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Longterm Safety and Efficacy of Subcutaneous Tocilizumab Monotherapy: Results from the 2-year Open-label Extension of the MUSASHI Study

Atsushi Ogata, Koichi Amano, Hiroaki Dobashi, Masayuki Inoo, Tomonori Ishii, Tsuyoshi Kasama, Shinichi Kawai, Atsushi Kawakami, Tatsuya Koike, Hisaaki Miyahara, Toshiaki Miyamoto, Yasuhiko Munakata, Akira Murasawa, Norihiro Nishimoto, Noriyoshi Ogawa, Tomohiro Ojima, Hajime Sano, Kenrin Shi, Eisuke Shono, Eiichi Suematsu, Hiroki Takahashi, Yoshiya Tanaka, Hiroshi Tsukamoto, and Akira Nomura, and the MUSASHI Study Investigators

ABSTRACT. Objective. To evaluate the longterm safety and efficacy of subcutaneous tocilizumab (TCZ-SC) as monotherapy in patients with rheumatoid arthritis (RA).

Methods. Of 346 patients who received 24 weeks of double-blind treatment with either TCZ-SC monotherapy, 162 mg every 2 weeks (q2w); or intravenous TCZ (TCZ-IV) monotherapy, 8 mg/kg every 4 weeks; 319 patients continued to receive TCZ-SC q2w in the 84-week open-label extension (OLE) of the MUSASHI study (JAPICCTI-101117). Efficacy, safety, and immunogenicity were evaluated for all patients treated with TCZ during 108 weeks.

Results. The proportions of patients who achieved American College of Rheumatology 20/50/70 responses, low disease activity [28-joint Disease Activity Score (DAS28) ≤ 3.2], or remission (DAS28 < 2.6) at Week 24 were maintained until Week 108. The incidences of adverse events and serious adverse events were 498.3 and 16.9 per 100 patient-years (PY), respectively. The overall safety of TCZ-SC monotherapy was similar to that of TCZ-IV monotherapy. Rates of injection site reactions (ISR) through 108 weeks remained similar to rates through 24 weeks. ISR were mild and did not cause any patient withdrawals. No serious hypersensitivity events (including anaphylactic reactions) occurred. Anti-TCZ antibodies were present in 2.1% of patients treated with TCZ-SC monotherapy.

Conclusion. TCZ-SC monotherapy maintained a favorable safety profile and consistent efficacy throughout the 108-week study. Like TCZ-IV, TCZ-SC could provide an additional treatment option for patients with RA. (First Release April 1 2015; J Rheumatol 2015;42:799–809; doi:10.3899/jrheum.140665)

Key Indexing Terms:
RHEUMATOID ARTHRITIS   HUMANIZED MONOCLONAL ANTIBODIES
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Rheumatoid arthritis (RA) is a chronic, progressive, systemic autoimmune disease characterized by synovitis leading to damage of diarthrodial joints. For patients with an insufficient response to disease-modifying antirheumatic drugs (DMARD), the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) guidelines recommend treatment with biologic agents[1,2]. Biologics have become available that target key cytokines in the pathogenesis of RA, including inhibitors of tumor necrosis factor (TNF)-α, interleukin 6 (IL-6), IL-1, CD20, and cytotoxic T lymphocyte antigen 4[3]. These biologics have demonstrated efficacy in patients with RA, yet differences in the route of administration, frequency of dosing, and safety profile can affect patient satisfaction and compliance[4,5,6]. For a fuller assessment of the longterm risk/benefit profiles of these therapeutics in patients with RA, it is necessary to evaluate their safety and efficacy over a significant period of time.

Tocilizumab (TCZ) is a humanized monoclonal antibody directed against the IL-6 receptor. Upon binding to the IL-6 receptor, TCZ blocks IL-6 receptor signaling and subsequent proinflammatory activities[7]. The efficacy and safety profiles of TCZ were comparable among phase III studies and were associated with a risk/benefit ratio that supported its use in patients with RA[8,9,10,11,12,13,14]. TCZ by intravenous (IV) administration has been approved in more than 100 countries for the treatment of patients with RA. TCZ by subcutaneous (SC) administration was recently approved in Japan and the United States for patients with RA. The TCZ-SC formulation has a shorter infusion time compared with TCZ-IV, does not require an infusion facility for administration, and can be administered at home by self-injection.

The initial efficacy, safety, and pharmacokinetics of TCZ-SC monotherapy (TCZ-SC-mono) were evaluated in an open-label phase I/II study conducted in Japan at 3 doses [81 mg every 2 weeks (q2w), 162 mg q2w, and 162 mg weekly (qw)] over 6 months[15]. The MUSASHI study (Multicenter Double-Blind Study of Actemra Subcutaneous Injection in Patients Having Rheumatoid Arthritis to Verify Noninferiority Against Intravenous Infusion) a multicenter, parallel-group, double-blind, 24-week phase III trial was conducted to compare the efficacy and safety of TCZ-SC-mono 162 mg q2w and TCZ-IV-mono 8 mg/kg every 4 weeks (q4w) in Japanese patients with RA. The study met its primary endpoint by demonstrating the noninferiority of TCZ-SC-mono to TCZ-IV-mono regarding ACR20 response rates at Week 24[16]. Because body mass index (BMI) can affect treatment responses, we investigated the effect of body weight–related adjustment of TCZ-SC administration on efficacy.

In the present study, an 84-week open-label extension (OLE), we evaluated the longterm efficacy and safety profile of TCZ-SC-mono 162 mg q2w in patients with RA. In addition, we evaluated adjustment of the administration interval.

MATERIALS AND METHODS

Study design. This was a 108-week, randomized, double-dummy, parallel-group phase III trial with a double-blind period of 24 weeks (MUSASHI) followed by an OLE period of 84 weeks in Japanese patients with RA (JAPICCTI-101117). The protocol was approved by the Japanese Ministry of Health, Labor, and Welfare and the institutional review boards at all study sites, and the study was completed in accordance with the ethical standards of the current version of the 1964 Declaration of Helsinki. At enrollment in the double-blind study, all patients provided signed informed consent.

At the start of the double-blind period, patients were randomized 1:1 into 2 groups: TCZ-SC-mono 162 mg q2w plus placebo-TCZ-IV q4w or TCZ-IV-mono 8 mg/kg q4w plus placebo-TCZ-SC q2w. After 24 weeks, patients received open-label TCZ-SC-mono 162 mg q2w for 84 weeks. The eligibility criteria for participation in this study have been described[16]. In brief, patients 20 to 70 years of age with RA for ≥ 6 months (1987 ACR criteria) who had an inadequate response to any synthetic DMARD, biologic DMARD, or immunosuppressant were included. The first dose of TCZ-SC-mono in the OLE was administered at Week 24 in the double-blind period. During the OLE, if the investigator assessed for lack of efficacy as defined by not achieving a > 20% improvement in swollen or tender joint count compared with baseline (start of the double-blind period) and a C-reactive protein (CRP) level > 0.3 mg/dl in the last laboratory test, the principal investigator could shorten the dosing interval to qw. If patients maintained low disease activity, as indicated by a 28-joint Disease Activity Score using erythrocyte sedimentation rate (DAS28-ESR) of ≤ 3.2 for 24 weeks, the principal investigator could extend the dosing interval to every 3 weeks (q3w).

Safety and immunogenicity assessment. Safety was evaluated through both the double-blind period and the OLE period for all patients who received ≥ 1 dose of TCZ irrespective of their treatment group during the double-blind period. Adverse events (AE) and serious AE (SAE) were classified using the *Medical Dictionary for Regulatory Activities* (MedDRA, version 13.0). An AE was considered to be a treatment-emergent AE if it occurred during the study or if the severity of a preexisting condition increased during the study. All events occurring at the injection site, as judged by the investigator, were classified as injection site reactions (ISR). An SAE was any event that resulted in death, was life-threatening, required hospitalization or medical or surgical intervention, or resulted in a persistent or significant disability, cancer, or congenital defect.

Anti-TCZ antibodies were measured q4w during the double-blind period and then every 12 weeks in the OLE period using the ELISA method described previously[17].

Pharmacokinetics. Serum TCZ concentration was measured every 12 weeks throughout the OLE period as described[18]. The below limit of quantitation (BLQ) of TCZ was 0.1 μg/ml.

Efficacy assessment. Efficacy was evaluated for patients who received ≥ 1 dose of TCZ during the 108 weeks of treatment. Disease activity in both the double-blind and the OLE periods was monitored every 4 weeks. Disease activity was evaluated by DAS28-ESR, ACR core set, and Clinical Disease Activity Index (CDAI). The percentages of patients with low disease activity (DAS28-ESR ≤ 3.2), remission (DAS28-ESR < 2.6), CDAI remission (CDAI ≤ 2.8), and EULAR response were also calculated.

Statistical analysis. Baseline demographic data and clinical characteristics were analyzed descriptively for patients who received ≥ 1 dose of TCZ during the double-blind period. Safety was evaluated for all patients who received ≥ 1 dose of TCZ during the double-blind period, and AE were included in the analyses if they occurred in the TCZ-IV group during the double-blind period. ISR were evaluated as events that occurred after the first TCZ-SC dose for patients who received ≥ 1 dose of TCZ-SC-mono. Efficacy was evaluated for all patients who received ≥ 1 dose of TCZ during the double-blind period, irrespective of their treatment group during the period. For missing data, nonresponder imputation was applied to ACR response data (ACR20/50/70), DAS28 remission, and CDAI remission, while last observation carried forward (LOCF) was applied to continuous data (DAS28). These efficacy data were expressed with 95% CI. For the patients who changed dosing intervals, safety was evaluated using the incidence rate during the dose-changing period, and efficacy was evaluated as trends over time after changing the dosing interval. The study design was not initially powered for the posthoc analyses presented here.

RESULTS

Patient disposition. Of 346 patients who were treated in 24 weeks of double-blind treatment with either TCZ-SC-mono,

162 mg q2w, or TCZ-IV-mono, 8 mg/kg q4w, a total of 319 patients (92.2%) continued to receive TCZ-SC q2w in the OLE (Figure 1). Exposure to TCZ-SC-mono was 561.71 patient-years (PY) over the 108 weeks, including the 24-week double-blind period and the following 84-week OLE period. A total of 278 patients (80.3%) remained in the study after 108 weeks. AE were the most common reason for withdrawal from the study over the 108 weeks (Figure 2); there was no clustering of AE that were predominantly responsible for patient withdrawals.

Baseline demographics, disease characteristics, and RA treatment at entry into the double-blind study have been published[16]. Patient baseline characteristics were as follows: mean ± SD body weight 54.0 ± 9.5 kg, mean ± SD disease duration 7.7 ± 7.4 years, percentage of patients with a history of TNF-α inhibitor use 22.0%, and the percentage of patients using steroids at baseline 63.3% (Table 1). DAS28-ESR (LOCF, n = 346) improved from 6.21 ± 0.90 at Week 0 to 2.76 ± 1.36 at Week 24 and serum IL-6 level changed from 35.4 ± 43.6 pg/ml at Week 0 to 49.7 ± 69.6 pg/ml at Week 24.

Safety. The incidence of AE and SAE were 498.3 per 100 PY and 16.9 per 100 PY, respectively. The safety profile of TCZ-SC-mono remained stable over time. The most frequently reported AE were nasopharyngitis, pharyngitis, upper respiratory infection, hypercholesterolemia, and injection site erythema (Table 2). All discontinuations and the subsets of discontinuations due to AE are presented in a Kaplan-Meier plot (Figure 2). Withdrawal owing to AE occurred at the same frequency throughout the trial, and the
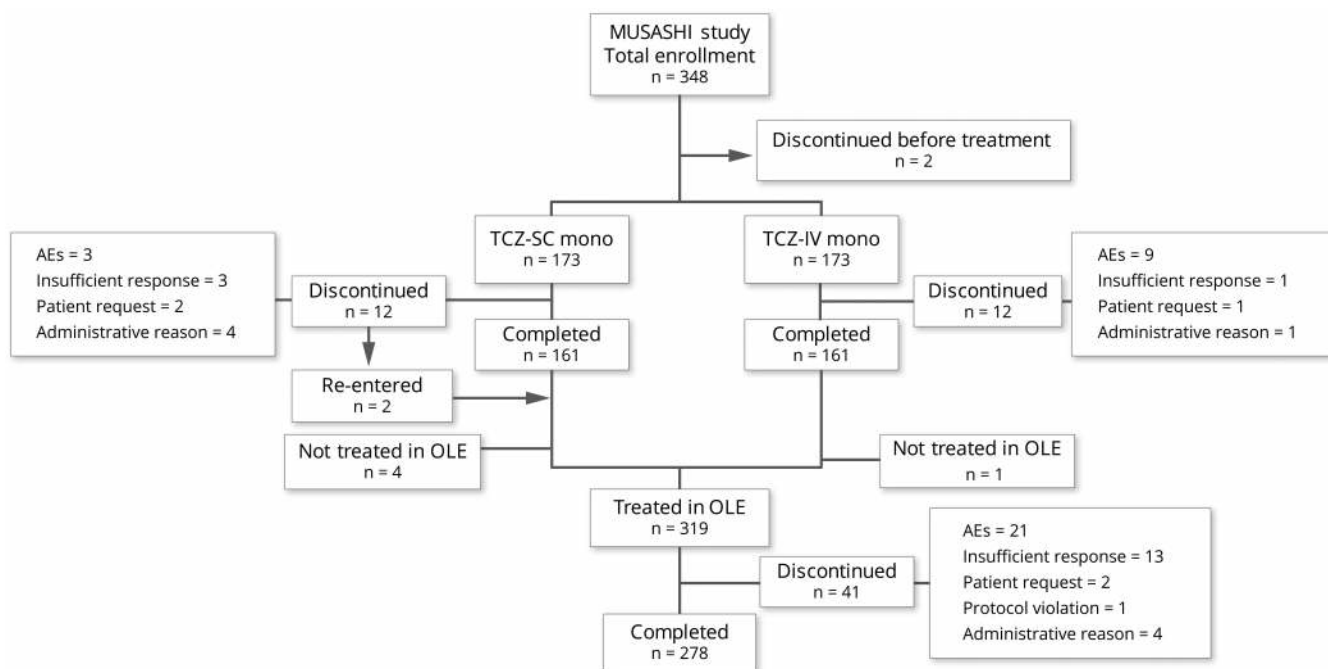

Figure 1. Patient disposition. AE: adverse event; OLE: open-label extension; TCZ-IV-mono: intravenous tocilizumab monotherapy; TCZ-SC-mono: subcutaneous TCZ monotherapy.
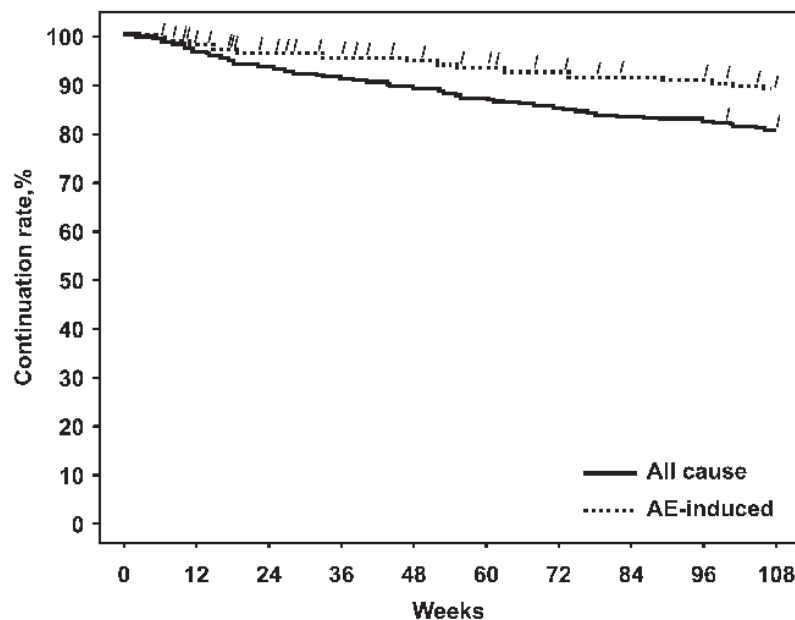
Figure 2. Kaplan-Meier plot of discontinuations over 108 weeks. AE: adverse events.

Table 1. Demographics and characteristics at baseline. Data are presented as n (%) or mean ± SD.

Characteristics	Baseline, n = 346
Female	287 (82.9)
Age, yrs	52.5 ± 12.4
Body weight, kg	54.0 ± 9.5
Disease duration, yrs	7.7 ± 7.4
Steinbrocker functional class	
I	48 (13.9)
II	253 (73.1)
III	45 (13.0)
Steinbrocker stage	
I	29 (8.4)
II	129 (37.3)
III	97 (28.0)
IV	91 (26.3)
RF-positive	283 (81.8)
Anti-CCP antibody–positive	312 (90.2)
IL-6, pg/ml	35.4 ± 43.6
DAS28-ESR	6.2 ± 0.9
Swollen joint count (66 joints)	14.3 ± 7.5
Tender joint count (68 joints)	18.3 ± 9.6
Patient global VAS, mm	57.4 ± 24.0
CRP, mg/dl	2.2 ± 2.2
ESR, mm/h	49.4 ± 24.4
Previous treatment with TNF inhibitor	76 (22.0)
Previous treatment with methotrexate	333 (96.2)
Oral corticosteroid treatment	219 (63.3)

CCP: cyclic citrullinated peptide; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS28-ESR: 28-joint Disease Activity Score using ESR; IL-6: interleukin 6 (normal range: < 4.0 pg/ml); RF: rheumatoid factor; TNF: tumor necrosis factor; VAS: visual analog scale.

Table 2. Frequently reported treatment-emergent adverse events (≥ 2%).

Adverse Event	% of Patients
Nasopharyngitis	46.5
Upper respiratory tract infections	21.1
Blood cholesterol increased	20.2
Low-density lipoprotein cholesterol increased	18.5
Pharyngitis	15.0
Blood triglycerides increased	13.3
ALT increased	13.0
Stomatitis	11.3
Eczema	11.3
γ-GT increased	10.7
Injection site erythema	10.7
White blood cells decreased	10.7

ALT: alanine aminotransferase; γ-GT: γ-glutamyl transpeptidase.

gradient of the Kaplan-Meier plot was constant over time. In the 24-week double-blind period, 3.5% (12 of 346) of patients withdrew because of AE. Three patients did not enter the OLE because of AE; in the 84-week OLE period, 6.6% (21 of 319) withdrew because of AE. The most common reasons for AE-related withdrawal were infections, which included shingles (0.9%), pneumonia (0.9%), and atypical mycobacterial infection (0.9%).

Rates of SAE were stable over time (Table 3). A total of 108 SAE were reported during the study; 26 resulted in discontinuation and 1 resulted in death due to gastric cancer with disseminated intravascular coagulation that developed in the OLE period. The most common SAE were infections,

Table 3. Safety summary. Multiple occurrences of the same adverse event (AE) in 1 individual were counted only once.

	Week			
	0–24, n = 346	24–48, n = 319	48–72, n = 309	72–108, n = 294
Total exposure period, PY	154.7	144.6	138.2	201.3
AE				
Total no. patients	311	249	233	235
Total no. AE (events/100 PY)	1148 (742.0)	724 (500.8)	593 (429.2)	719 (357.2)
(95% CI for rate)	(699.7–786.2)	(465.0–538.6)	(395.4–465.2)	(331.6–384.3)
Death				
Total no. patients (deaths/100 PY)	0	0	1 (0.72)	0
(95% CI for rate)			(0.02–4.03)	
Infections				
Total no. patients	150	139	130	158
Total no. (events/100 PY)	228 (147.4)	206 (142.5)	174 (125.9)	276 (137.1)
(95% CI for rate)	(128.9–167.8)	(123.7–163.3)	(107.9–146.1)	(121.4–154.3)
Malignancy				
Total no. patients	1	0	3	1
Total no. (events/100 PY)	1 (0.65)		3 (2.17)	1 (0.50)
(95% CI for rate)	(0.02–3.60)		(0.45–6.35)	(0.01–2.77)
Serious AE				
Total no. patients	24	23	20	22
Total no. (events/100 PY)	32 (20.7)	25 (17.3)	24 (17.4)	27 (13.4)
(95% CI for rate)	(14.2–29.2)	(11.2–25.5)	(11.1–25.9)	(8.8–19.5)
Serious infections				
Total no. patients	7	10	6	10
Total no. (events/100 PY)	7 (4.52)	10 (6.92)	6 (4.34)	11 (5.46)
(95% CI for rate)	(1.82–9.32)	(3.32–12.72)	(1.59–9.45)	(2.73–9.78)

PY: patient-years.

which included pneumonia, shingles, gastroenteritis, and cellulitis (Table 4). Thirty patients (34 AE; 5.3 events per 100 PY) reported serious infections over 108 weeks. Four malignancies were reported during the OLE. Times to the event and resolution were ovarian cancer (64 weeks, unresolved), colon cancer (97 weeks, unresolved), gastric cancer (61 weeks, death), and breast carcinoma *in situ* (67 weeks, unresolved). In addition, 1 patient developed a lumbar facet cyst (3 weeks, resolving).

ISR occurred in 13.2% of patients (44 of 333) treated with TCZ-SC monotherapy over 108 weeks. The most common were erythema (32 patients), pruritus (8 patients), hemorrhage (7 patients), and swelling (5 patients). All ISR were mild, and no cases resulted in withdrawal from the study. The incidence of systemic injection reactions from TCZ-SC-mono was 4.8% (16 of 333 patients). The most common injection reactions were headache (5 patients) and fever (3 patients). No serious hypersensitivity events, including anaphylactic reactions, were reported.

The number of patients who experienced elevations in lipid levels and liver function tests during 108 weeks is shown in Table 5. The number of patients who experienced a worst value in liver transaminase [aspartate aminotransferase and alanine aminotransferase (ALT)] is also shown in Table 5. The proportion of patients who experienced a grade 3 or grade 4 decrease in neutrophils (< 1000 cells/mm^3) was 5.5% (19 of 346 patients) through Week 108.

Immunogenicity. The proportion of patients who received TCZ-SC-mono who tested positive for anti-TCZ antibodies in the screening and confirmation assays was 2.1% (7 of 333). Of these 7 patients, anti-TCZ antibodies appeared before Week 12 in 5 patients. Anti-TCZ antibodies were detected after switching from TCZ-IV-mono to TCZ-SC-mono in only 1 patient. No patients who developed anti-TCZ antibodies experienced a lack of efficacy or a decrease in serum TCZ concentration after developing anti-TCZ antibodies. There was no correlation between anti-TCZ antibodies and ISR. No ISR or anaphylactic reactions were observed in patients who tested positive for anti-TCZ antibodies.

Efficacy. ACR20, ACR50, and ACR70 response rates, CDAI remission, and DAS28 remission were analyzed by non-responder imputation, and DAS28-ESR was analyzed by LOCF. There was similar efficacy among patients who received TCZ-IV-mono or TCZ-SC-mono in the double-blind period (weeks 0–24; Figure 3). At Week 108, the response rates (95% CI) for the TCZ-IV-mono and TCZ-SC-mono groups were ACR20 of 77.5% (71.2, 83.7) and 71.7% (65.0, 78.4), ACR50 of 65.3% (58.2, 72.4) and 64.7% (57.6, 71.9), ACR70 of 49.1% (41.7, 56.6) and 50.3% (42.8, 57.7), CDAI remission of 39.9% (32.6, 47.2) and 37.0% (29.8, 44.2), DAS28 remission of 64.7% (57.6, 71.9) and 63.6% (56.4, 70.8), and DAS28-ESR of 2.36 (2.14, 2.57) and 2.34 (2.11, 2.57), respectively. In total, the proportions of patients who

Table 4. Summary of serious adverse events (SAE) by body system. Data are presented as n (%), except where indicated. Multiple occurrences of the same AE in 1 individual were counted only once.

Body System or AE	n = 346
Total exposure period, PY	639.0
All body systems	
Total no. patients with ≥ 1 SAE	77
Total no. SAE	108 (16.9)
Infections and infestations	
Total no. SAE, PY	34 (5.3)
Pneumonia	10 (1.6)
Shingles	6 (0.9)
Gastroenteritis	3 (0.5)
Cellulitis	3 (0.5)
Musculoskeletal and connective tissue disorders	
Total no. SAE, PY	17 (2.7)
Joint destruction	5 (0.8)
Foot deformity	3 (0.5)
Synovitis	2 (0.3)
Osteoarthritis	2 (0.3)
Gastrointestinal problems	
Total no. SAE, PY	14 (2.2)
Colon polyps	5 (0.8)
Injury, poisoning, and procedural complications	
Total no. SAE, PY	9 (1.4)
Joint dislocation	2 (0.3)
Vertebral compression fracture	2 (0.3)
Tendon rupture	2 (0.3)
Respiratory, thoracic, and mediastinal disorders	
Total no. SAE, PY	6 (0.9)
Asthma	2 (0.3)
Cataract	2 (0.3)

AE ≥ 0.2 per 100 PY in total (safety). AE: adverse event; PY: patient-year.

Table 5. Laboratory values of lipid and liver function.

Change Observed	No. Patients Treated with TCZ-SC-mono, total = 346
Shift in total cholesterol from baseline < 200 mg/dl to last observed value over Week 108	
N	266
< 200	132
≥ 200 to < 240	102
≥ 240	32
Shift in HDL cholesterol from baseline < 40 mg/dl to last observed value over Week 108	
N	43
< 40	12
≥ 40 to < 60	26
≥ 60	5
Shift in LDL cholesterol from baseline < 100 mg/dl to last observed value over Week 108	
N	166
< 100	74
≥ 100 to < 130	75
≥ 130 to < 160	13
≥ 160 to < 190	3
≥ 190	1
Shift in ALT from normal at baseline to worst CTC grade	
N	329
Normal	223
Grade 1	91
Grade 2	12
Grade 3	3
Grade 4	0
Shift in AST from normal at baseline to worst CTC grade	
N	338
Normal	257
Grade 1	73
Grade 2	7
Grade 3	1
Grade 4	0
Shift in total bilirubin from normal at baseline to worst CTC grade	
N	345
Normal	277
Grade 1	55
Grade 2	13
Grade 3	0
Grade 4	0
Shift in neutrophils from normal at baseline to worst CTC grade	
N	342
Normal	205
Grade 1	51
Grade 2	67
Grade 3	18
Grade 4	1
Shift in platelets from normal at baseline to worst CTC grade	
N	341
Normal	311
Grade 1	29
Grade 2	1
Grade 3	0
Grade 4	0

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTC: common terminology criteria; HDL: high-density lipoprotein; IV: intravenous; LDL: low-density lipoprotein; SC: subcutaneous; TCZ: tocilizumab; TCZ-SC-mono: subcutaneous TCZ monotherapy.

achieved ACR20/50/70 (95% CI) responses were 79.2% (74.9, 83.5)/61.6% (56.4, 66.7)/37.3% (32.2, 42.4) at Week 24, 80.6% (76.5, 84.8)/65.0% (60.0, 70.1)/44.8% (39.6, 50.0) at Week 48, and 74.6% (70.0, 79.2)/65.0% (60.0, 70.1)/49.7% (44.4, 55.0) at Week 108, respectively (Figure 4A). The DAS28-ESR (mean ± SD) values in patients who received TCZ-SC-mono were 6.21 ± 0.90 at baseline, 2.76 ± 1.36 at Week 24, 2.61 ± 1.39 at Week 48, and 2.35 ± 1.49 at Week 108 (Figure 4B). The proportion of patients who achieved DAS28-ESR remission or low disease activity (95% CI) also improved over time, from 52.3% (47.0, 57.6) and 68.5% (63.6, 73.4) at Week 24 to 64.2% (59.1, 69.2) and 71.1% (66.3, 75.9) at Week 108, respectively (Figure 4C). The proportion of patients who achieved CDAI remission also improved over time, from 18.5% at Week 24 to 38.4% at Week 108 (Figure 4C). The proportion of patients who received TCZ-SC-mono and achieved a good EULAR response at Week 24 (68.5%) and maintained the response through Week 108 was 70.8%.

The proportion of patients who withdrew owing to lack of efficacy remained stable, from 1.2% at Week 24 to 4.9% at Week 108.
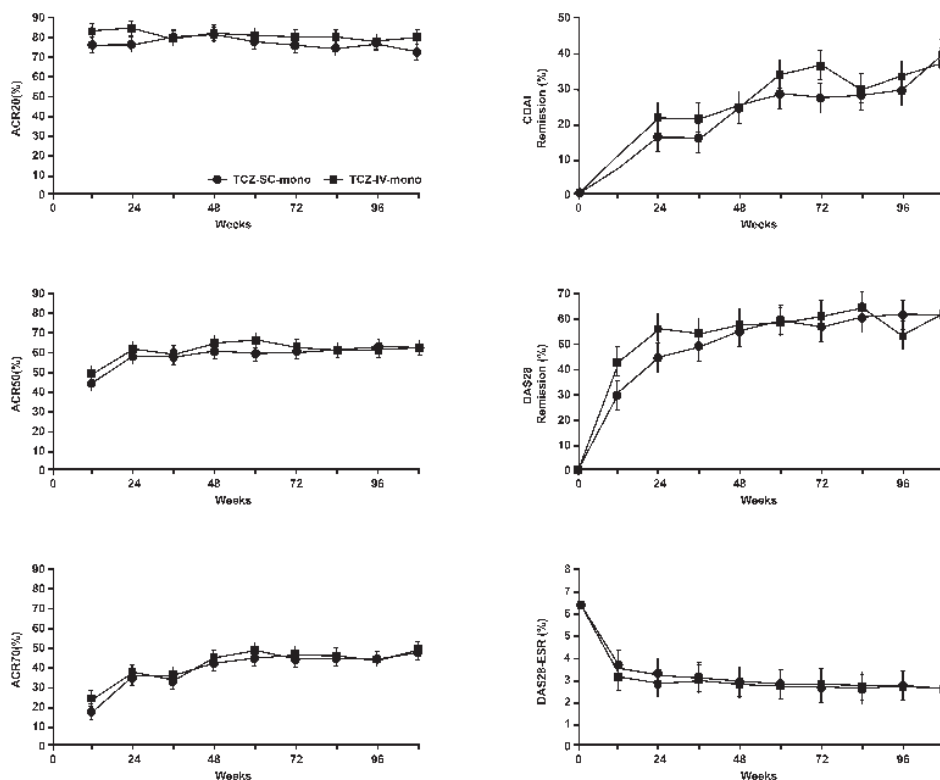
Figure 3. Efficacy of the open-label extension period (weeks 24–108) between patients who received TCZ-SC-mono or TCZ-IV-mono in the double-blind periods (weeks 0–24). American College of Rheumatology (ACR) response rate of 20% (ACR20), 50% (ACR50), and 70% (ACR70), Clinical Disease Activity Index (CDAI) remission, and Disease Activity Score in 28 joints (DAS28) remission were analyzed by nonresponder imputation. DAS28 using the erythrocyte sedimentation rate (DAS28-ESR) was analyzed by last observation carried forward method. Data are presented with 95% CI. TCZ-IV-mono: intravenous tocilizumab monotherapy; TCZ-SC-mono: subcutaneous TCZ monotherapy.

Increase and reduction of dosing interval. Twenty-four patients received TCZ-SC-mono qw; 62.5% (15 of 24) weighed ≥ 60 kg. The mean body weight (± SD) in these patients with insufficient response was 63.0 ± 10.8 kg, and that of the overall patient population was 54.0 ± 9.5 kg, while the baseline mean BMI (± SD) in patients with insufficient response was 24.45 ± 4.19 kg/m^2, and that of the overall patient population was 21.68 ± 3.42 kg/m^2. In 58.3% (14 of 24) of these patients, CRP values did not decrease below the institutional reference value (< 0.30 mg/dl) and in 62.5% (15 of 24), serum TCZ concentrations were decreased to < 1 μg/ml. Twenty-four weeks after the administration interval was shortened, DAS28-ESR improved from 4.6 ± 1.6 to 2.3 ± 1.6 (n = 20, Figure 5A); and the concentration of serum TCZ [median (Q1:Q3)] increased from 0.16 (BLQ: 3.80 μg/ml) to 18.60 (14.95: 35.70 μg/ml; Figure 5B). The proportion of patients who achieved DAS28-ESR remission or low disease activity increased from 8.3% (2 of 24) and 16.7% (4 of 24) to 70.0% (14 of 20) and 80.0% (16 of 20) at Week 24, respectively.

In contrast, dosing intervals were changed to q3w for 26 patients (mean ± SD body weight 51.5 ± 10.6 kg) who agreed

to this change after achieving DAS28-ESR remission; 11.5% of these patients (3 of 26) weighed ≥ 60 kg, and 92.3% (24 of 26) had serum TCZ concentrations > 1 μg/ml just before the TCZ q3w treatment period. Before extension of the interval, the proportion of patients who achieved DAS28-ESR remission or low disease activity was 88.5% (23 of 26) and 96.2% (25 of 26), respectively. The DAS28-ESR remission or low disease activity achievement was 78.3% (18 of 23) and 95.7% (22 of 23) at 24 weeks after extension of the interval (TCZ-SC-mono q3w), respectively. CRP level in all patients was maintained below the institutional normal range. The mean concentration of TCZ was maintained until 12 weeks after q3w extension of the TCZ-SC injection interval. From Week 12 to Week 24 after extension, the median (Q1:Q3) concentration of TCZ decreased from 12.35 (6.36:24.20) μg/ml to 0.19 (BLQ 2.56 μg/ml), but DAS28-ESR was maintained (Figure 5C-D).

Of the 24 patients with a reduced dosing interval (TCZ-SC-mono qw), 22 patients had 82 AE (414.8 events per 100 PY), a rate comparable to that with a normal dosing interval of TCZ-SC-mono q2w (538.0 events per 100 PY). Four SAE were observed in the patients who received
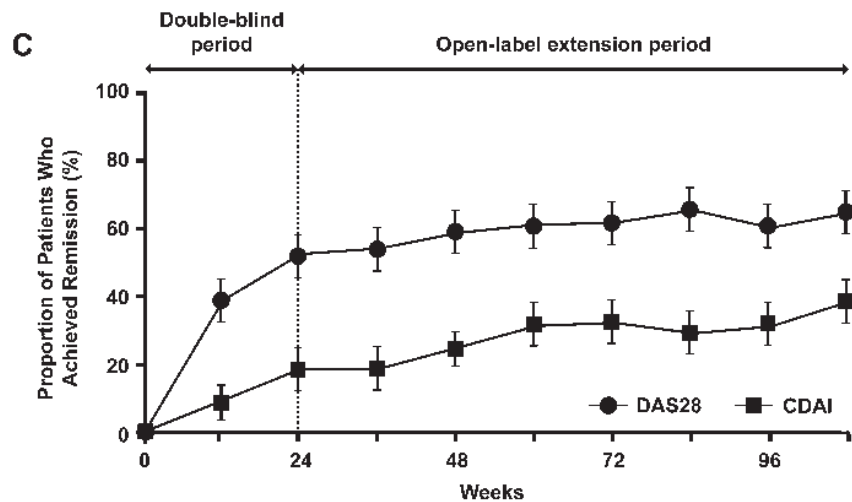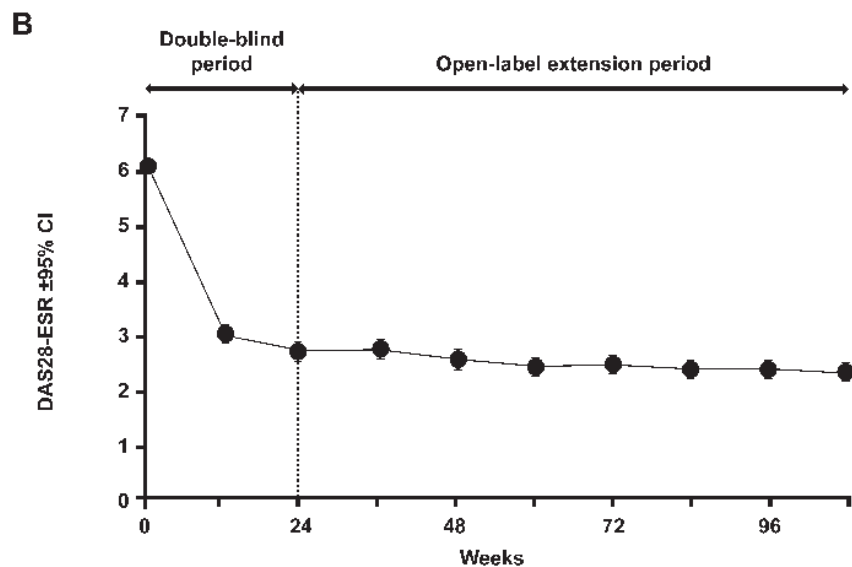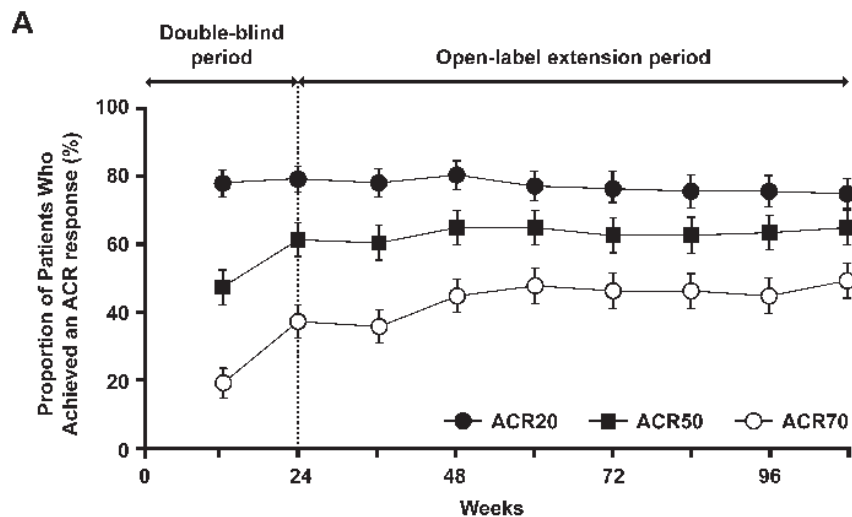
Figure 4. Maintenance of clinical response during longterm treatment with subcutaneous tocilizumab monotherapy. A. Proportions of patients who achieved an American College of Rheumatology (ACR) response rate of 20% (ACR20), 50% (ACR50), and 70% (ACR70). B. Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28-ESR). C. Proportions of patients who achieved clinical remission [DAS28-ESR < 2.6 and Clinical Disease Activity Index (CDAI) ≤ 2.8]. For missing data, nonresponder imputation was applied to response data (ACR20/50/70), DAS28 remission, and CDAI remission, while last observation carried forward was applied to continuous data (DAS28). Data are presented with 95% CI. Both double-blind (Day 1 to Week 24) and longterm extension (weeks 24–108) data are presented.
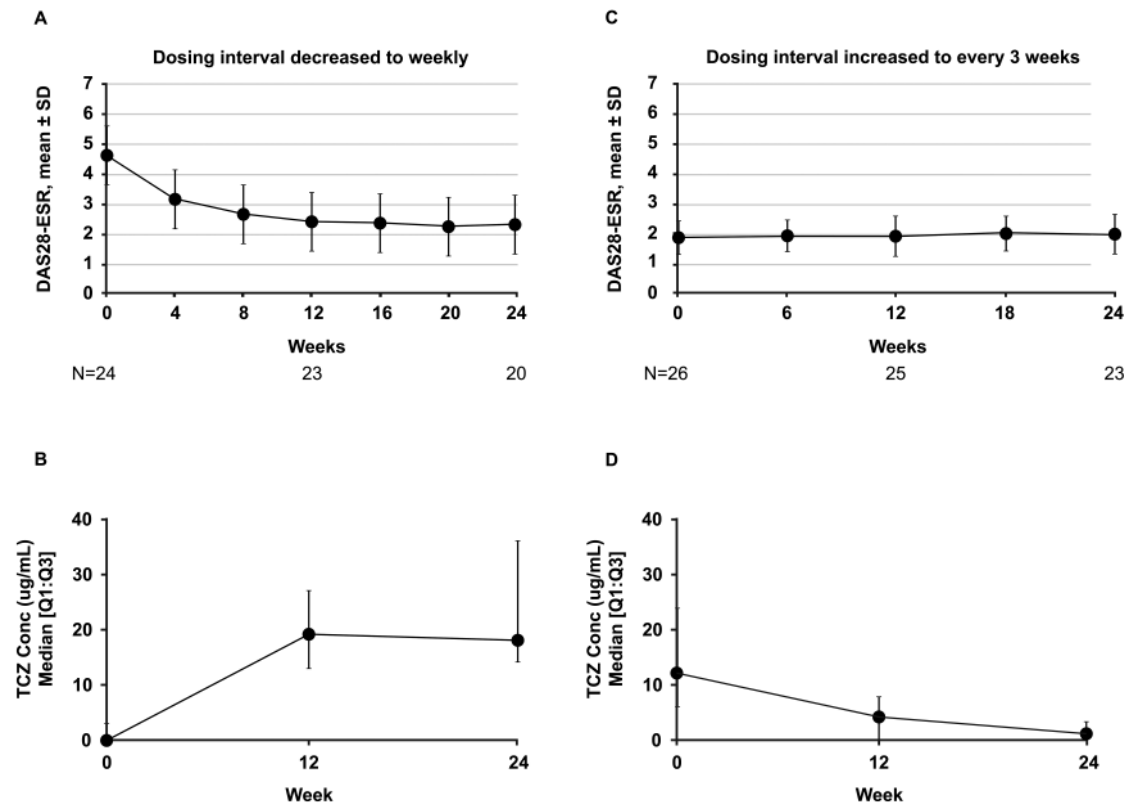
Figure 5. Mean 28-joint Disease Activity Score (DAS28-ESR) and the serum concentration (Conc) of tocilizumab (TCZ) observed after changing the dosing interval to weekly (panels A, B) in inadequate response to subcutaneous TCZ monotherapy every 2 weeks (TCZ-SC-mono q2w) or every 3 weeks (panels C, D) after achieving remission by TCZ-SC-mono q2w. Reasons for the patients' withdrawal from interval shortening were adverse event (n = 1), low efficacy (n = 1), and other (n = 2). DAS28 are expressed as mean ± SD and TCZ concentrations are expressed as the median with the first and third quartile. ESR: erythrocyte sedimentation rate.

TCZ-SC-mono qw. After the dosing interval was decreased from TCZ-SC-mono q2w to qw, the proportion of patients with AE with increased triglycerides or ALT or decreased platelets or neutrophils did not increase.

DISCUSSION

The OLE period of the MUSASHI study evaluated the longterm safety and efficacy of TCZ-SC-mono 162 mg q2w in Japanese patients with RA. These results confirmed our original findings at 24 weeks and demonstrated that TCZ-SC-mono provided a sustained favorable safety and efficacy profile. The safety profile of TCZ-SC-mono was observed in previous studies of TCZ-IV and was associated with a risk/benefit ratio that supports its use in patients with RA[14,19,20]. The proportions of patients who achieved an ACR20/50/70 response, low disease activity (DAS28-ESR ≤ 3.2), or remission (DAS28-ESR < 2.6) at Week 24 were maintained over the 108 weeks. Retention rates were similar to those seen in longterm studies of TCZ-IV[19,20].

The longterm safety profile of TCZ-SC-mono was determined during the 108 weeks of our study. The treatment was generally well tolerated, and the associated AE profile was consistent with the known and well-established safety profile of TCZ. Although the short-term safety profiles of TCZ-SC-mono and TCZ-IV-mono were similar, there is no direct comparison of the longterm safety profiles of TCZ-SC-mono and TCZ-IV-mono. Because half the patients received TCZ-IV-mono for 24 weeks and then switched to TCZ-SC-mono for 84 weeks, we can only indirectly compare the longterm safety of TCZ-SC-mono and TCZ-IV-mono. In comparing the TCZ-SC-mono data from our study to the cumulative safety data from TCZ-IV phase III trials[20], we saw no additional concerns about TCZ-SC-mono. Future direct comparison of longterm safety of TCZ-SC-mono and TCZ-IV-mono will be necessary.

Maintenance of longterm efficacy is a key consideration in the management of RA. From Week 24 to Week 108, there was a gradual increase in the proportion of patients who achieved an ACR20/50/70 response, an improvement of category in ACR response, and a clinical response as evaluated by DAS28-ESR. Overall, after 108 weeks of exposure, there was no attenuation of the therapeutic

response. In our study, the efficacy of TCZ-SC-mono was analyzed by nonresponder imputation or LOCF method because most patients had discontinued owing to an insufficient therapeutic response. However, fewer than 5% of patients discontinued because of an insufficient response. No clinical intolerance during longterm administration of TCZ-SC-mono was observed.

We evaluated adjustment of the administration interval of TCZ-SC in various situations in a limited number of patients (open-label setting). Previous studies had demonstrated that maintenance of serum trough concentration of TCZ is important for sufficient maintenance of efficacy[18]. Shortening of the administration interval (qw administration of TCZ-SC) was evaluated in patients with inadequate response to TCZ-SC-mono q2w. Shortening of the TCZ-SC-mono q2w dosing interval to qw improved DAS28-ESR and increased the proportion of patients who achieved clinical remission. In most of these patients, TCZ-SC-mono qw enhanced the efficacy with an increased serum TCZ concentration, suggesting that inadequate clinical response was due to insufficient maintenance of serum TCZ concentrations, and that shortening the dosing interval to qw would be an effective solution for patients who still have high disease activity after receiving TCZ-SC-mono q2w. Extension of the administration interval (q3w administration of TCZ-SC) was evaluated in patients who achieved clinical remission by TCZ-SC-mono q2w. In these patients, TCZ-SC-mono q3w maintained efficacy without CRP elevation for ≥ 6 months. These results suggest that extension of the administration interval may be possible in good responders to TCZ. Further studies will help validate the results that were shown in this small patient population.

The reasons for insufficient response to TCZ-SC have not been thoroughly elucidated. The main cause seems to be lower serum concentration of TCZ. Because TCZ-SC-mono was administered as a single dose regardless of body weight, low efficacy may have occurred in patients with higher body weight and/or with higher BMI; they received a relatively lower dosage. As previously reported for the MUSASHI study, the TCZ mean serum trough concentrations were lower in patients with high BMI, and the effectiveness of TCZ-SC-mono may be lower in patients with high BMI[16]. In other reports about patients with RA, a high BMI has been associated with decreased clinical responses to treatments including biologics[21,22,23]. In addition, the BREVACTA study[24] evaluated the effectiveness of a biweekly dosing interval for TCZ-SC combined with MTX, as stratified by body weight. Those results[16,24] suggested that shortening of the TCZ-SC treatment interval may be a good option to improve disease activity in patients with higher body weight. Future studies will be necessary to uncover the reasons for the insufficient response to TCZ-SC-mono, effect of dosing interval shortening, and the relation to the serum trough concentration, because our present study was small.

In 23 of 26 patients who achieved remission, efficacy was maintained after extension of the injection interval (q3w). Although the concentration of TCZ was decreased, the small amount of TCZ may have been enough to neutralize IL-6 function in patients who achieved remission because IL-6 production was decreased. The concentration of TCZ was decreased from 12 weeks after the interval extension through 36 weeks (data not shown). Therefore, some patients for whom the dosing interval is changed to q3w may need to return to the q2w dosing interval.

A limitation of this study is that the design had a double-blind period with patients receiving TCZ-IV-mono or TCZ-SC-mono followed by an OLE period of patients only receiving TCZ-SC-mono. Therefore, in half of patients who were enrolled from TCZ-IV after 24 weeks, the safety and efficacy of TCZ-SC-mono were not assessed for the entire 108 weeks. However, there were no differences in the efficacy and safety between TCZ-IV-mono and TCZ-SC-mono at Week 24[16] in the double-blind period, nor any differences in efficacy and safety between TCZ-IV-mono and TCZ-SC- mono at Week 108 in our study. Additional longterm data from studies with TCZ-SC-mono will confirm the efficacy and safety observed in our study and will provide further information about the longterm risk/benefit ratio.

The safety and efficacy results of this 108-week longterm extension study in Japanese patients with RA are consistent with those in previously published 24-week TCZ-SC-mono studies. It was determined that TCZ-SC-mono demonstrated a favorable risk benefit profile in this cohort of patients because it was well tolerated and the therapeutic responses over time were not attenuated.

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APPENDIX.

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