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ORIGINAL ARTICLE

Phase III Study of the Efficacy and Safety of Subcutaneous Versus Intravenous Tocilizumab Monotherapy in Patients With Rheumatoid Arthritis

ATSUSHI OGATA,[1] KAZUHIDE TANIMURA,[2] TOYOHIKO SUGIMOTO,[3] HIROSHI INOUE,[4] YUKITOMO URATA,[5] TSUKASA MATSUBARA,[6] MASAKAZU KONDO,[7] YUKITAKA UEKI,[8] MITSUHIRO IWAHASHI,[9] SHIGETO TOHMA,[10] SHUJI OHTA,[11] YUKIHIKO SAEKI,[12] TOSHIO TANAKA,[1] AND THE MUSASHI STUDY INVESTIGATORS

Objective. **To evaluate the efficacious noninferiority of subcutaneous tocilizumab injection (TCZ-SC) monotherapy to intravenous TCZ infusion (TCZ-IV) monotherapy in Japanese patients with rheumatoid arthritis (RA) with an inadequate response to synthetic and/or biologic disease-modifying antirheumatic drugs (DMARDs).**

Methods. **This study had a double-blind, parallel-group, double-dummy, comparative phase III design. Patients were randomized to receive TCZ-SC 162 mg every 2 weeks or TCZ-IV 8 mg/kg every 4 weeks; no DMARDs were allowed during the study. The primary end point was to evaluate the noninferiority of TCZ-SC to TCZ-IV regarding the American College of Rheumatology criteria for 20% improvement in disease activity (ACR20) response rates at week 24 using an 18% noninferiority margin. Additional efficacy, safety, pharmacokinetic, and immunogenicity parameters were assessed.**

Results. **At week 24, ACR20 response was achieved in 79.2% (95% confidence interval [95% CI] 72.9, 85.5) of the TCZ-SC group and in 88.5% (95% CI 83.4, 93.5) of the TCZ-IV group; the weighted difference was −9.4% (95% CI −17.6, −1.2), confirming the noninferiority of TCZ-SC to TCZ-IV. Remission rates of the Disease Activity Score in 28 joints using the erythrocyte sedimentation rate and the Clinical Disease Activity Index at week 24 were 49.7% and 16.4% in the TCZ-SC group and 62.2% and 23.1% in the TCZ-IV group, respectively. Serum trough TCZ concentrations were similar between the groups over time. Incidences of all adverse events and serious adverse events were 89.0% and 7.5% in the TCZ-SC group and 90.8% and 5.8% in the TCZ-IV group, respectively. Anti-TCZ antibodies were detected in 3.5% of the TCZ-SC group; no serious hypersensitivity was reported in these patients.**

Conclusion. **TCZ-SC monotherapy demonstrated comparable efficacy and safety to TCZ-IV monotherapy. TCZ-SC could provide additional treatment options for patients with RA.**

INTRODUCTION

Tocilizumab (TCZ) is a humanized monoclonal antibody directed against the interleukin-6 (IL-6) receptor that is approved for the treatment of patients with rheumatoid arthritis (RA), polyarticular-course and systemic juvenile idiopathic arthritis, and Castleman's disease by intravenous (IV) administration. Multiple phase III trials of TCZ, in combination with synthetic disease-modifying antirheumatic drugs (DMARDs) or as monotherapy, demonstrated an improvement of clinical symptoms and prevention of joint destruction (1–7).

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[1]Atsushi Ogata, MD, PhD, Toshio Tanaka, MD, PhD: Osaka University, Osaka, Japan; [2]Kazuhide Tanimura, MD: Hokkaido Medical Center for Rheumatic Diseases, Hokkaido, Japan; [3]Toyohiko Sugimoto, MD: National Hospital Organization, Shimoshizu Hospital, Chiba, Japan; [4]Hiroshi Inoue, MD: Inoue Hospital, Gunma, Japan; [5]Yukitomo Urata, MD: Seihoku Central Hospital, United Municipalities of Tsugaru, Aomori, Japan; [6]Tsukasa Matsubara, MD: Matsubara Mayflower Hospital, Hyogo, Japan; [7]Masakazu Kondo, MD: Kondo Clinic of Rheumatology and Orthopedic Surgery, Fukuoka, Japan; [8]Yukitaka Ueki, MD: Sasebo Chuo Hospital, Nagasaki, Japan; [9]Mitsuhiro Iwahashi, MD:

Significance & Innovations

- A subcutaneous formulation of tocilizumab (TCZ) would greatly contribute to improving the quality of life in patients with rheumatoid arthritis (RA) because it would allow for a shorter administration time compared with an intravenous formulation and for home administration.
- Subcutaneous TCZ monotherapy demonstrated comparable efficacy and safety to intravenous TCZ monotherapy in patients with RA who have had an inadequate response to synthetic and/or biologic disease-modifying antirheumatic drugs.

Previously, patients with RA who did not respond to treatment, such as the 19th century French impressionist painter Pierre-Auguste Renoir, had limited alternatives available (8). Many treatment choices are now available that have proven clinical efficacy, including anti–tumor necrosis factor (anti-TNF) agents and TCZ. Most anti-TNF agents require concomitant methotrexate (MTX) for maximum efficacy, whereas TCZ has similar efficacy with and without MTX (9).

To optimize a patient's treatment, the efficacy, safety, and route of administration for each therapy should be considered along with a patient's disease status in order to achieve clinical, functional, and structural remission or the lowest disease activity state possible (10,11). Some patients prefer therapies with a biologic agent that can be administered by subcutaneous (SC) injection rather than IV formulations, and prefer to receive treatments at home (12–14). An SC formulation of TCZ (TCZ-SC) would provide an additional treatment option for patients with RA.

The efficacy and pharmacokinetics of TCZ-SC monotherapy were evaluated in an open-label, phase I/II study conducted in Japan at 3 doses (81 mg every 2 weeks, 162 mg every 2 weeks, and 162 mg weekly) over 6 months (15). To further expand on these results, the noninferiority, multicenter phase II study MUSASHI (Multi-Center Double-Blind Study of Tocilizumab Subcutaneous Injection in Patients Having Rheumatoid Arthritis to Verify Noninferiority Against Intravenous Infusion) was conducted to compare the efficacy and safety of TCZ-SC monotherapy 162 mg every 2 weeks and TCZ-IV monotherapy 8 mg/kg every 4 weeks in Japanese patients with RA with an inadequate response to synthetic and/or biologic DMARDs.

Higashihiroshima Memorial Hospital, Hiroshima, Japan; [10]Shigeto Tohma, MD: National Hospital Organization, Sagamihara Hospital, Kanagawa, Japan; [11]Shuji Ohta, MD: Taga General Hospital, Ibaraki, Japan; [12]Yukihiko Saeki, MD: National Hospital Organization, Osaka Minami Medical Center, Osaka, Japan.

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Address correspondence to Atsushi Ogata, MD, PhD, Department of Respiratory Medicine, Allergy and Rheumatic Disease, Osaka University Graduate School of Medicine, 2-2, Yamadaoka, Suita, Osaka 565-0871, Japan. E-mail: ogata@imed3.med.osaka-u.ac.jp.

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PATIENTS AND METHODS

Patient population. Eligible patients were ages 20–75 years and had RA for ≥6 months, as diagnosed using the 1987 criteria of the American College of Rheumatology (ACR) for the classification of RA (16). Additional inclusion criteria were as follows: an inadequate response of ≥12 weeks to any synthetic DMARD (MTX, sulfasalazine, bucillamine, and leflunomide), biologic DMARD (infliximab, etanercept, and adalimumab), or immunosuppressant (e.g., tacrolimus); ≥8 tender joints (of 68 joints); ≥6 swollen joints (of 66 joints); and an erythrocyte sedimentation rate (ESR) ≥30 mm/hour or a C-reactive protein level ≥1.0 mg/dl.

Exclusion criteria included active tuberculosis, a history of serious allergies, and active hepatitis B or C. All candidates underwent tuberculin reaction or QuantiFERON testing. Patients testing positive for latent tuberculosis were enrolled if treatment with isoniazid was initiated 3 weeks prior to initial administration of TCZ and continued for 9 months. Patients with class IV Steinbrocker functional activity were excluded. Patients were also excluded if they had received previous treatment with TCZ; had received plasmapheresis, surgical procedures (except with locally and low invasive operations), or dose changes or added-in DMARDs or immunosuppressants within 4 weeks of TCZ treatment; had received oral glucocorticoids at a dosage of >10 mg/day of prednisolone or equivalent; or had a dose increase, new administration, or IV or intramuscular injections of glucocorticoids within 2 weeks of TCZ treatment.

Study design. MUSASHI was a 24-week, phase III, randomized, double-blind, double-dummy study in Japanese

patients with RA. The study protocol was approved by the Ministry of Health, Labour and Welfare of Japan and by the local ethical committees. All patients gave their written informed consent.

Patients were randomized 1:1 into 2 groups: 162 mg of TCZ-SC monotherapy every 2 weeks plus placebo TCZ-IV every 4 weeks or 8 mg/kg of TCZ-IV monotherapy every 4 weeks plus placebo TCZ-SC every 2 weeks. Throughout the study, DMARDs or immunosuppressants were not permitted. There was no washout period for synthetic DMARDs as long as treatment and dose were stable a minimum of 4 weeks prior to initial TCZ treatment. Concomitant use of low-dosage oral glucocorticoids (≤10 mg/day of prednisolone or equivalent without escalation from the baseline dosage) and 1 oral nonsteroidal antiinflammatory drug was permitted during the 24 weeks. Intraarticular injections of corticosteroids and hyaluronate preparations were avoided as much as possible.

Efficacy assessments. Efficacy assessments were conducted every 4 weeks. The primary end point was to demonstrate the noninferiority of TCZ-SC monotherapy to TCZ-IV monotherapy regarding the proportion of patients with 20% improvement in disease activity for ACR criteria (ACR20) responses at week 24 (17). Additional end points included ACR50 and ACR70 response rates, ACR/European League Against Rheumatism Boolean Index remission rates, Clinical Disease Activity Index (CDAI) remission rates, Disease Activity Score in 28 joints using the ESR (DAS28-ESR) remission rates, and a low disease activity rate at week 24. Mean changes in DAS28-ESR, CDAI score, and the proportion of patients who improved in the Japanese version of the Health Assessment Questionnaire (HAQ) by ≥0.3 units from baseline were assessed over time (18). For efficacy assessments, the per-protocol set (PPS) was used, excluding patients with protocol violations, early withdrawal, violations concerning concomitant medication use, or violations concerning the dose and administration. The last observation carried forward was used for any missing values. For patients receiving glucocorticoids or hyaluronic acid via intraarticular administration, any treated joints were treated as positive tender and swollen joints for that defined period.

Pharmacokinetics. Samples for pharmacokinetic analysis were collected at weeks 0, 2, 4, 8, 12, 16, 20, and 24. TCZ, which is not bound with the IL-6 receptor (free TCZ) in the serum, was determined by enzyme-linked immunosorbent assay (19). The lower limit of detection for free TCZ in serum was 0.1 μg/ml.

Safety and immunogenicity assessments. Safety and immunogenicity data were analyzed using the safety population, defined as all patients who received at least 1 dose of TCZ. Adverse events (AEs) and serious AEs were classified using the Medical Dictionary for Regulatory Activities, version 13.0. The number of patients with AEs and the total number of AEs were tabulated. Infusion and/or injection reactions were prespecified and classified as SC injection site reactions (ISRs; AEs at the site of SC injection), systemic reactions to SC injection (SIRs; AEs not at the site of SC injection within 24 hours of treatment), or IV infusion–related reactions (IRRs; AEs occurring within 24 hours of treatment). All AEs were graded as severe, moderate, or mild by physicians. Laboratory investigations were graded by Common Terminology Criteria for Adverse Events.

Blood samples for the anti-TCZ antibody screening assay were collected every 4 weeks. The anti-TCZ antibody screening assay was performed as previously described using a bridging enzyme-linked immunosorbent assay with an additional competitive displacement step as the confirmation assay (20).

Statistical analysis. The primary end point was analyzed using the PPS for the primary analysis and the modified intent-to-treat (ITT) population for the sensitivity analysis. The modified ITT population included all patients who received at least 1 dose of treatment. The noninferiority margin was set at 18%, as determined using the difference between the ACR20 results of SATORI (Study of Active Controlled Tocilizumab Monotherapy for Rheumatoid Arthritis Patients with an Inadequate Response to Methotrexate) (7); 18% was the more conservative criterion because it was less than one-third of the difference of the ACR20 response rate between the TCZ-IV monotherapy group and the control group in the SATORI study. Furthermore, it is less than half of the lower limit of the 95% confidence interval (95% CI) for the difference between the groups. The adjusted 95% CI for the difference between the ACR20 response rate in the TCZ-SC monotherapy and TCZ-IV monotherapy groups was calculated using the Mantel-Haenszel method, with patients stratified according to weight at enrollment (<60 or ≥60 kg) and previous use of anti-TNF agents. Noninferiority was demonstrated if the lower limit was not below the confidence limit for noninferiority (−18%). A sample size of 330 was calculated to provide 90% power to demonstrate the noninferiority of TCZ-SC monotherapy to TCZ-IV monotherapy. To determine the sample size, the ACR20 response rate was set to 70% because of the following assumptions: the ACR20 response rate at 24 weeks was 79.7% in the SATORI trial and the overall response rate potentially could be lower in the MUSASHI trial than in the SATORI trial because the patient population of inadequate anti-TNF responders was larger.

Simple logistic analysis was used to screen for potential predictive variables, including sex, age, weight (in kg, the fourth quartile versus the first to third quartiles), body mass index (BMI; in kg/m^2, the fourth quartile versus the first to third quartiles), disease duration, Steinbrocker class/stage, history of anti-TNF agents, rheumatoid factor, anti–cyclic citrullinated peptide antibody, glucocorticoid dose, number of previous DMARDs, DAS28-ESR, ACR core components, and IL-6 levels at baseline. Multiple logistic regression was used to identify the contributing baseline parameters to ACR20, ACR50, and ACR70 response rates in the TCZ-SC monotherapy group at week 24. The initial model contained the potential predictive variables and the predicting factor ($P \leq 0.05$) was identified in the final model by using a stepwise procedure.

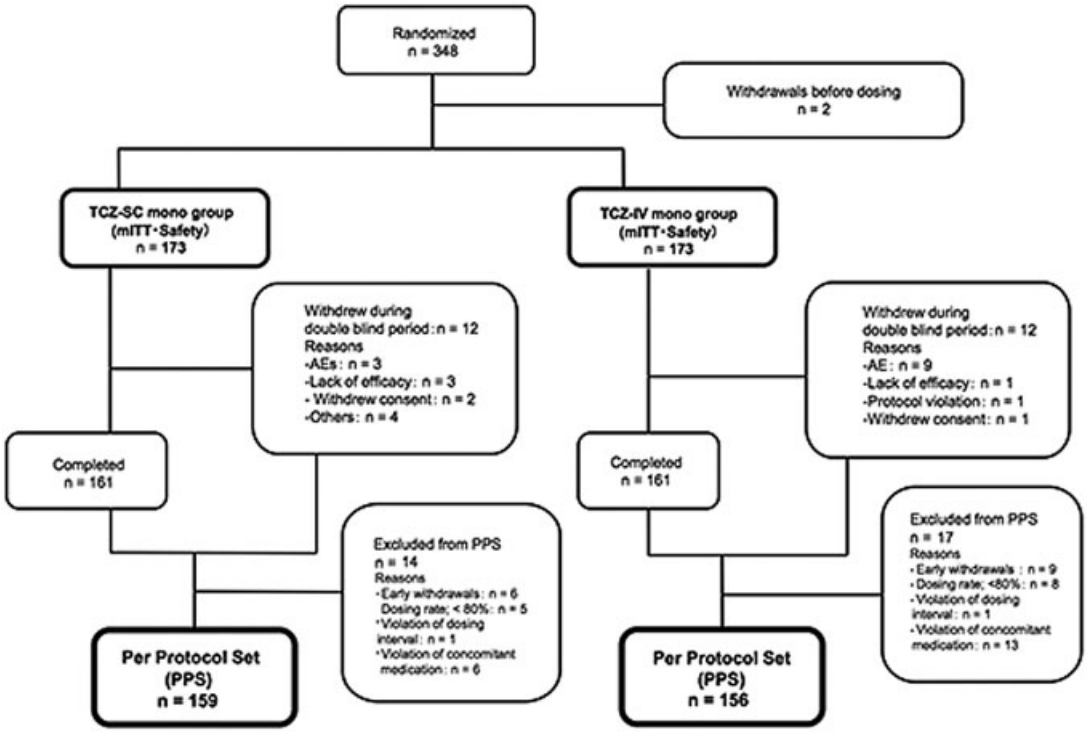


Figure 1. Patient disposition over 24 weeks (in the per-protocol set [PPS]). Two patients withdrew before treatment with tocilizumab (TCZ) was initiated. In the group receiving a subcutaneous injection of TCZ monotherapy (TCZ-SC mono), 3 patients withdrew because of adverse events (AEs), 3 patients withdrew because of a lack of efficacy, 2 patients withdrew consent, and 4 patients withdrew because of other reasons. In the group receiving an intravenous infusion of TCZ monotherapy (TCZ-IV mono), 9 patients withdrew because of AEs, 1 patient withdrew because of a lack of efficacy, 1 patient withdrew consent, and 1 patient withdrew because of a protocol violation. mITT = modified intent-to treat.

RESULTS

Patient disposition. A total of 348 patients were randomized (Figure 1). Two patients withdrew before treatment with TCZ and 346 patients were randomized into 2 groups; 173 patients in each group received the study drugs. Of these 173 patients, 161 (93.1%) completed the double-blind period in each group (Figure 1). In the PPS, 159 patients in the TCZ-SC monotherapy group and 156 patients in the TCZ-IV monotherapy group were eligible for analysis. The major reasons for patient exclusion from the PPS were receipt of <80% of the total dose, early withdrawal, and violations concerning concomitant medication use.

Baseline demographics and clinical characteristics. Patient demographics and clinical characteristics were similar between the TCZ-SC monotherapy and TCZ-IV monotherapy groups (Table 1). The patient population weighing ≥60 kg consisted of 23.3% in the TCZ-SC monotherapy group and 25.6% in the TCZ-IV monotherapy group. The percentages of patients who previously received anti-TNF agents were 18.9% in the TCZ-SC monotherapy group and 23.7% in the TCZ-IV monotherapy group (Table 1).

Clinical efficacy. The study met its primary end point of demonstrating the noninferiority of TCZ-SC monotherapy to TCZ-IV monotherapy. In the PPS, the ACR20 response rate at week 24 was achieved in 79.2% (95% CI 72.9, 85.5) of the TCZ-SC monotherapy patients and in 88.5% (95% CI 83.4, 93.5) of the TCZ-IV monotherapy patients (Figure 2A). The weighted difference between the groups was −9.4% (95% CI −17.6, −1.2), confirming the noninferiority of TCZ-SC monotherapy to TCZ-IV monotherapy. In the modified ITT population, the ACR20 response at week 24 was achieved in 79.2% (95% CI 73.1, 85.2) of the TCZ-SC monotherapy patients and in 86.0% (95% CI 80.9, 91.2) of the TCZ-IV monotherapy patients. The weighted difference between the groups was −7.0% (95% CI −15.0, 1.0), confirming the noninferiority of TCZ-SC monotherapy to TCZ-IV monotherapy in the sensitivity analysis. Another sensitivity analysis was conducted that was stratified according to disease duration and previous use of an anti-TNF agent. The weighted difference was −9.4% (95% CI −17.7, −1.1) and was consistent with the results of the PPS and modified ITT populations. ACR50 and ACR70 response rates at week 24 were also similar between the groups (Figure 2A).

The DAS28-ESR, CDAI, and Boolean Index remission rates at week 24 were 49.7%, 16.4%, and 15.7%, respectively, in the TCZ-SC monotherapy group. Conversely, the DAS28-ESR, CDAI, and Boolean Index remission rates at week 24 were 62.2%, 23.1%, and 16.0%, respectively, in the TCZ-IV monotherapy group (Figure 2B). A higher proportion of patients in the TCZ-IV monotherapy group (82.1% [95% CI 76.0, 88.1]) than in the TCZ-SC mono-

Table 1. Patient characteristics at baseline (per-protocol set)*

	TCZ-SC monotherapy (n = 159)	TCZ-IV monotherapy (n = 156)
Women, no. (%)	133 (83.6)	128 (82.1)
Age, years†	52.1 ± 12.6	51.8 ± 11.8
Body weight, median (min, max) kg†	53.0 (36.3, 83.3)	53.1 (37.5, 96.3)
Body weight, kg†	53.8 ± 8.7	54.4 ± 10.1
<60 kg, no. (%)	122 (76.7)	116 (74.4)
≥60 kg, no. (%)	37 (23.3)	40 (25.6)
Disease duration, years	7.3 ± 7.5	8.0 ± 7.3
Disease duration, median years	5.1	5.9
Steinbrocker functional class, no. (%)†		
I	25 (15.7)	20 (12.8)
II	112 (70.4)	118 (75.6)
III	22 (13.8)	18 (11.5)
Steinbrocker stage, no. (%)†		
I	20 (12.6)	8 (5.1)
II	53 (33.3)	60 (38.5)
III	47 (29.6)	42 (26.9)
IV	39 (24.5)	46 (29.5)
RF positive, no. (%)	126 (79.2)	131 (84.0)
ACPA antibodies, no. (%)	142 (89.3)	142 (91.0)
IL-6, pg/ml	39.1 ± 46.1	32.2 ± 42.8
SJC (in 66 joints)	14.3 ± 6.7	13.5 ± 6.8
TJC (in 68 joints)	18.1 ± 8.8	17.6 ± 9.4
Japanese HAQ score	1.18 ± 0.64	1.25 ± 0.65
Patient's pain assessment, mm	52.6 ± 23.1	58.4 ± 22.5
Patient's global assessment, mm	53.6 ± 24.9	59.7 ± 22.9
Physician's global assessment, mm	62.4 ± 20.0	61.3 ± 19.0
CRP, mg/dl	2.2 ± 2.3	2.1 ± 2.0
ESR, mm/hour	47.9 ± 24.4	48.8 ± 22.5
DAS28-ESR	6.1 ± 0.9	6.2 ± 0.9
CDAI score	34.2 ± 10.3	33.7 ± 10.8
Oral glucocorticoids administered, no. (%)	110 (69.2)	92 (59.0)
Dosage, mg/day‡	4.6 ± 2.3	4.7 ± 2.1
Previous MTX, no. (%)§	128 (80.5)	129 (82.7)
Dosage, mg/week§	8.2 ± 2.2	8.2 ± 2.3
Previous anti-TNF agents, no. (%)	30 (18.9)	37 (23.7)

* Values are the mean ± SD unless indicated otherwise. TCZ-SC = subcutaneous tocilizumab; TCZ-IV = intravenous tocilizumab; RF = rheumatoid factor; ACPA = anti–citrullinated protein antibody; IL-6 = interleukin-6; SJC = swollen joint count; TJC = tender joint count; HAQ = Health Assessment Questionnaire; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; DAS28-ESR = Disease Activity Score in 28 joints using the ESR; CDAI = Clinical Disease Activity Index; MTX = methotrexate; anti-TNF = anti–tumor necrosis factor.
† At randomization.
‡ Dosage is prednisolone or equivalent.
§ Patients who previously received MTX were analyzed within 4 weeks of initial TCZ treatment.

therapy group (65.4% [95% CI 58.0, 72.8]) achieved DAS28-ESR low disease activity at week 24. The mean change in DAS28-ESR and CDAI score decreased similarly over 24 weeks in both groups (Figures 2C and D). The proportions of patients who improved in physical function by ≥0.3 units (per the HAQ) from baseline between the TCZ-SC monotherapy and TCZ-IV monotherapy groups were 56.6% (95% CI 48.9, 64.3) and 67.9% (95% CI 60.6, 75.3), respectively, at week 24. The mean ± SD change in serum matrix metalloproteinase 3 (MMP-3) was similar in both groups (from 288.9 ± 204.7 ng/ml at baseline to 123.3 ± 89.9 ng/ml at week 24 in the TCZ-SC monotherapy group and from 290.0 ± 211.3 ng/ml at baseline to 101.7 ± 64.2 ng/ml at week 24 in the TCZ-IV monotherapy group).

To identify the background factors that influence efficacy, logistic regression analyses were applied to the ACR response rate. The result from stepwise regression, BMI in the fourth quartile (from 23.4 to 29.6 kg/m^2) at baseline, was detected as a significant variable for ACR20 response rate (63.4%; odds ratio [OR] 0.31 [95% CI 0.14, 0.70], P = 0.0048), ACR50 response rate (51.2%; OR 0.47 [95% CI 0.22, 0.98], P = 0.0444), and ACR70 response rate (24.4%; OR 0.39 [95% CI 0.17, 0.90], P = 0.0271).

Pharmacokinetics. The serum trough TCZ concentrations in the TCZ-SC monotherapy and TCZ-IV monotherapy groups were similar over time (Figure 3). More than 80% of patients maintained TCZ concentrations ≥1 μg/ml from week 4 onward in the TCZ-SC monotherapy group (Figure 3).

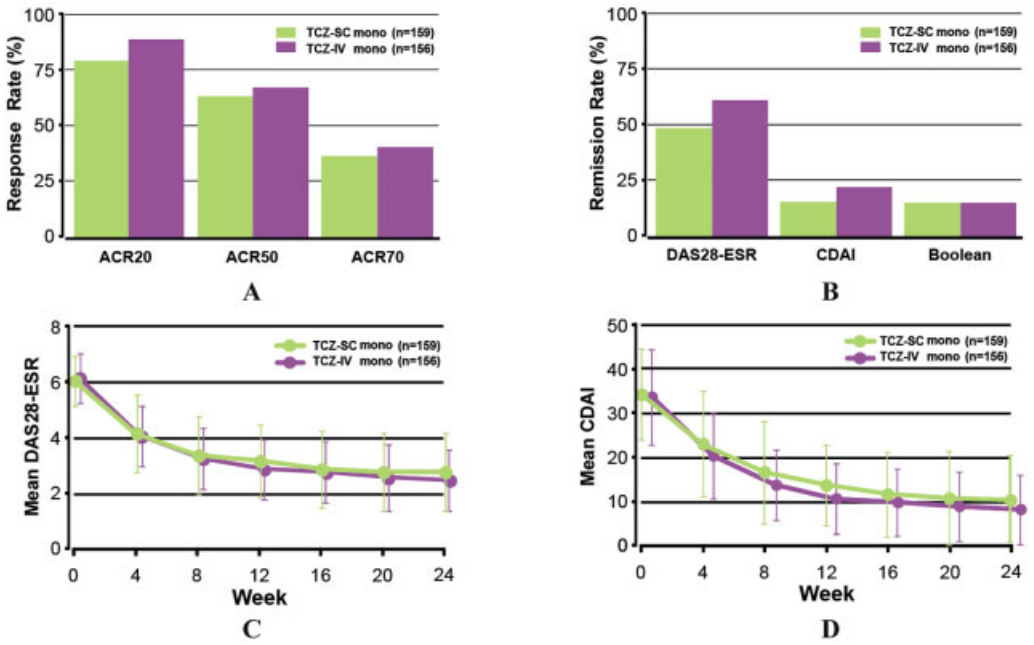


Figure 2. **A**, American College of Rheumatology (ACR) response rates of 20% (ACR20), 50% (ACR50), and 70% (ACR70) at week 24 (in the per-protocol set [PPS]) in patients receiving an intravenous infusion of tocilizumab monotherapy (TCZ-IV mono; n = 156) or a subcutaneous injection of tocilizumab monotherapy (TCZ-SC mono; n = 159). The ACR50 response rate in the TCZ-SC mono group was 63.5% (95% confidence interval [95% CI] 56.0, 71.0) and in the TCZ-IV mono group was 67.3% (95% CI 59.9, 74.7). The ACR70 response rate in the TCZ-SC mono group was 37.1% (95% CI 29.6, 44.6) and in the TCZ-IV mono group was 41.0% (95% CI 33.3, 48.7). The weighed differences of ACR50 and ACR70 response were −4.3% (95% CI −14.7, 6.0) and −3.8% (95% CI −14.5, 6.8), respectively. **B**, Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28-ESR), Clinical Disease Activity Index (CDAI), and Boolean Index remission rates at week 24 (in the PPS). The rate of DAS28-ESR remission (<2.6) in the TCZ-SC mono group was 49.7% (95% CI 41.9, 57.5) and in the TCZ-IV mono group was 62.2% (95% CI 54.6, 69.8). The rate of CDAI remission (CDAI score ≤2.8) in the TCZ-SC mono group was 16.4% (95% CI 10.6, 22.1) and in the TCZ-IV mono group was 23.1% (95% CI 16.5, 29.7). The Boolean Index remission rate in the TCZ-SC mono group was 15.7% (95% CI 10.1, 21.4) and in the TCZ-IV mono group was 16.0% (95% CI 10.3, 21.8). **C**, DAS28-ESR over 24 weeks. The mean ± SD change in DAS28-ESR from baseline to week 24 in the TCZ-SC mono group was 6.1 ± 0.9 to 2.8 ± 1.4 and in the TCZ-IV mono group was 6.2 ± 0.9 to 2.5 ± 1.1. **D**, CDAI scores over 24 weeks. Error bars show the SD of the mean. The mean ± SD change in CDAI score from baseline to week 24 in the TCZ-SC mono group was 34.2 ± 10.3 to 10.3 ± 9.5 and in the TCZ-IV mono group was 33.7 ± 10.8 to 8.2 ± 7.8.

Safety. The safety profiles were comparable between the TCZ-SC monotherapy and TCZ-IV monotherapy groups, with the exception of ISRs, which occurred at a higher frequency in the TCZ-SC monotherapy group than in the TCZ-IV monotherapy group. Over 24 weeks, AEs occurred in 89.0% (154 of 173) and 90.8% (157 of 173) of patients, serious AEs occurred in 7.5% (13 of 173) and 5.8% (10 of 173) of patients, adverse drug reactions occurred in 83.2% (144 of 173) and 86.1% (149 of 173) of patients, and serious adverse drug reactions occurred in 3.5% (6 of 173) and 5.8% (10 of 173) of patients in the TCZ-SC monotherapy and TCZ-IV monotherapy groups, respectively. No deaths or malignancies were reported.

Infections were reported in 41.6% of the TCZ-SC monotherapy group and in 45.1% of the TCZ-IV monotherapy group. Nasopharyngitis was the most common event, occurring in 17.9% of the TCZ-SC monotherapy group and in 20.8% of the TCZ-IV monotherapy group. Serious infections (Table 2) occurred in 1.2% of patients in the TCZ-SC monotherapy group and in 2.9% of patients in the TCZ-IV monotherapy group.

ISRs occurred in 12.1% of patients (21 of 173) in the TCZ-SC monotherapy group and in 5.2% of patients (9 of 173) in the TCZ-IV monotherapy group (placebo injection). The most common event was injection site erythema (16 patients [9.2%] in the TCZ-SC monotherapy group and 5 patients [2.9%] in the TCZ-IV monotherapy group). Other ISRs included injection site hemorrhage, pruritus, hematoma, swelling, pain, and urticaria (see Supplementary Table 1, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22110/abstract). All ISRs were mild, and no cases resulted in withdrawal from the study.

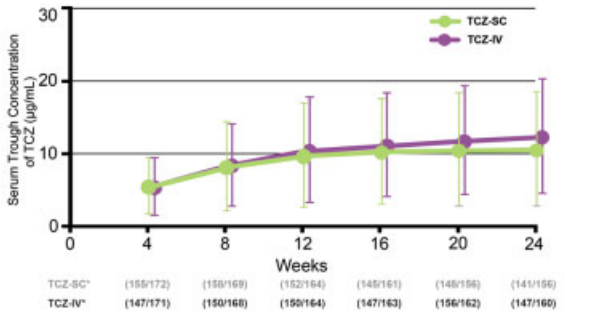
The incidence of SIRs from SC injection was 3.5% (6 of 173 patients) in the TCZ-SC monotherapy group, and the incidence of IV IRRs was 6.9% (12 of 173 patients) in the TCZ-IV monotherapy group. One patient (0.6%) in the TCZ-IV monotherapy group had an anaphylactic reaction after the second infusion (at week 4) and withdrew from

the study; this patient tested negative for anti-TCZ antibodies and recovered without sequelae. No patients in the TCZ-SC monotherapy group experienced serious hypersensitivity, including anaphylactic reactions.

The proportion of patients who experienced elevations in lipid levels and liver function tests during the blinded period was similar between the TCZ-SC monotherapy and TCZ-IV monotherapy groups (Table 3). The proportion of patients who experienced a grade 3 decrease in neutrophils (<1,000 to 500 cells/mm^3) was 2.9% (5 of 173 patients) in each group; 1 patient in the TCZ-SC monotherapy group withdrew. No grade 4 neutropenia (<500 cells/mm^3) was reported.

The incidence of elevated serum levels of Krebs von den Lungen-6 (KL-6) that exceeded the upper limit of normal (500 units/ml) and reached ≥1.5 times the baseline value was 3.8% in the TCZ-SC monotherapy group and 1.9% in the TCZ-IV monotherapy group. The incidence of elevated serum levels of pulmonary surfactant protein D (SP-D) that exceeded the upper limit of normal (110 ng/ml) and reached ≥1.5 times the baseline value was 6.9% in the TCZ-SC monotherapy group and 6.2% in the TCZ-IV monotherapy group. Patients who experienced increased levels of KL-6 and SP-D did not have any events of interstitial lung disease.

The proportion of patients who tested positive for anti-TCZ antibodies in the screening and confirmation assays was 3.5% (6 of 173) in the TCZ-SC monotherapy group and 0% in the TCZ-IV monotherapy group. Five of the 6 patients tested positive for anti-TCZ antibodies before week 12. No patients who developed anti-TCZ antibodies experienced ISRs, SIRs, or lack of efficacy after developing anti-TCZ antibodies.



Proportion of patients whose serum trough concentration of TCZ ≥ 1 μg/mL

Week	4	8	12	16	20	24
TCZ-SC mono (%)	80.2	85.8	87.2	85.7	91.7	85.9
TCZ-IV mono (%)	73.1	83.3	86.6	84.7	90.1	89.4

*Numbers of patients whose serum TCZ concentrations were above the limit of detection (> 0.1 μg/mL) and were collected at each point.

Figure 3. Mean serum trough tocilizumab (TCZ) concentrations over 24 weeks in patients receiving an intravenous infusion of TCZ monotherapy (TCZ-IV mono) or a subcutaneous injection of TCZ monotherapy (TCZ-SC mono). The table below the figure shows the proportion of patients in the TCZ-SC mono and TCZ-IV mono groups who had a serum trough TCZ concentration ≥1 μg/ml. At week 24, the mean ± SD serum trough TCZ concentration in the TCZ-SC mono group was 10.6 ± 7.8 μg/ml and in the TCZ-IV mono group was 12.4 ± 7.9 μg/ml.

Table 2. Summary of serious adverse events by patient*

SOC, preferred term	TCZ-SC monotherapy (n = 173)	TCZ-IV monotherapy (n = 173)
Infections and infestations		
Herpes zoster	–	2 (1.2)†
Pneumonia	–	2 (1.2)†
Cellulitis	1 (0.6)	1 (0.6)
Gastroenteritis	1 (0.6)	–
Gastrointestinal disorders		
Subileus	1 (0.6)†	–
Gastrointestinal hemorrhage	1 (0.6)	–
Ischemic colitis	–	1 (0.6)
Colonic polyp	1 (0.6)‡	–
Large intestine perforation	–	1 (0.6)
Vomiting	1 (0.6)†	–
Injury, poisoning, and procedural complications		
Spinal compression fracture	1 (0.6)‡	1 (0.6)†
Subdural hematoma	1 (0.6)†	–
Injury	1 (0.6)‡	–
Brain contusion	1 (0.6)†	–
Musculoskeletal and connective tissue disorders		
Synovitis	1 (0.6)‡	–
Spinal column stenosis	–	1 (0.6)†
Foot deformity	1 (0.6)‡	–
Respiratory, thoracic, and mediastinal disorders		
Pleurisy	–	1 (0.6)†
Chronic bronchitis	1 (0.6)‡	–
Asthma	1 (0.6)	–
Hepatobiliary disorders		
Hepatic function abnormal	–	1 (0.6)
Vascular disorders		
Hypertensive emergency	1 (0.6)†	–
Ear and labyrinth disorders		
Ménière disease	–	1 (0.6)
Nervous system disorders		
Intracranial hemorrhage	1 (0.6)†	
Metabolism and nutrition disorders		
Hyponatremia	1 (0.6)†	–
Immune system disorders		
Anaphylactic reaction	–	1 (0.6)
Benign, malignant, and unspecified neoplasms (including cysts and polyps)		
Neoplasm (benign)	1 (0.6)	–

* Values are the number (percentage). SOC = standard of care; TCZ-SC = subcutaneous tocilizumab; TCZ-IV = intravenous tocilizumab.
† Not related to the study drug. Occurred in the same patients, respectively.
‡ Not related to the study drug.

DISCUSSION

This noninferiority study was conducted to compare the efficacy of TCZ-SC monotherapy and TCZ-IV monotherapy in Japanese patients with RA who had inadequate responses to synthetic and/or biologic DMARDs. For the primary efficacy end point of ACR20 response rate at week

Table 3. Laboratory values*

	TCZ-SC monotherapy (n = 173)	TCZ-IV monotherapy (n = 173)
Shift in total cholesterol from baseline <200 mg/dl to worst value		
N	136	130
<200	39	37
200 to <240	65	58
≥240	32	35
Shift in HDL cholesterol from baseline <40 mg/dl to worst value		
N	29	14
<40	11	11
40 to <60	18	3
≥60	0	0
Shift in LDL cholesterol from baseline <100 mg/dl to worst value		
N	93	73
<100	17	17
100 to <130	51	44
130 to <160	24	8
160 to <190	1	4
≥190	0	0
Shift in ALT from normal at baseline to worst CTC grade		
N	164	165
Normal	124	124
Grade 1	35	32
Grade 2	4	7
Grade 3	1	2
Grade 4	0	0
Shift in AST from normal at baseline to worst CTC grade		
N	168	170
Normal	145	139
Grade 1	21	25
Grade 2	1	6
Grade 3	1	0
Grade 4	0	0
Shift in total bilirubin from normal at baseline to worst CTC grade		
N	173	172
Normal	149	154
Grade 1	21	13
Grade 2	3	5
Grade 3	0	0
Grade 4	0	0
Shift in neutrophils from normal at baseline to worst CTC grade		
N	170	172
Normal	130	125
Grade 1	19	20
Grade 2	16	22
Grade 3	5	5
Grade 4	0	0

* TCZ-SC = subcutaneous tocilizumab; TCZ-IV = intravenous tocilizumab; HDL = high-density lipoprotein; LDL = low-density lipoprotein; ALT = alanine aminotransferase; CTC = Common Terminology Criteria; AST = aspartate aminotransferase.

24, TCZ-SC monotherapy demonstrated noninferiority to TCZ-IV monotherapy in the PPS. The primary noninferiority analysis was made in the PPS, as recommended by the International Conference on Harmonisation E9 (21). To test the robustness of the noninferiority result, the results were validated by demonstrating the noninferiority of

TCZ-SC monotherapy to TCZ-IV monotherapy in the modified ITT population. From the results of secondary end points, the difference between TCZ-SC monotherapy and TCZ-IV monotherapy of ACR50 and ACR70 was smaller than ACR20. Furthermore, the mean change of the DAS28-ESR and CDAI score of TCZ-SC monotherapy was comparable to TCZ-IV monotherapy. These results support the noninferiority of TCZ-SC monotherapy to TCZ-IV monotherapy.

Two additional randomized, double-blind, phase III global studies (SUMMACTA and BREVACTA) evaluated TCZ-SC in combination with DMARDs in patients with RA from North America, Europe, South America, and Asia (other than Japan) (22,23). In the SUMMACTA study, TCZ-SC 162 mg every week was demonstrated to be noninferior to TCZ-IV 8 mg/kg every 4 weeks in combination with DMARDs using an ACR20 responder end point (noninferiority margin of 10%). The BREVACTA study demonstrated the superiority of TCZ-SC 162 mg every 2 weeks compared to placebo regarding the percentage of patients who achieved an ACR20 response at week 24. In both studies, the patients' mean body weight was 70–80 kg. In the MUSASHI study, TCZ-SC monotherapy dosing of every 2 weeks would be the most appropriate for Japanese patients with RA who have a lower body weight than patients in Western countries.

In Japan, the dose of TCZ-SC monotherapy of 162 mg every 2 weeks was selected from the previous phase I/II study with a mean body weight of 56 kg because it had a pharmacodynamic profile and TCZ trough concentration similar to those of the approved TCZ-IV dose of 8 mg/kg (15,24). In the current study, TCZ-SC monotherapy actually demonstrated TCZ trough concentrations comparable with those of TCZ-IV monotherapy despite a decrease in the given dose of TCZ in the TCZ-SC monotherapy group compared with the TCZ-IV monotherapy group if the weight is the same.

A previous TCZ-IV study reported that ≥ 1 μg/ml of serum TCZ was considered enough to suppress IL-6 signal transduction in the sera (19). In the current study, serum trough TCZ concentrations in the TCZ-SC monotherapy group were approximately equal to those in the TCZ-IV monotherapy group from week 4 onward, and most patients in both groups had TCZ concentrations ≥ 1 μg/ml. Prompt inhibition of IL-6 signaling by TCZ-SC monotherapy was also reflected in the time to improvement of disease activity, whereby the effectiveness of TCZ-SC monotherapy was approximately equal to that of TCZ-IV monotherapy from week 4 onward.

TCZ-SC monotherapy was administered as a fixed dose (162 mg), whereas the TCZ-IV monotherapy formulation was administered by body weight (8 mg/kg). In fact, trough TCZ concentrations tend to be lower in Japanese patients with a high body weight treated with TCZ-SC monotherapy (data not shown).

From the stepwise regression analyses, BMI in the fourth quartile at baseline was identified as a factor that contributed to low ACR response rates. However, more than half of patients in the fourth quartile of BMI achieved an ACR50 response. Therefore, it is unlikely that patients with high BMIs (23.4–29.6 kg/m^2) at baseline will have less response to therapy. With regard to the association between BMI and efficacy, further investigations are needed because the number of patients in the high BMI category was limited in this study. Previous use of anti-TNF agents was not identified as a factor that affected ACR response rates in the TCZ-SC monotherapy group. This suggests that the effect of TCZ-SC monotherapy on disease activity may be similar to that of TCZ-IV monotherapy in patients who have previously received anti-TNF agents.

Several studies have reported that TCZ as both monotherapy and in combination with DMARDs prevents joint destruction (4,6,9,23). The MMP-3 level in the TCZ-SC monotherapy group decreased at week 24 compared with baseline and was comparable with that in the TCZ-IV monotherapy group. Furthermore, the efficacy and serum TCZ trough concentrations were comparable between the TCZ-SC monotherapy and TCZ-IV monotherapy groups. These facts suggest that TCZ-SC monotherapy may also inhibit the progression of joint damage.

No new or unexpected safety issues were observed in this study. The safety profile of the TCZ-SC monotherapy group was similar to that of the TCZ-IV monotherapy group, except for ISRs. The incidence rate of ISRs was higher in the TCZ-SC monotherapy group than in the TCZ-IV monotherapy group. However, all events were mild and manageable. Although a direct comparison was difficult, the incidence of ISRs was not higher than that observed with other biologic agents that are administered by SC injection (10.4% with golimumab plus MTX and $>$30% with adalimumab monotherapy) (25,26). While the incidence rate of serious infection with TCZ-SC monotherapy was lower than with TCZ-IV monotherapy, there are not enough data to determine if this is a true difference. Additional data are being collected in the extension period. The serum levels of KL-6 and SP-D were reported to be elevated in patients with interstitial lung disease. The observed increase in serum KL-6 and SP-D levels was consistent with that in previous reports (27,28).

The number of patients who developed anti-TCZ antibodies was higher in the TCZ-SC monotherapy group than in the TCZ-IV monotherapy group. However, neither of these rates was numerically higher than the antidrug antibody rates reported for other biologic agents used to treat RA (29–32). None of the patients who tested positive for anti-TCZ antibodies experienced serious ISRs or hypersensitivity events, including anaphylaxis. The impact of anti-TCZ antibodies on efficacy was unclear because of the low number of patients who developed anti-TCZ antibodies. However, no patients who developed anti-TCZ antibodies experienced a lack of efficacy after developing anti-TCZ antibodies in this study.

The current study assessed the efficacy and safety of TCZ monotherapy without concomitant DMARDs. However, TCZ in combination with MTX was more commonly associated with elevated transaminases (9), and although the data on combination therapy with TCZ-SC are not yet available, the same effect is likely to be seen. Studies are currently ongoing to evaluate TCZ-SC in combination with DMARDs (22,23).

An SC formulation of TCZ would greatly shorten the administration time compared with the IV formulation

and would allow for home administration. Moreover, it would shorten the time and effort involved in the preparation of TCZ prior to administration and therefore would be more convenient for both patients with RA and health care professionals.

In summary, the noninferiority of TCZ-SC monotherapy to TCZ-IV monotherapy was confirmed. TCZ-SC monotherapy provided efficacy, safety, and serum trough concentrations of TCZ that were comparable with those of TCZ-IV monotherapy. The use of TCZ-SC monotherapy would provide an additional administration option for patients with RA.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Ogata had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ogata.

Acquisition of data. Ogata, Tanimura, Sugimoto, Inoue, Urata, Matsubara, Kondo, Ueki, Iwahashi, Tohma, Ohta, Saeki, Tanaka.

Analysis and interpretation of data. Ogata.

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