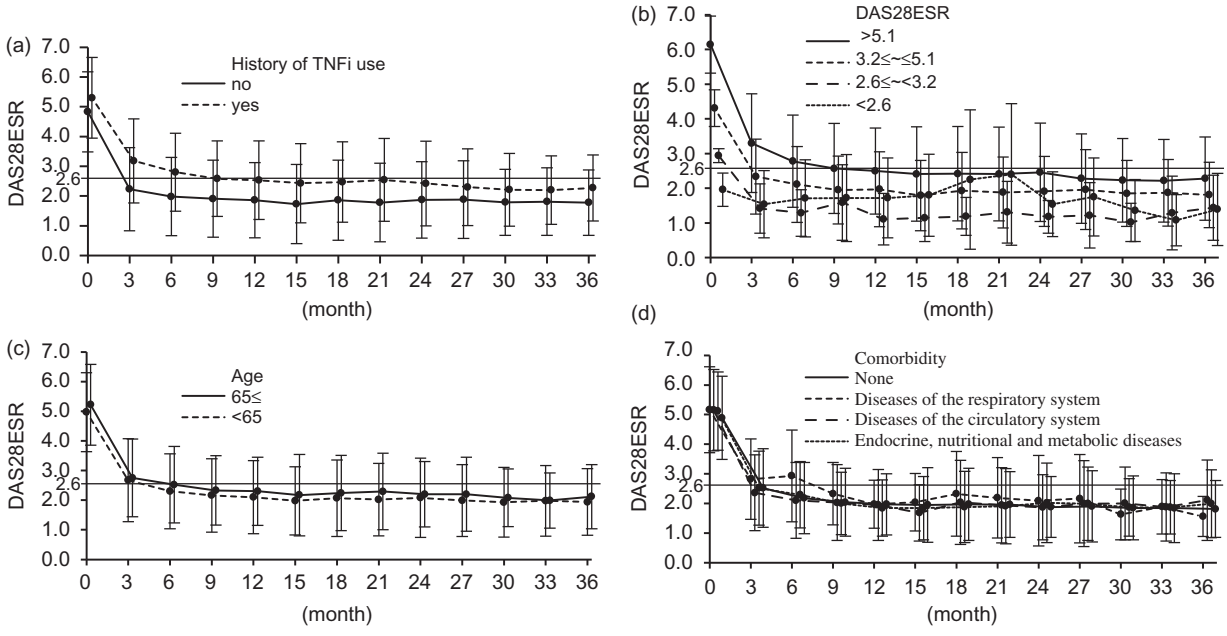

Figure 2. (a) Changes in DAS28-ESR according to the history of TNFi use. Mean values are shown. Bars indicate SD. (b) Changes in DAS28-ESR according to disease activity at baseline. (c) Changes in DAS28-ESR according to age. (d) Change in DAS28-ESR according to comorbidities.

mean values for CRP, ESR, TJC, SJC, and PGA-VAS in both groups were as follows (TNFi-naive: TNF treated; *P* by Welch's *t* test): CRP, 0.2 ± 0.6: 0.1 ± 0.4, $p = 0.29$; ESR, 9.6 ± 16.5: 8.5 ± 9.3, $p = 0.47$; TJC, 0.8 ± 1.9: 1.8 ± 3.5, $p < 0.01$; SJC, 0.5 ± 1.4: 1.5 ± 2.9, $p < 0.01$; and PGA-VAS, 18.8 ± 21.0: 23.0 ± 23.8, $p = 0.11$.

Second, we classified the patients based on their baseline level of disease activity into a high-activity group (DAS28-ESR > 5.1; $n = 269$), a moderate-activity group (DAS28-ESR of 3.2–5.1; $n = 229$), a low-activity group ($2.6 \leq$ DAS28-ESR < 3.2; $n = 29$), and a group in DAS28-ESR remission (DAS28-ESR < 2.6; $n = 17$) (Figure 2b). Patients who were classified in the DAS28-ESR remission group had arthritis in the joints not assessed by DAS28-ESR (e.g. they had arthritis in their feet). In the moderate and low disease activity groups, the mean baseline DAS28-ESR scores of 4.3 ± 0.5 and 2.9 ± 0.2, respectively, fell below the remission threshold at 3 months to 2.3 ± 1.1 and 1.4 ± 0.7, respectively. Although the mean baseline DAS28-ESR score was 6.1 ± 0.8 in the high-activity group, it fell to below the remission threshold (2.6 [2.57] $\pm$ 1.3) at 9 months. TCZ proved to be effective, regardless of baseline disease activity.

Third, with age, physical capacity generally declines, and comorbidities often increase. In the joints in particular, increasing frequency of pain can be associated with osteoarthritis.

To investigate whether such factors would produce differences in the efficacy of TCZ therapy, we divided the subjects into an elderly group (age 65 years and over; 71.4 ± 4.8 years; $n = 210$) and a nonelderly group (age less than 65 years; 51.9 ± 10.6 years; $n = 334$) in accordance with the WHO classification. The mean DAS28-ESR scores of both groups remained below the remission threshold from 6 months onward (Figure 2c). Age had no effect on the efficacy of TCZ.

Lastly, we investigated the effects of comorbidities, which were categorized according to the International Statistical Classification of Disease and Related Health Problems, 10th Revision (ICD-10) scoring system. We selected three common representative categories and divided the patients into four groups: group 1, patients with diseases of the respiratory system ($n = 33$); group 2, patients with diseases of the circulatory system ($n = 70$); group 3, patients with endocrine, nutritional, and metabolic diseases ($n = 82$); and group 4, patients without comorbidities ($n = 149$). Patients with multiple comorbidities were counted in every applicable group. Mean baseline DAS28-ESR scores were 5.2 ± 1.5, 5.2 ± 1.4, 5.1 ± 1.3, and 4.9 ± 1.4 in groups 1, 2, 3, and 4, respectively (Figure 2d). From 9 months onward, the mean DAS28-ESR scores of all groups were below the remission threshold. The efficacy of TCZ was not affected by comorbidities.

Structural efficacy

Joint damage over 3 years was evaluated in 50 patients. The change in erosion score during the first year was 0.19 ± 0.16, and the worst score noted was 3.50 (Figure 3a). During the second year, the change in erosion score and the worst score decreased to 0.04 ± 0.15 and 3.00, respectively. During the third year, the change in erosion score decreased to less than zero (-0.06 ± 0.11) and converged to 0.00 ± 1.00. The worst score was only 1.00. Similarly, the change in JSN decreased from year to year; scores were 0.39 ± 0.33, 0.06 ± 0.21, and 0.08 ± 0.06 during the first, second, and third years, respectively. The worst score decreased from 10.50 at 1 year to 1.00 at 3 years. Changes in mTSS also decreased from 0.57 ± 0.46 at 1 year to 0.10 ± 0.33 and 0.02 ± 0.15 at 2 and 3 years, respectively.

The cumulative probability plots of the first, second, and third years are shown in Figure 3(b). The structural remission rates were 69.4%, 78.6%, and 88.9% during the first, second, and third years, respectively. In 33 patients (66% of 50 patients), the change in mTSS over the 3-year period was less than 1.5 (≤ 0.5/year $\times$ 3 year) (Figure 3c). Moreover, the change in mTSS in 30 patients (60% of 50 patients) was less than 0.5 over the 3-year period. These results demonstrated that bone and joint destruction was markedly inhibited from year to year during the long-term administration of TCZ.

Possible clinical predictors of structural remission

A simple and easy-to-use predictor of structural outcomes in actual clinical practice would be beneficial for clinicians. Therefore, we next investigated whether DAS28-ESR, Boolean remission, or their components (TJC, SJC, CRP, and ESR) within 1 year could be applied a clinical predictor of structural remission during the

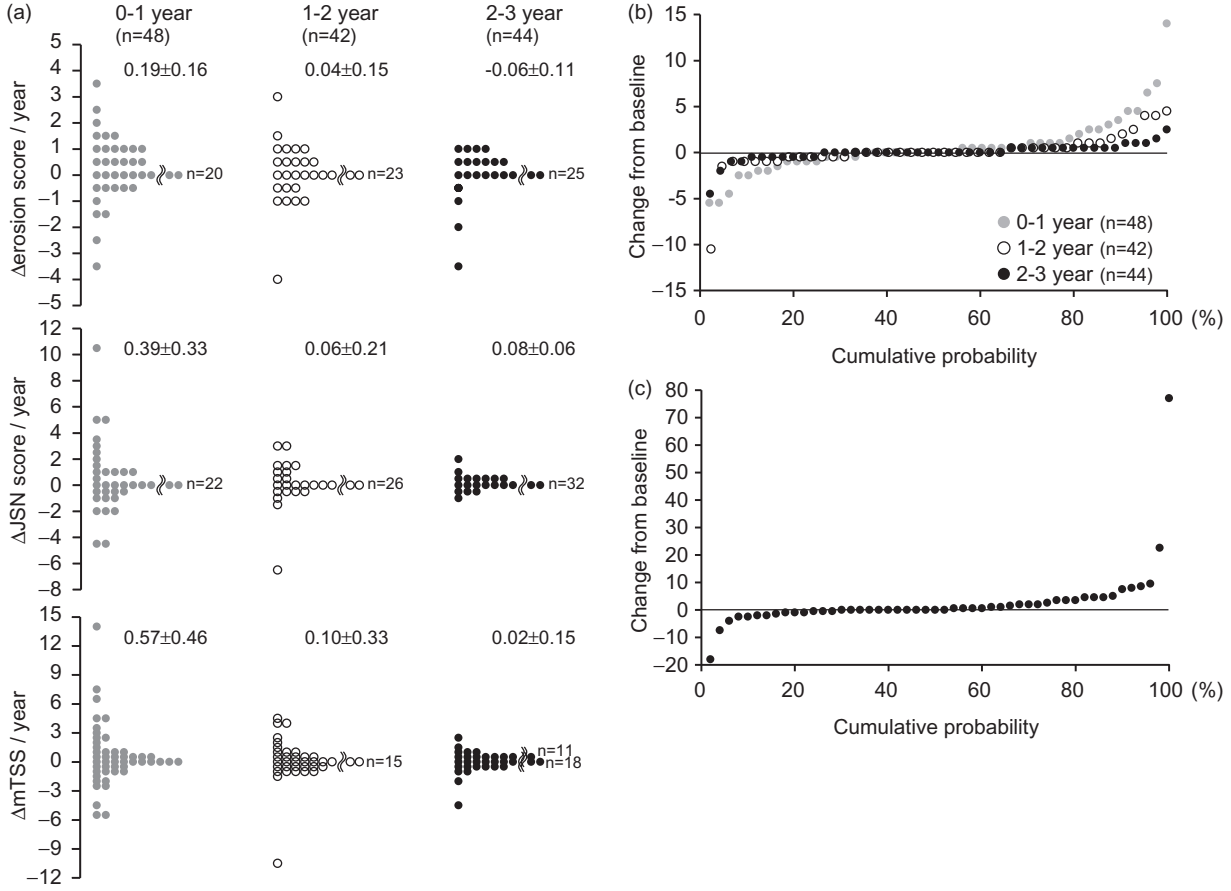

Figure 3. (a) Annual radiographic progression over 3 years. Data from plain radiography were compared between baseline and 1 year in 48 patients, between 1 year and 2 years in 42 patients, and between 2 years and 3 years in 44 patients to calculate the ΔmTSS/year. (b) Cumulative probability plot of annual changes in mTSS from baseline to 1 year, from 2 to 2 years, and from 2 to 3 years. (c) Cumulative probability plot of changes in mTSS from baseline to 3 years. Data from plain radiography were compared between baseline and 3 years in 50 patients to calculate the ΔmTSS/3 years.

first 3 years of therapy. The normal range of ESR was defined as $\leq$15 mm/1 h. A total of 50 patients (group III in Table 1) were not sufficient for multivariate analyses, and hence the baseline characteristics were compared between the two groups (ΔmTSS/3 years $\leq$ 1.5 and ΔmTSS/3 years $>$ 1.5). Statistical significance testing was carried out by performing hypothesis testing of the difference between two population proportions (female, history of TNFi use, baseline MTX use, and baseline PSL use) or Welch's *t* test (age, disease durations, CRP, ESR, TJC, SJC, VAS, and DAS28-ESR). Only ''history of TNFi use'' was significantly different ($p = 0.03$). There is a possibility that the following results were somewhat affected by this difference. The *p* values for ΔmTSS < 1.5 during the 3-year study, as determined by Fisher's exact tests, are shown in Table 3. CRP $\leq$ 1 mg/dL, ESR $\leq$ 15 mm/1 h, TJC $\leq$ 1, and DAS28SR < 2.6 were unsuitable as predictors because their *p* values were not continually less than 0.0125. However, the *p* value for Boolean remission was less than 0.0125 from 9 months onward. Therefore, Boolean remission from 9 months onward could be a predictor of efficacy. We previously reported that DAS28SR < 1.54 corresponded to Boolean remission in patients with RA receiving TCZ [10]. However, the *p* value associated with DAS28SR < 1.54 was more than 0.0125 at all time points. Therefore, DAS28-ESR was unsuitable as a predictor, even though a lower cut-off value was adopted. The *p* value of SJC $\leq$ 1, which was 0.2121 at baseline, was consistently less than 0.0125 from 6 months onward and decreased from 0.0364 at 3 months to 0.0010 at 12 months when measured at 3-month intervals. Thus, SJC $\leq$ 1 from 6 months onward could be a good clinical predictor of long-term structural remission.

Discussion

The first part of this discussion compares our results to data reported in other analyses. In the STREAM study, 143 patients receiving TCZ monotherapy (8 mg/kg/4 weeks) were enrolled, and 94 patients completed 5 years of follow up [5]. The continuation rate at 3 years was 76%, and the most common reasons for discontinuation were IR or AEs. Similarly, in our study, if the reason for discontinuation was limited to IR or AEs (representing the majority of cases of discontinuation until 1 year), the continuation rate at 3 years was 72.2%. For the STREAM study, the DAS28-ESR scores at baseline, 12, and 36 months (6.7, 3.1, and 2.6, respectively) were similar to those of the high disease activity group in our study.

Similar results were observed in the SAMURAI study. For the TCZ group in the SAMURAI study, the DAS28-ESR scores at baseline, 12, and 36 months (6.4, 2.3, and 2.1, respectively) [4,11] were comparable to the results in the high disease activity group in our study. However, the structural remission rate during year 1 was higher in our study (69.4%) than in the SAMURAI study (56% for the TCZ group). Changes in the erosion score, JSN score, and mTSS over a 3-year period (2.04, 4.28, and 6.18, respectively) were higher in the TCZ group in the SAMURAI study than in our study. Additionally, baseline DAS28-ESR scores of 50 patients in our study (4.8) were lower than those of patients in the TCZ group in the SAMURAI study (6.4), whereas disease duration in our study (10.9 years) was longer than that of patients in the TCZ group in the SAMURAI study. Thus, our study showed better efficacy and continued therapeutic management than the SAMURAI study.

Table 3. Predictor of structural remission during 3 years.

Month	3	6	9	12
CRP $\leq$ 1 mg/dL	c.i.	0.5951	c.i.	c.i.
ESR $\leq$ 15 mm/1 h	**0.0102**	0.2532	0.6327	0.5878
TJC $\leq$ 1	0.0754	**0.0023**	0.6046	0.1206
SJC $\leq$ 1	0.0364	**0.0063**	**0.0013**	**0.0010**
Boolean	0.1794	0.0276	**0.0002**	**0.0073**
DAS28ESR < 2.6	0.0920	**0.0076**	0.1301	0.1206
DAS28ESR < 1.54	0.0150	0.1234	0.1775	0.0471

p values were determined by Fisher's exact test. c.i., computation incapable. The significance level was adjusted by Bonferroni method and set at 0.05/4 = 0.0125. The numbers which were less than 0.0125 were boldfaced.

In the LITHE study, patients were treated with TCZ 8 mg/kg plus MTX. DAS28-ESR scores at baseline, 12, and 24 months (6.5, 2.9, and 2.6, respectively) [12] were similar to those in patients in the high disease activity group in our study. Moreover, changes in erosion scores, JSN, and mTSS over 2 years in the LITHE study (0.22, 0.15, and 0.37, respectively) were equivalent to those observed in our current study. Thus, our results were highly consistent with the results of the LITHE study.

In all-patient PMS, 7901 patients were enrolled [6], including the patients enrolled in this study. Efficacy was evaluated in 4745 patients by DAS28-ESR. The DAS28-ESR scores at baseline and 28 weeks were 5.5 and 2.9, respectively, and the DAS28-ESR remission rates at baseline and 28 weeks were 1.3% and 47.6%, respectively. Therefore, the results of our study were consistent with the findings in the overall PMS analysis.

Nakashima et al. reported results from 3 years of prospectively registered data in routine clinical practice [13]. In total, 236 patients were enrolled from Fukuoka RA Biologics Registry, and 114 patients were analyzed. The mean age at baseline was 52.2 years, which was approximately 7 years less than the mean age of patients in our study. Importantly, efficacy data, including DAS28-ESR scores at baseline, 12, 24, and 36 months; Boolean remission rates at baseline, 12, 24, and 36 months; and changes in the four required Boolean criteria (i.e. CRP $\leq$ 1 mg/dL, TJC $\leq$ 1, SJC $\leq$ 1, and PGA-VAS $\leq$ 1 cm), were similar between our study and the study of Nakashima et al. These two studies were performed at around the same time, but in different regions of Japan (the Kyushu and Tohoku areas). Thus, the similar results obtained from these two separate studies provide additional support for the clinical efficacy of TCZ in Japanese individuals.

In summary, when comparing our results to the data reported in other studies, our data were consistent with other findings or even demonstrated improved efficacy. Therefore, this comparison further validated the results of our study and supported the efficacy of TCZ therapy.

The second part of this discussion focuses on the factors affecting the efficacy of TCZ. Multivariate analysis revealed that Steinbrocker stage, PGA-VAS, and history of TNFi use affected Boolean remission at 36 months (Table 2). Unexpectedly, these three factors did not directly reflect inflammation. A comparison between the TNFi-treated group and the TNFi-naive group revealed no significant differences in Steinbrocker stage, but the Steinbrocker class, CRP, ESR, TJC, SJC, PGA-VAS, DAS28-ESR, and baseline PSL use variables in the TNFi-treated group indicate higher disease activity in the TNFi-treated group than in the TNFi-naïve group at baseline (Table 1). However, TJC and SJC, but not CRP and PGA-VAS, were significantly different between the two groups at 36 months and may have contributed to the lower Boolean remission rate in the TNFi-treated group. Accordingly, although the mean DAS28-ESR score in the TNFi-treated group was lower than 2.6, it was significantly higher than that in the TNF-naive group ($p < 0.01$ by Welch's *t* test). These results suggest possible treatment resistance in the TNFi-treated patients.

This multivariate analysis was limited by the following: (i) The conventionally selected factors were included whether they were appropriate or not; (ii) a confounding bias cannot be excluded

completely, as Steinbrocker stage may affect PGA-VAS or TJC, because advanced joint destruction causes loss of joint function, pain during motion, and neurological damage, among other sequelae; and (iii) issues regarding multiple comparisons were not resolved because this study was an observational cohort study.

Finally, the last part of this discussion examines ways to prevent joint destruction over the long-term. Since there is no definition of structural remission over several years, we provisionally defined structural remission at 3 years as ΔmTSS/3 years ≤ 1.5 ($\leq 0.5 \times 3$) in this study. The effect of aging over 3 years should be considered especially in elderly patient, but there is currently no standardized adjustment for age. Even without consideration for aging, the remission rate for the first year (69.4%) was close to that at 3 years (66%), which may suggest that achieving structural remission within the first year is necessary to achieve ΔmTSS/3 years ≤ 1.5. Indeed, to achieve remission as soon as possible is undoubtedly beneficial, because tissue damage progresses until inflammation is halted.

Notably, the mean erosion score decreased from year to year and finally reached a negative value. In a previous report, bone erosion was shown to be repaired by long-term administration of TCZ, even in very elderly patients [14]. This may explain the observed increases in structural remission rates over time. To obtain good long-term structural outcomes, a predictor (or predictors) that could be applied easily in actual clinical practice is desired. CRP and ESR are not suitable parameters because they are often normal in patients with active RA [15]. TJC depends on both the pain threshold of the patient and the pressure applied by the evaluator, and tenderness does not always reflect inflammation. Moreover, our results supported that TJC ≤ 1 did not provide significant prediction for the outcome. Therefore, we excluded this parameter as a predictor.

We next evaluated SJC and ESR as potential predictors. Clinically, joint swelling is indicative of joint inflammation that causes joint destruction. A meta-analysis demonstrated that only SJC and ESR were associated with radiographic progression [16]. Moreover, IL-6 levels, which are associated with structural damage, are strongly correlated with the SJC [17]. We found that the p value for SJC ≤ 1 decreased over time, suggesting that assessment of joint swelling by rheumatologists is generally reliable. Evaluation of joint swelling is typically part of clinical examinations and therefore does not require additional time or cost. Thus, we propose that SJC ≤ 1 could be an excellent, easy-to-use predictor of structural remission in actual clinical practice. Accordingly, Boolean remission was also found to be a good predictor for the outcome, albeit from later times (9 months onward), likely owing to the other parameters used for determining Boolean remission, including CRP, TJC, and PGA-VAS, which can be easily affected by conditions other than RA.

The criteria for DAS28-ESR were established in 2005, before the widespread use of biologics [18]. However, arthritis often exists and joint destruction progresses, even among patients in DAS28-ESR remission. In fact, DAS28-ESR < 2.6 was not a predictor in our study. We previously reported that a DAS28-ESR cutoff value of 1.54 may correspond to Boolean remission [10]. However, when we tested DAS28-ESR < 1.54 in this current study, this parameter was also not a suitable predictor. Although joint swelling remains, the DAS28-ESR score decreases because ESR is a weighted factor in DAS28-ESR and TCZ can normalize ESR quickly.

Taken together, these results suggest that it is necessary to dissipate joint swelling as soon as possible to prevent joint destruction. Achievement of SJC ≤ 1 within 6 months may be an appropriate goal for achieving long-term structural remission.

The characteristic feature of RA is the persistence of synovitis, the mechanism of which involves IL-6, which is a cytokine that stimulates the production and activation of platelets [19,20]. Microparticles released from activated platelets in turn prominently induce the release of IL-6 and IL-8 from synovial fibroblasts [21], creating a positive feedback loop of IL-6 production. An alternative method for IL-6 production in inflamed joints has also been reported [22]. IL-6 stimulates synoviocytes to produce IL-7, and IL-6 and IL-7 then collaboratively activate Th17 cells to produce IL-17. IL-6 and IL-17 collaboratively stimulate synoviocytes, thereby inducing the production of IL-6. Moreover, IL-17 induces resistance to endoplasmic reticulum stress-induced apoptosis in synoviocytes via expression of synoviolin, thereby promoting the growth of synoviocytes [23,24]. These mechanisms may play a central role in the persistent synovitis observed in patients with RA. Therefore, the production of inflammatory cytokines should be avoided, and any comorbidities, particularly chronic infectious diseases (e.g. periodontitis and sinusitis), should be treated or controlled before and during administration of antirheumatic drugs. Understandably, smoking cessation is integral. These countermeasures are critical for achieving the true efficacy of antirheumatic drugs and for reducing the occurrence of AEs.

The generalizability of this study is limited because this study was a non-controlled observational cohort study. However, population bias may be minimal because it was a large, multicenter study. Most of the participating doctors were skilled rheumatologists, and our results are consistent with those of other studies. We, therefore, believe that our inferences are credible, including that SJC might be an easy-to-use indicator of joint destruction in actual clinical practice. TCZ was found to yield high levels of sustained structural remission in patients with RA. To prevent joint destruction, the positive feedback loop of IL-6 production should be blocked as soon as possible, and TCZ appears to be an effective option for achieving this goal. Our future work will aim to further improve the treatment protocol using TCZ.

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Conflict of interest

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