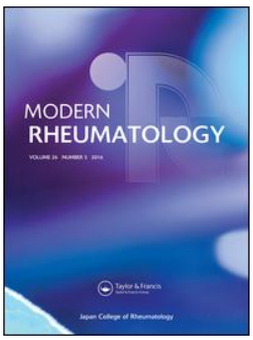

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ORIGINAL ARTICLE

Effectiveness and safety of tocilizumab in achieving clinical and functional remission, and sustaining efficacy in biologics-naive patients with rheumatoid arthritis: The FIRST Bio study

Naoki Ishiguro[1], Tatsuya Atsumi[2], Masayoshi Harigai[3], Tsuneyo Mimori[4], Norihiro Nishimoto[5], Takayuki Sumida[6], Tsutomu Takeuchi[7], Yoshiya Tanaka[8], Ayako Nakasone[9], Nobuhiro Takagi[10], and Hisashi Yamanaka[11]

[1]Department of Orthopedic Surgery, Nagoya University Graduate School & Faculty of Medicine, Nagoya, Japan, [2]Hokkaido University Graduate School of Medicine, Sapporo, Japan, [3]Department of Pharmacovigilance, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan, [4]Department of Rheumatology and Clinical Immunology, Kyoto University, Kyoto, Japan, [5]Osaka Rheumatology Clinic, Tokyo Medical University, Osaka, Japan, [6]Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, [7]Division of Rheumatology, Department of Internal Medicine, Keio University, Minato, Japan, [8]The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, [9]Pharmacovigilance Department, Chugai Pharmaceutical Co. Ltd., Tokyo, Japan, [10]Medical Science Department, Chugai Pharmaceutical Co. Ltd., Tokyo, Japan, and [11]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Abstract

Objective: To evaluate effectiveness and safety of tocilizumab (TCZ) in biologic-naive Japanese patients with rheumatoid arthritis (RA) in real-world settings, and to analyze the relationship between disease duration and clinical outcomes.

Methods: The FIRST Bio study was a postmarketing surveillance study of intravenous TCZ in biologics-naive patients who had a prior inadequate response or were intolerant to $\geq$1 conventional synthetic disease-modifying antirheumatic drug (csDMARD). Effectiveness, safety, and concomitant csDMARD administration were assessed.

Results: Of the 839 patients analyzed, 72.3% completed 52 weeks of treatment. The Clinical Disease Activity Index (CDAI) remission rate at week 52 was 36.8%. Contributing factors for CDAI remission were younger age, early disease stage, and no comorbidities. Health Assessment Questionnaire Disability Index $\leq$0.5 was achieved in 65.1% of patients, and was significantly associated with disease duration. Discontinuation of concomitant methotrexate (MTX) and glucocorticoids (GCs) was possible in 19.3% and 34.1% of patients, respectively, without decreasing remission rate. The incidence (events/100 patient-years) of serious adverse events was 18.09, the most common being infection.

Conclusion: These data validate the importance of TCZ treatment in the early stages of RA in biologic-naive patients to achieve increased effectiveness. The safety profile of TCZ was reconfirmed. Furthermore, TCZ therapy may allow discontinuation of concomitant MTX and GCs without affecting remission.

Keywords

Biologics-naive; Rheumatoid arthritis; Intravenous; Tocilizumab

History

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Introduction

Phase III clinical studies of the recombinant humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody tocilizumab (TCZ) demonstrated improved disease activity and inhibition of joint destruction in patients with rheumatoid arthritis (RA) with or without concomitant use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) including methotrexate (MTX) [1–7]. TCZ has since received marketing approval as an antirheumatic agent in more than 100 countries, including Japan in 2008, the European Union in 2009, and the United States in 2010. Upon TCZ approval, its safety and effectiveness in the Japanese real-world clinical setting were evaluated in the all-patient postmarketing surveillance (PMS) program in patients with RA, with a 28-week follow-up period in 7901 patients (PMS7901) [8]. A subsequent 3-year follow-up PMS evaluated the long-term safety in 5573 patients [8,9]. A benefit-risk balance analysis of TCZ was performed with the 28-week PMS program to characterize which patients obtained the best clinical outcomes with TCZ [8]. The benefit-risk balance revealed that patients categorized as having a higher predicted probability of achieving American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) Boolean-based remission criteria and a lower predicted probability of developing a serious infection (SI) after receiving TCZ were more likely to be younger and biologics naive, with a shorter disease duration and an earlier Steinbrocker disease stage and functional class. These patients were also less likely to have comorbidities and concomitant use of glucocorticoids (GCs). These results suggested that early initiation of TCZ treatment in patients with

Correspondence to: Dr. Naoki Ishiguro, Department of Orthopedic Surgery, Nagoya University Graduate School & Faculty of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan. Tel: +81-52-741-2111. E-mail: n-ishi@med.nagoya-u.ac.jp

less advanced RA may result in the most beneficial outcomes for these patients.

In this study, we aimed to evaluate the effectiveness and safety of TCZ in biologics-naive patients with RA over a 52-week period in real-world clinical settings in Japan. In addition, we examined the possibility of decreasing or discontinuing concomitant MTX and GC dosage during treatment with TCZ.

Methods

Patients

Biologics-naive patients with RA who met the ACR/EULAR 2010 classification criteria for RA and had an inadequate response or were intolerant to one or more csDMARDs were enrolled [10]. Patients were enrolled in this study prospectively. In accordance with the Japan College of Rheumatology Guidelines for receiving TCZ, it was recommended that patients meet all the following criteria before starting TCZ treatment: $\geq$6 tender joints (68-joint count), $\geq$6 swollen joints (66-joint count), erythrocyte sedimentation rate (ESR) $\geq$ 28 mm/h or C-reactive protein (CRP) $\geq$ 2.0 mg/dl, white blood cell count $\geq$4000/mm^3, lymphocyte count $\geq$1000/mm^3, and serum β-D-glucan–negative. Before TCZ treatment was initiated, all patients were required to undergo screening for tuberculosis [11].

Protocol

The FIRST Bio study is a single-arm observational PMS study that began in January 2012. Patient registration, which occurred before starting TCZ treatment, was centrally controlled. Patients received TCZ 8 mg/kg intravenously once every 4 weeks. During the TCZ treatment period, there were no restrictions on the use of concomitant csDMARDs such as MTX or GCs. Data were collected using case report forms, and patients were evaluated for 52 weeks after TCZ was initiated or within 4 weeks of the last TCZ infusion. Effectiveness was assessed at weeks 0, 12, 24, 36, and 52. Disease activity was measured by the Clinical Disease Activity Index (CDAI) and by the Disease Activity Score based on 28-joint-ESR (DAS28-ESR) [12–14]. The rate of remission was assessed using CDAI (CDAI $\leq$2.8), DAS28-ESR (DAS28-ESR <2.6), and ACR/EULAR Boolean-based remission criteria [15]. Because it may be possible to underestimate disease activity using composite measures such as CRP that include acute phase reactants associated with IL-6 CDAI, which does not include the acute phase reaction as estimate factor, was mainly used to analyze the effectiveness of TCZ in improving RA signs and symptoms in this study. The activity of daily life, an aspect of quality of life, was evaluated by the Health Assessment Questionnaire Disability Index (HAQ-DI) [16,17]. The frequency of achieving HAQ-DI $\leq$0.5 was also assessed, which signifies normal physical function. Doses of concomitant MTX and GCs were measured at weeks 0, 12, 24, 36, and 52 [18]. All adverse events (AEs) that occurred during the 52 weeks after the first TCZ infusion were included in the safety analysis.

Statistical analysis

All AEs and serious AEs (SAEs) were coded using the *Medical Dictionary for Regulatory Activities* (MedDRA, vol. 16.1). The last-observation-carried-forward method and non-responder imputation method were utilized to analyze outcomes from baseline to week 52. Patients without either baseline or last observation point values of disease activities were excluded from each effectiveness analysis model. Paired *t*-tests were used to detect differences between the mean CDAI, DAS28-ESR, HAQ-DI, MTX dosage, and oral GC dosage from baseline to week 52. Chi-square tests were used to detect differences between groups of patients using frequency data. Cochran–Armitage tests were used to detect the difference between the patients in the respective disease duration subgroups. A Kaplan–Meier plot was used to display time to withdrawal in patients who received TCZ and who did not change their hospital during the study period. Patients were stratified by baseline characteristics, and clinical and functional outcomes were compared. Statistical analysis of patient background was nominally done to determine the effect of patient characteristics on the achievement of CDAI remission. A p value <0.05 was considered to be statistically significant.

Results

Patient demographics

In total, 298 sites participated in this study, and 850 patients were enrolled. Eleven patients were excluded from the safety analysis population due to no collection of case report forms (seven patients), and retroactive enrollment (four patients); 839 patients were included in the final analysis (Supplementary Figure 1). The cumulative exposure to TCZ was 718.4 patient-years (PY). Patient characteristics are described in Table 1. The median age (min–max) was 62.0 (15–90) years with a median (min–max) disease duration of 3.46 (0.0–54.4) years. A total of 319 patients (38.0%) had a history of $\geq$1 previous comorbidity, the most common being appendicitis in 23 patients (2.7%), uterine leiomyoma and interstitial lung disease, each with 18 patients (2.1%). A total of 483 patients (57.6%) had $\geq$1 current comorbidity, with the most common being hypertension in 154 patients (18.4%). A total of 680 patients (81.0%) and 506 patients (60.3%) were classified as Steinbrocker functional class 1 or 2 and Steinbrocker radiographic stages I and II, respectively. Concomitant csDMARDs and MTX were administered in 81.2% and 62.7% of patients, respectively.

Of the 805 patients who were treated with TCZ and did not change their hospital, 692 (86.0%) and 582 (72.3%) were still receiving TCZ at weeks 24 and 52, respectively (Supplementary Figure 2). Of the 223 patients who discontinued TCZ in the safety analysis population ($n = 839$), the primary reasons were onset of AEs in 74 patients (33.2%), insufficient effectiveness in 47 patients (21.1%), request from patients in 41 cases (18.4%), and 18 patients discontinued study visits (8.1%).

Effectiveness

There was a significant improvement in mean (SD) CDAI from baseline to week 52 (23.3 [11.8] versus 6.6 [7.5]; $p < 0.0001$) (Figure 1A). The proportion of patients who achieved CDAI remission (CDAI $\leq$2.8) was 36.8%; low disease activity (CDAI >2.8 to $\leq$10) was 43.0%; moderate disease activity (CDAI >10 to $\leq$22) was 14.8%; and high disease activity (CDAI >22) was 5.4% at week 52 (Figure 1B). Of the patients who achieved CDAI remission at week 24, 73.7% sustained this remission at week 52. When stratified by disease duration, there was a significant difference in the proportion of patients who achieved CDAI remission at week 24 across disease duration subgroups ($p < 0.0001$; Figure 1C): patients with disease duration <2 years (40.2%), $\geq$2 to <5 years (29.6%), $\geq$5 to <10 years (29.9%), and $\geq$10 years (20.5%). However, the rate of CDAI remission in patients with disease duration $\geq$10 years increased after 24 weeks, and there was no significant difference in the proportion of patients who achieved CDAI remission at week 52 across disease duration subgroups ($p = 0.0601$; Figure 1C): patients with disease duration <2 years (42.9%), $\geq$2 to <5 years (33.6%), $\geq$5 to <10 years (35.6%), and $\geq$10 years (33.5%). This trend was confirmed when assessed by non-responder imputation methods. There was a significant difference in CDAI remission rates at week

Table 1. Characteristics of patients with RA participating in the FIRST Bio study.

Characteristics	Patients receiving TCZ ($N = 839$)
Total PY	718.4
Female, *n* (%)	646 (77.0)
Age, years, mean (SD)	59.6 (13.5)
Median, range	62 (15–90)
≥ 65, *n* (%)	335 (39.9)
Body weight, kg, mean (SD)	54.4 (10.7)
Body weight <40 kg, *n* (%)	35 (4.2)
Disease duration, years, mean (SD)	7.5 (8.9)
Median, range	3.5 (0.0–54.4)
History of comorbidities, *n* (%)	319 (38.0)
Appendicitis	23 (2.7)
Uterine leiomyoma	18 (2.1)
Interstitial lung disease	18 (2.1)
Tuberculosis	16 (1.9)
Pneumonia	13 (1.5)
Gastric ulcer	13 (1.5)
Breast cancer	12 (1.4)
Comorbidities, *n* (%)	483 (57.6)
Hypertension	154 (18.4)
Osteoporosis	153 (18.2)
Hyperlipidemia	91 (10.8)
Diabetes mellitus	70 (8.3)
Interstitial lung disease	52 (6.2)
Gastritis	48 (5.7)
Gastroesophageal reflux disease	34 (4.1)
Anemia	27 (3.2)
Clinical characteristics	
Steinbrocker radiographic stage, *n* (%)	
I	216 (25.7)
II	290 (34.6)
III	184 (21.9)
IV	149 (17.8)
Steinbrocker functional class, *n* (%)	
1	156 (18.6)
2	524 (62.5)
3	145 (17.3)
4	14 (1.7)
RF +, (%)	64.5
Baseline DAS28-ESR, mean (SD)	5.2 (1.2)
Baseline CDAI, mean (SD)	23.3 (11.8)
Baseline HAQ-DI, mean (SD)	1.0 (0.8)
Baseline CRP, mg/dl, mean (SD)	2.4 (2.8)
Baseline ESR, mm/h, mean (SD)	46.2 (30.1)
Concomitant csDMARD use, *n* (%)[a]	681 (81.2)
Concomitant MTX, *n* (%)[a]	526 (62.7)
MTX dose, mg/week, mean (SD)	9.1 (3.9)
MTX dose, mg/week, min–max	2.0–64.0[b]
Concomitant oral corticosteroid use, *n* (%)[a]	440 (52.4)
Corticosteroid dose, mg/d, mean (SD)	5.4 (3.2)
Corticosteroid dose, mg/d, min–max	0.5–25.0

[a]Concomitant use at baseline.

[b]One patient received 64.0 mg/week of MTX for 1 week due to incorrect administration before starting TCZ treatment. After that, the patient received 4 mg/week of MTX.

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-ESR, Disease Activity Score based on 28-joint-erythrocyte sedimentation rate; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; MTX, methotrexate; PY, patient-years; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; TCZ, tocilizumab.

24 in patients with disease duration <2 years, ≥2 to <5 years, ≥5 to <10 years, and ≥10 years (37.5%, 28.0%, 28.8%, and 19.9%, respectively; $p = 0.0001$); however, a significant difference in the rates of CDAI remission was not observed at week 52 (36.7%, 25.6%, 31.4%, and 27.8%, respectively; $p = 0.0918$).

The rate of CDAI remission was significantly higher in patients who were younger and had an earlier Steinbrocker stage and better functional class, and a lower HAQ-DI score, with no concomitant use of GCs and non-steroidal anti-inflammatory drugs, and had no comorbidities such as respiratory disorders (Table 2). The CDAI remission rate at week 52 was not affected by the presence or absence of concomitant MTX, concomitant MTX dose, or the presence or absence of rheumatoid factor (Table 2).

DAS28-ESR (mean [SD]) also significantly improved from baseline to week 52 (5.2 [1.2] versus 2.1 [1.3]; $p < 0.0001$) (Figure 2A). The proportion of patients who achieved DAS28-ESR remission (DAS28-ESR <2.6) was 68.5%; low disease activity (DAS28 ≥ 2.6 to <3.2) was 14.0%; moderate disease activity (DAS28 ≥ 3.2 to ≤5.1) was 15.5%; and high disease activity (DAS28 > 5.1) was 2.0% (Figure 2B). The proportion of patients who achieved ACR/EULAR Boolean-based remission criteria was 33.1% at week 52 (Figure 2C). Of the patients who achieved DAS28-ESR or ACR/EULAR Boolean-based remission criteria at week 24, 90.0% and 74.6% sustained this remission at week 52, respectively.

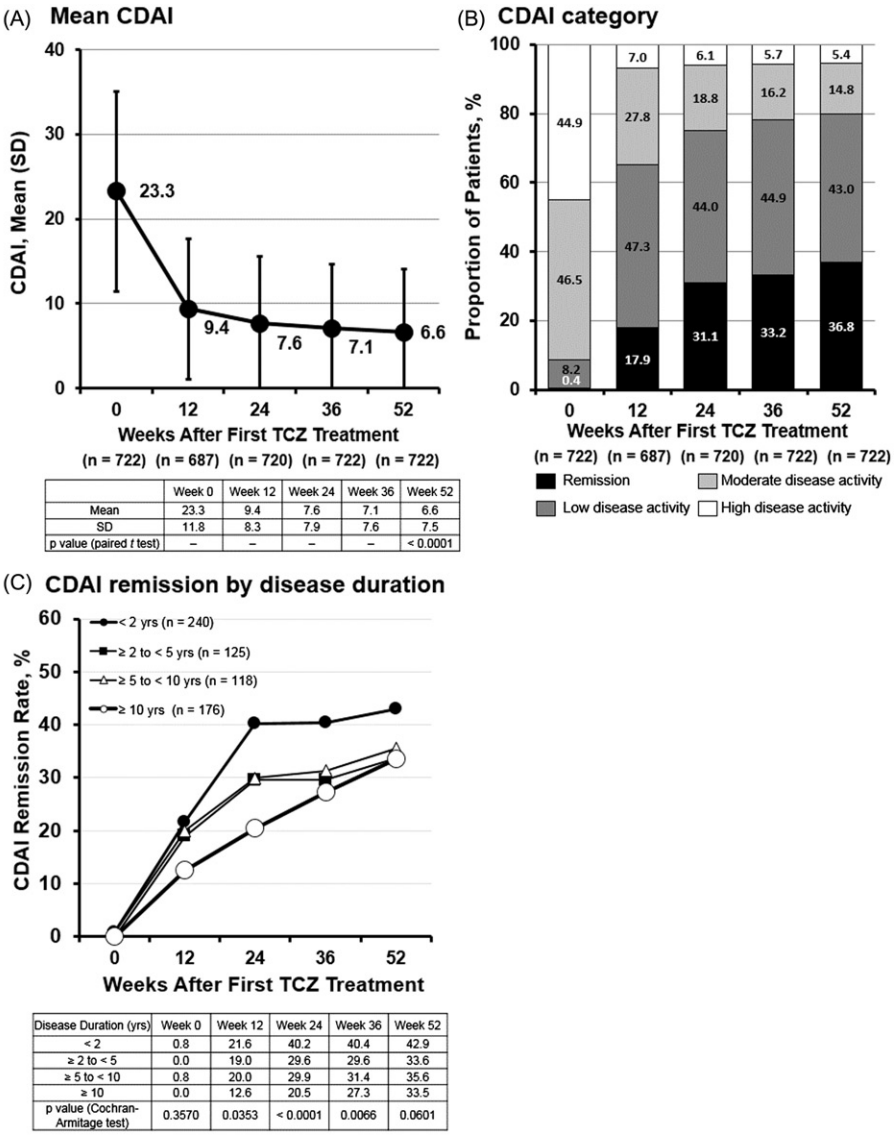
Quality of life, measured by HAQ-DI (mean [SD]), significantly improved from baseline to week 52 (1.0 [0.8] versus 0.5 [0.7]; $p < 0.0001$; Figure 3A), with 65.1% of patients demonstrating normal physical function (HAQ-DI score ≤0.5) at week 52 (Figure 3B). Of the patients who achieved an HAQ-DI score ≤0.5 at week 24, 95.6% sustained an HAQ-DI score ≤0.5 at week 52. When stratified by disease duration, there was a statistically significant difference in the proportion of patients whose HAQ-DI score was ≤0.5 across patients with disease duration <2 years, ≥2 to <5 years, ≥ 5 to <10 years, and ≥10 years from weeks 12 to 52, with a gradual increase in the difference during the 52 weeks of TCZ treatment, especially between the <2 year and ≥10 year disease duration groups (Figure 3C).

Concomitant drugs

Among patients receiving concomitant MTX, the mean dose of MTX decreased from 9.1 mg/week at baseline to 6.4 mg/week at week 52 ($p < 0.0001$; Figure 4A); 72 patients (19.3%) discontinued MTX. Oral GCs were administered in 440 patients (one patient with unknown dose) (52.4%) at baseline and the mean GC dose (prednisolone-equivalent) of these patients was reduced from 5.4 mg/d at baseline to 2.6 mg/d at week 52 ($p < 0.0001$; Figure 4B). GC administration was discontinued in 102 (34.1%) patients. CDAI (mean [SD]) in patients who discontinued concomitant MTX or GCs significantly improved from baseline to week 52 (24.8 [15.2] to 5.1 [5.4], $p < 0.0001$, and 22.1 [9.9] to 5.1 [4.9], $p < 0.0001$, respectively). The rate of CDAI remission did not decrease by week 52 in patients who discontinued MTX or GC administration (Supplementary Figure 3).

Safety

Overall, during the 52-week observation period there were 544 AEs in 308 patients (36.71%, 75.72 events/100 PY) and 130 SAEs in 101 patients (12.03%, 18.09 events/100 PY) (Table 3). The most common AEs and SAEs were infections (128 AEs in 103 patients [12.27%], 17.81 AEs/100 PY), with 42 SIs occurring in 38 patients (4.52%, 5.84 SAEs/100 PY). The incidence rate of SI was not significantly associated with age (4.16% in patients <65 years of age, and 5.07% in patients ≥65 years of age, [$p = 0.536$]). Pneumonia was the most frequent SI (seven events in seven patients [0.83%], 0.97 events/100 PY).



	Week 0	Week 12	Week 24	Week 36	Week 52
Mean	23.3	9.4	7.6	7.1	6.6
SD	11.8	8.3	7.9	7.6	7.5
p value (paired *t* test)	–	–	–	–	< 0.0001

Disease Duration (yrs)	Week 0	Week 12	Week 24	Week 36	Week 52
< 2	0.8	21.6	40.2	40.4	42.9
≥ 2 to < 5	0.0	19.0	29.6	29.6	33.6
≥ 5 to < 10	0.8	20.0	29.9	31.4	35.6
≥ 10	0.0	12.6	20.5	27.3	33.5
p value (Cochran-Armitage test)	0.3570	0.0353	< 0.0001	0.0066	0.0601

Figure 1. Effect of TCZ over time on (A) mean CDAI, (B) categorization of CDAI disease activity, and (C) achievement of CDAI remission (CDAI $\leq$2.8) by disease duration subgroups. CDAI, Clinical Disease Activity Index; TCZ, tocilizumab.

Six patients developed malignancies (0.71%, 0.83 events/100 PY). Six deaths were reported, due to interstitial lung disease in one patient, gastric cancer in one patient, hemorrhagic shock in one patient that occurred after a liver biopsy to investigate the cause of hepatic dysfunction during TCZ treatment, ruptured aortic aneurysm/sepsis in one patient, and with an unknown cause in two patients. Gastrointestinal perforations occurred in two patients (0.23%, 0.27 events/100 PY); of these, one patient had a history of intestinal inflammation. No cases of anaphylaxis were reported. Serious hepatobiliary disorders occurred in 10 patients (1.19%, 1.53 events/100 PY). Interstitial lung diseases occurred in nine patients (1.07%, 1.25 events/100 PY); of these, one patient had a concurrent medical history of interstitial lung disease at baseline. A serious cardiovascular disorder (angina pectoris) occurred in one patient (0.11%, 0.13 events/100 PY).

Discussion

This study demonstrated that TCZ treatment in the early stages of RA in biologics-naive patients achieves better effectiveness and control of RA. Moreover, it was shown that TCZ therapy may allow discontinuation of concomitant MTX and GCs without affecting remission.

The benefit-risk balance analysis of PMS7901 revealed that patients with a higher probability of remission and lower probability of developing SI were more likely to be biologics naive, have had RA for a shorter duration, and have less advanced disease stage and class [8]. Patients in the FIRST Bio study were biologics naive with shorter median disease duration than the population studied in PMS7901 (7.5 years versus 10.4 years, respectively) and had less advanced Steinbrocker functional class than those in PMS7901 (81.0% versus 73.8% of patients with class 1 or 2, respectively) [9]. Median age was similar in the FIRST Bio study and PMS7901 (62.0 and 60.0 years, respectively), and more than half (57.6%) of the patients had a comorbidity in the FIRST Bio study. Although the FIRST Bio study and PMS7901 were single-arm observational studies and not comparative studies due to differences in the patient population, observation period, and clinical experience, the ACR/EULAR Boolean-based remission rate at week 24 in the FIRST Bio study (27.7%) was higher than the result from PMS7901 at week 28 (15.1%). Moreover, the DAS28-ESR remission rate at week 24 in the FIRST Bio

Table 2. Effect of patient characteristics on the development of CDAI remission.[a]

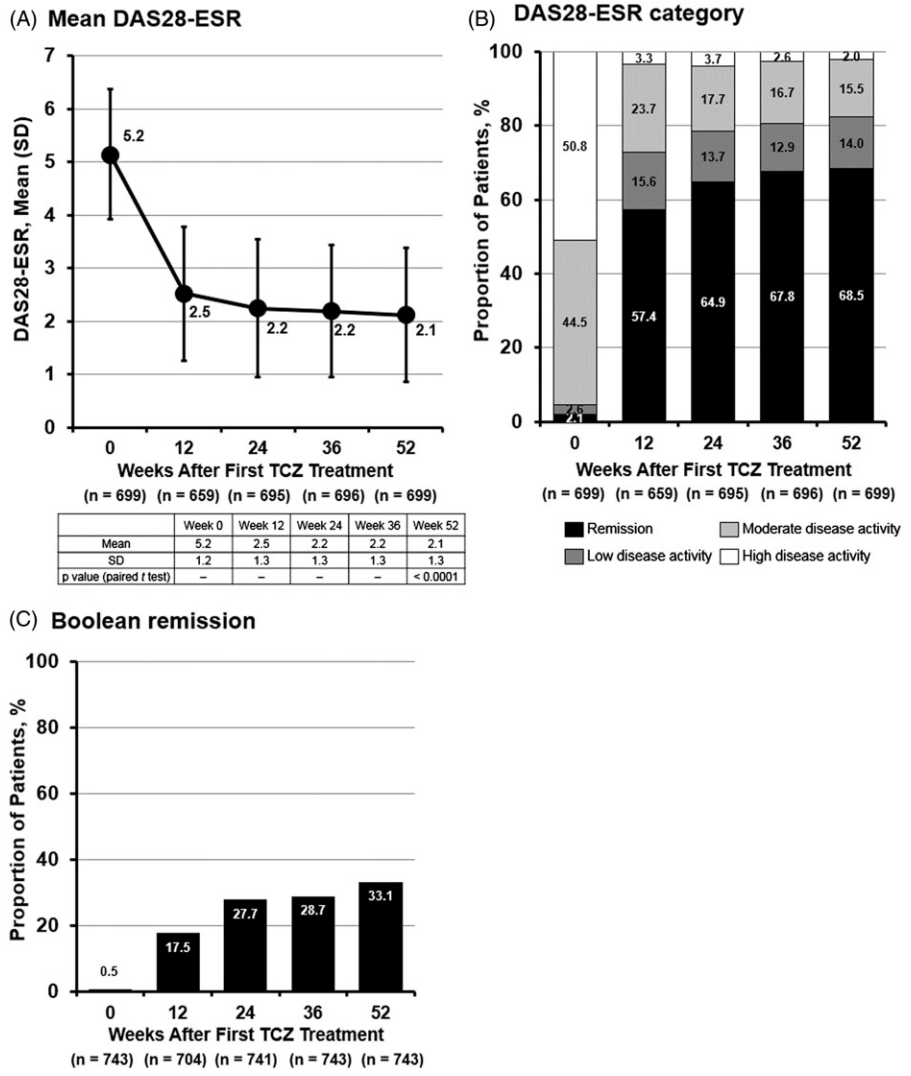
	Patients receiving TCZ ($N = 722$)	Patients in remission ($N = 266$)	Remission rate, % (36.8%)	p
Age, years				
<15	0	0	–	*
≥15 to <65	435	173	39.8	0.0446
≥65	287	93	32.4	
Steinbrocker radiographic stage				
I	180	84	46.7	***
II	254	100	39.4	0.0005
III	159	42	26.4	
IV	129	40	31.0	
Steinbrocker functional class				
1	138	66	47.8	***
2	450	169	37.6	0.0003
3	123	29	23.6	
4	11	2	18.2	
Baseline DAS28				
≤5.1	340	138	40.6	NS
>5.1	349	120	34.4	0.0925
Unknown	33	8	24.2	
Baseline HAQ-DI score				
≤1	326	127	39.0	*
>1 to ≤2	170	55	32.4	0.0184
>2 to ≤3	58	12	20.7	
Unknown	168	72	42.9	
Baseline RF				
Positive	483	176	36.4	NS
Negative	103	44	42.7	0.2321
Unknown	136	46	33.8	
Medication at baseline				
MTX, no	134	43	32.1	NS
MTX, yes	460	177	38.5	0.1777
Dose, mg/week				
>0 to <8	121	46	38.0	NS
≥8	339	131	38.6	0.9032
Glucocorticoids, no	346	145	41.9	**
Glucocorticoids, yes	376	121	32.2	0.0067
Dose, mg/d				
>0 to <2.5	43	14	32.6	NS
≥2.5 to <5.0	106	33	31.1	0.8077
≥5.0 to <7.5	137	49	35.8	
≥7.5 to <10.0	39	12	30.8	
≥10.0	49	13	26.5	
Unknown	2	0	0	
NSAIDS, no	395	160	40.5	*
NSAIDs, yes	327	106	32.4	0.0248
Comorbidity, no	313	147	47.0	***
Comorbidity, yes	409	119	29.1	<0.0001
Respiratory disease, no	641	246	38.4	*
Respiratory disease, yes	81	20	24.7	0.0161

NS: $p \geq 0.05$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

[a]The following patient characteristics were analyzed: sex, age (years), body weight (kg), disease duration (years), disease stage classified by Steinbrocker, function classified by Steinbrocker, baseline DAS28, baseline HAQ-DI score, baseline RF, medication history of conventional synthetic DMARDs, number of conventional synthetic DMARDs, concomitant use of MTX, dose of MTX (mg/week) at baseline, concomitant use of glucocorticoids, dose of glucocorticoids (mg/d) at baseline, concomitant use of NSAIDs, medical history of infection, comorbidity of respiratory disease, hepatic function disorder, renal disease, and diabetes mellitus. CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic disease-modifying antirheumatic drugs; DAS28, Disease Activity Score in 28 joints; HAQ-DI, Health Assessment Questionnaire Disability Index; MTX, methotrexate; NS, not significant; NSAID, non-steroidal anti-inflammatory drug; RF, rheumatoid factor; TCZ, tocilizumab.

study (64.9%) was numerically higher than in PMS7901 at week 28 (47.6%). A strength of the present study comes from the measurement of the CDAI remission rate (36.8% at 52 weeks), which was not reported in PMS7901. Stratification of the effectiveness results in this study by patient characteristics revealed that younger age, early disease stage and class, and low HAQ-DI score were associated with higher rates of CDAI remission, confirming the benefit-risk balance analysis of PMS7901, which showed that patients with a high probability of remission and low probability of developing SI were more likely to be biologics naive, younger, and have early and less advanced RA. Future studies with multivariate analysis are needed to verify these findings.

The effectiveness of TCZ was evaluated in groups of patients stratified by disease duration. In patients with disease duration ≥10 years, the CDAI remission rate continuously improved after week 24, and by 52 weeks, there was no statistically significant difference between the proportion of patients achieving CDAI



	Week 0	Week 12	Week 24	Week 36	Week 52
Mean	5.2	2.5	2.2	2.2	2.1
SD	1.2	1.3	1.3	1.3	1.3
p value (paired *t* test)	–	–	–	–	< 0.0001

Figure 2. Effect of TCZ over time on (A) mean DAS28-ESR, (B) categorization of DAS28-ESR disease activity, and (C) ACR/EULAR Boolean-based remission rate. DAS28-ESR, Disease Activity Score based on 28-joint-erythrocyte sedimentation rate; TCZ, tocilizumab.

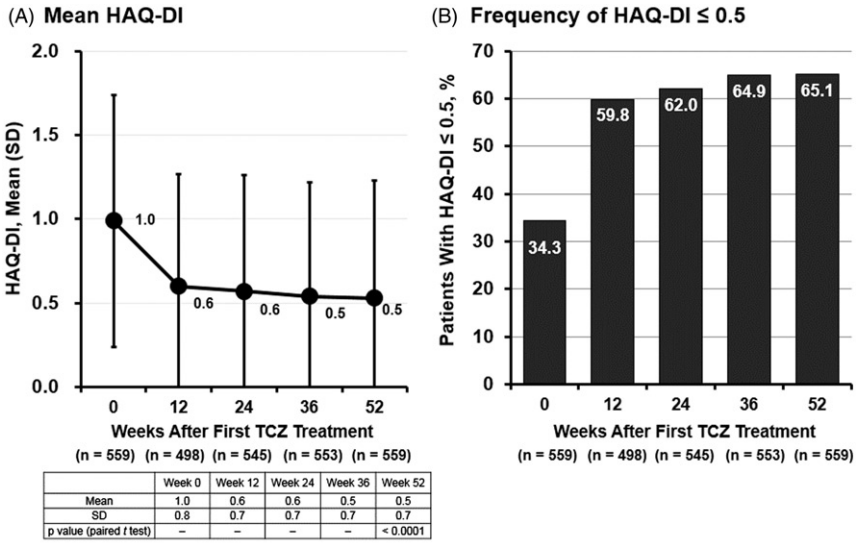
remission in the ≥10-year and <2-year disease duration groups. However, the proportion of patients with HAQ-DI score ≤0.5 at both weeks 24 and 52 was significantly higher among patients with disease duration <2 years than those with disease duration ≥10 years. These data further suggest that aggressive therapy with TCZ for patients with RA in the early stage of disease development is more beneficial than at later stages. Notably, these results imply that the signs and symptoms of RA in patients with established RA may be well controlled by long-term TCZ treatment.

The presence of RF was not associated with CDAI remission rates during TCZ treatment, and a similar result was reported in a previous study with TCZ [19]. Conflicting data exist for TNF inhibitor therapy, with some studies suggesting that the status of RF is associated with a clinical response and some studies reporting no such correlation [20–26]. In the case of abatacept, efficacy was reported to be lower in patients who were RF negative than those who were RF positive [27]. The results of this study suggest that RF status is not a factor that affects the ability of TCZ to improve disease activity.

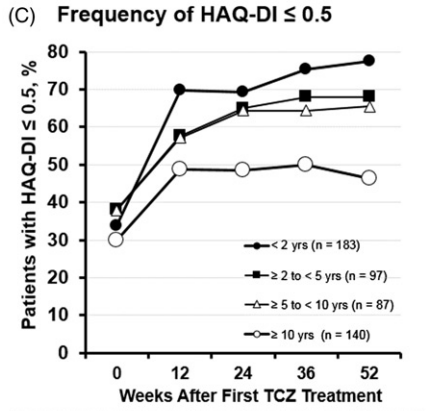
In this study, the concomitant medication of MTX during TCZ treatment did not affect remission rates. In contrast, other biologics with different mechanisms of action are reported to be more effective in treating RA when administered with concomitant MTX [19,28–34]. Further studies are needed to determine the mechanisms that account for this difference.

Interestingly, concomitant MTX and GC doses were significantly reduced during TCZ treatment without disease flare in this study. The risk of MTX-associated lymphoproliferative disorders (MTX-LPD) has been reported during long-term usage of MTX, which is widely used for the treatment of RA [35]. Thus, if MTX can be tapered or discontinued after improving disease activity with TCZ treatment, patients may have the benefit of reduced risk of MTX-LPD. In the case of TNF inhibitor therapy, literature reporting that concomitant MTX could be reduced without impacting disease activity is limited [36–38]. Long-term use of GCs is well known to be associated with various adverse drug reactions, and the guidelines recommend tapering GC dose after improvement of disease activity [39–41]. Prospective studies are necessary to evaluate safe and effective methods for discontinuing MTX and/or GCs in patients with RA receiving TCZ.

The incidence rates of total AEs and SAEs were numerically lower in the FIRST Bio study than PMS7901 (75.72 events/100 PY versus 168.59 events/100 PY for AEs, and 18.09 events/100 PY versus 27.40 events/100 PY for SAEs, respectively) [8]. Further, the incidence rates of total and SIs were numerically

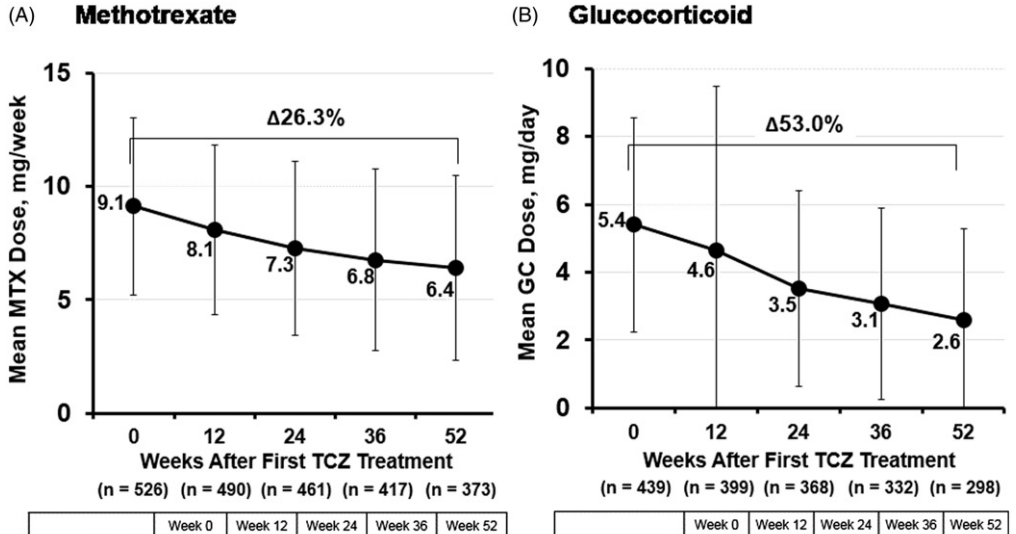


	Week 0	Week 12	Week 24	Week 36	Week 52
Mean	1.0	0.6	0.6	0.5	0.5
SD	0.8	0.7	0.7	0.7	0.7
p value (paired *t* test)	–	–	–	–	< 0.0001



Disease Duration (yrs)	Week 0	Week 12	Week 24	Week 36	Week 52
< 2	33.9	69.7	69.4	75.4	77.6
≥ 2 to < 5	38.1	57.6	64.9	68.0	68.0
≥ 5 to < 10	37.9	57.1	64.4	64.4	65.5
≥ 10	30.0	48.8	48.5	50.0	46.4
p value (Cochran-Armitage test)	0.5426	0.0004	0.0003	< 0.0001	< 0.0001

Figure 3. Effect of TCZ over time on (A) mean HAQ-DI, (B) achievement of HAQ-DI ≤0.5, and (C) achievement of HAQ-DI ≤0.5 by disease duration subgroups. DAS28-ESR, Disease Activity Score based on 28-joint-erythrocyte sedimentation rate; TCZ, tocilizumab.



	Week 0	Week 12	Week 24	Week 36	Week 52
Mean	9.1	8.1	7.3	6.8	6.4
SD	3.9	3.8	3.8	4.0	4.1
p value (paired *t* test)	–	–	–	–	< 0.0001

	Week 0	Week 12	Week 24	Week 36	Week 52
Mean	5.4	4.6	3.5	3.1	2.6
SD	3.2	4.9	2.9	2.8	2.7
p value (paired *t* test)	–	–	–	–	< 0.0001

Figure 4. Change in concomitant (A) MTX and (B) GC (oral) dose during TCZ treatment. GC, glucocorticoid; MTX, methotrexate; TCZ, tocilizumab.

Table 3. AEs of interest and death.

	Serious AEs			Total AEs		
	No. of patients	Incidence rate (%)	Events/100 PY	No. of patients	Incidence rate (%)	Events/100 PY
Total AEs	101	12.03	18.09	308	36.71	75.72
Infections	38	4.52	5.84	103	12.27	17.81
Pneumonia	7	0.83	0.97	12	1.43	1.67
Pulmonary tuberculosis	0	0	0	0	0	0
Non-tuberculous mycobacteriosis	2	0.23	0.27	2	0.23	0.27
Pneumocystis pneumonia	0	0	0	0	0	0
Urinary tract infection	0	0	0	1	0.11	0.13
Gastric intestinal infection	0	0	0	7	0.83	0.97
Cellulitis	4	0.47	0.55	5	0.59	0.83
Herpes zoster	3	0.35	0.41	12	1.43	1.67
Cardiac dysfunction	1	0.11	0.13	2	0.23	0.27
Gastric intestinal perforation	2	0.23	0.27	2	0.23	0.27
Malignancies[a]	6	0.71	0.83	6	0.71	0.83
Anaphylaxis	0	0	0	0	0	0
Lipid-related test abnormality	0	0	0	2	0.23	0.27
Interstitial lung disease	9	1.07	1.25	9	1.07	1.25
Hepatobiliary disorders	10	1.19	1.53	55	6.55	8.07
Death	–	–	–	6	0.71	0.83

[a]One case of each of the following neoplasias were reported: gastric cancer, Hodgkin disease, esophageal carcinoma, lung neoplasm malignant, brain neoplasm, and penile neoplasm.
AE, adverse event; PY, patient-years.

lower in FIRST Bio study than PMS7901 (17.81 events/100 PY versus 27.87 events/100 PY in AEs, and 5.84 events/100 PY versus 8.61 events/100 PY in SAEs, respectively) [8]. In addition, the incidence rate of SIs in this study was similar to the rate in the long-term clinical studies of TCZ in Japan (5.84 events/100 PY versus 6.22 events/100 PY, respectively), which were also carried out in a high number of biologic-naive patients [42]; therefore, the FIRST Bio study validates the safety profile of TCZ in biologics-naive patients. Importantly, no new safety signals were identified in the present study.

In conclusion, these results highlight the importance of TCZ treatment in the early stages of RA in biologics-naive patients in achieving better control of signs and symptoms as well as safety. Furthermore, tapering of MTX or GC dose during concomitant therapy with TCZ was possible with the maintenance of remission in patients with RA.

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Conflict of interest

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