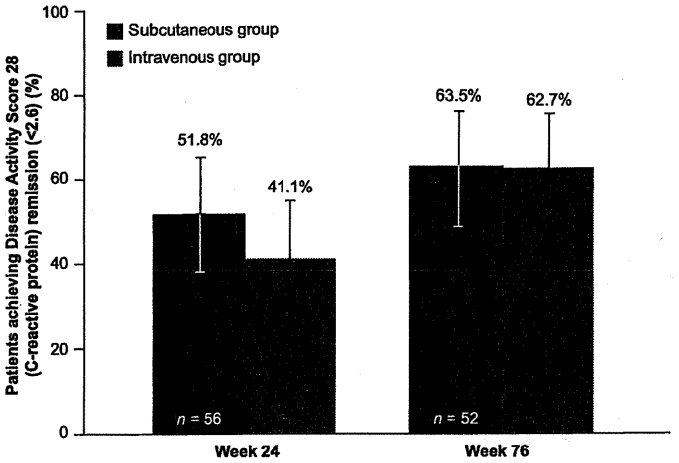


Figure 3. DAS28 (CRP) remission (<2.6) rates at Weeks 24 and 76 (Weeks 24–76)[a]. Error bars represent 95% CIs. [a]As-observed analysis.

groups (Figures 2–4). At Day 533 (Week 76), ACR 20, 50, and 70 response rates were 94.2, 78.8, and 57.7% in the SC group, and 96.1, 90.2, and 60.8% in the IV group, respectively (Figure 2).

DAS28 (CRP) <2.6 rates at Day 533 (Week 76) were 63.5% and 62.7% in the SC and IV groups, respectively (Figure 3). The mean (95% CI) changes from baseline in DAS28 (CRP) at Day 169 (Week 24) and Day 533 (Week 76) were −2.91 (−3.17, −2.65) and −3.27 (−3.58, −2.97) in the SC group, and −2.89 (−3.23, −2.54) and −3.49 (−3.82, −3.17) in the IV group, respectively. The percentages (95% CI) of patients with low disease activity at Day 169 (Week 24) and Day 533 (Week 76) were 69.6% (55.9, 81.2) and 86.5% (74.2, 94.4) in the SC group, and 67.9% (54.0, 79.7) and 82.4% (69.1, 91.6) in the IV group, respectively.

At Day 533 (Week 76), HAQ-DI response rates were 78.8% in the SC group and 60.8% in the IV group (Figure 4). Mean (95% CI) changes in HAQ-DI score from baseline at Day 169 (Week 24) and Day 533 (Week 76) were −0.60 (−0.74, −0.47) and −0.71 (−0.87, −0.55) in the SC group, and −0.63 (−0.78, −0.49) and −0.71 (−0.89, −0.52) in the IV group, respectively.

At baseline, 48 subjects in the SC group and 47 subjects in the IV group tested positive for RF (defined as RF>20 U/mL). Of these patients, conversion to seronegativity for RF was confirmed on Day 533 (Week 76) in 7 (14.6%) patients in the SC group and 4 (8.5%) patients in the IV group. Of the 7 patients in the SC group and 8 patients in the IV group who were RF negative at baseline, 1 subject in the IV group converted to seropositivity for RF on Day 533 (Week 76).

Results in patients with low body weight (≤ 50 kg)

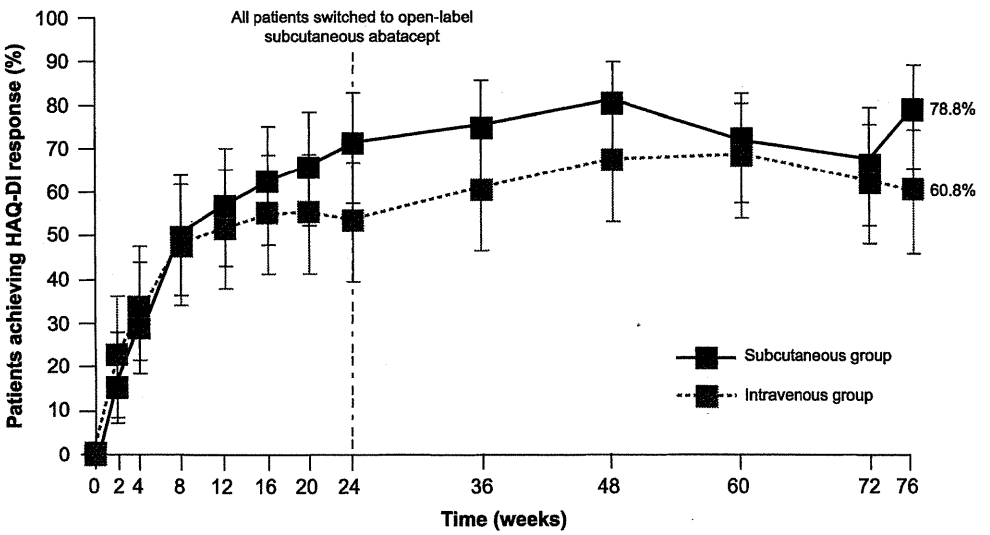
A total of 41 patients in the LTE period had a body weight ≤ 50 kg at baseline, and 2 patients in this subgroup discontinued from the LTE period (patient relocation and AE). During the 1-year LTE period, 23/41 (56.1%) patients with body weight ≤ 50 kg switched from weekly dosing of 125-mg abatacept to biweekly dosing; 15 patients were from the IV group and 8 were from the SC group. Of the 23 patients who switched to biweekly dosing of abatacept, 3 patients had a clinically meaningful increase in DAS28 (CRP) of ≥ 0.6 but did not switch back to weekly dosing, and 7 patients switched back to weekly dosing based on the investigator's judgment. The efficacy of abatacept (measured by DAS28 [CRP]) was maintained during the LTE period in the 18 patients with body weight ≤ 50 kg who did not switch to biweekly dosing. Temporary clinically meaningful increases in DAS28 (CRP) of ≥ 0.6 occurred in 3/18 patients with body weight ≤ 50 kg who did not switch to biweekly dosing; these increases in DAS28 (CRP) were normalized within 2 visits.

Discussion

The present study assessed the long-term safety and efficacy of weekly SC abatacept plus MTX in Japanese patients who were MTX inadequate responders in an LTE of the 24-week, double-blind ACQUIRE bridging study. Treatment with SC abatacept over 1 year in the LTE was associated with high patient retention; the majority of patients (92.9% in the SC abatacept group and 91.1% in the IV abatacept group) completed the LTE and there were only three discontinuations, all due to AEs. This high patient retention reduces selection bias due to patient attrition. Overall, the efficacy and safety profile of SC abatacept in Japanese patients was consistent with that observed in the global population [4–7,8].

No new abatacept safety signals were identified, and the safety profile of SC abatacept in the LTE was consistent with findings in the double-blind period [13], as well as with post-marketing surveillance data in Japanese patients [9]. During the LTE, rates of discontinuation owing to AEs and SAEs were low (0.9 and 2.7%, respectively). SC administration of biologics can be associated with injection-site reactions and injection-site pain [18,19]; however, there was a low incidence of local injection-site reactions in this study (1.8%). Long-term exposure to abatacept did not appear to result in an increased incidence of safety events, a finding that was consistent with safety results from an integrated analysis of five clinical trials involving SC abatacept, with patient exposure of up to 4.5 years [20,21].

Figure 4. HAQ-DI response rates during the double-blind period (Weeks 0–24) and the open-label LTE period (Weeks 24–76)[a]. Error bars represent 95% CIs. [a]As-observed analysis.



Biologic therapies have the potential to elicit an immune response, and the development of immunogenicity could reduce clinical response to abatacept in patients with RA [22]. In agreement with previous findings, a low number of patients had an immune response to abatacept (3.6% of patients, in both the SC and IV abatacept groups) [6].

Abatacept serum trough concentrations were maintained through continuous long-term therapy with weekly SC dosing of abatacept 125 mg, but were found to be higher in patients with body weight < 60 kg versus ≥ 60 kg. Peak serum abatacept concentrations (C_{max}) in the IV and SC groups ($n = 29$ and $n = 30$, respectively) during the 24-week, double-blind period were 277.4 and 42.6 μg/mL, respectively [13]. The C_{max} of SC abatacept (125 mg/week) in the LTE was not obtained in this study, as blood samples were collected just prior to SC abatacept administration and not at the necessary time points required to calculate the C_{max}.

ACR 20, 50, and 70 response rates; DAS28 (CRP) remission rates; and HAQ-DI response rates were similar in the SC and IV groups (as shown by overlapping 95% CIs) and were maintained from the end of the double-blind period to the end of the LTE period. SC abatacept was highly effective in achieving both clinical and functional improvements, even with a lower mean dose of concomitant MTX compared with international clinical trials (this may be due to the lower body weight of patients in this study) [4,6,7].

SC abatacept was injected by an investigator at the site in the double-blind period, and was self-injected by a patient or caregiver in the LTE period. After the introduction of self-injection to the study, the efficacy achieved in the double-blind period was maintained during the LTE period, and there were no new safety signals related to self-injection. These findings indicate that the self-administration of SC abatacept was a viable alternative to IV administration in Japanese patients with RA and inadequate response to MTX. Further studies are required to better understand the long-term efficacy, safety, and adherence to abatacept in a real-world setting in Japan.

A limited number of patients with body weight ≤ 50 kg switched from weekly to biweekly dosing in the LTE period (23/41 patients), and 10 patients who switched to biweekly dosing showed a clinically meaningful increase in DAS28 (CRP). Limited conclusions can be drawn from the data set; however, there is a suggestion that biweekly dosing of 125-mg SC abatacept may be inadequate to maintain efficacy in Japanese patients with RA and a body weight of ≤ 50 kg.

The safety and efficacy of SC abatacept beyond the duration of the LTE period (76 weeks of abatacept in total) is unknown in Japanese patients with RA. For chronic diseases such as RA, longer term safety data are important. Radiographic progression was not evaluated in this study.

In conclusion, the safety profile of SC abatacept during the LTE period was similar to that reported during the double-blind period. There were no new safety signals. The rate of immunogenicity was low in the LTE period. Immunogenicity did not appear to affect the safety, pharmacokinetics, or efficacy of abatacept. Rates of immunogenicity for SC abatacept in the LTE period (on-treatment [1 year] and post-treatment [6 months]) were similar to those historically found with SC abatacept. Improvements in RA signs and symptoms and physical function that were achieved in 6 months with IV or SC abatacept were maintained with SC abatacept through an additional 1-year period. The consistent long-term safety and maintained clinical efficacy support the use of SC abatacept as a treatment option for Japanese patients with RA who are MTX inadequate responders. The self-injection of SC abatacept was accepted and well controlled in Japanese patients with RA and was not associated with additional safety events.

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Conflicts of interest

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Original article

Biologic-free remission of established rheumatoid arthritis after discontinuation of abatacept: a prospective, multicentre, observational study in Japan

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Abstract

Objective. The aim of this study was to determine whether biologic-free remission of RA is possible with discontinuation of abatacept.

Methods. Japanese RA patients in 28-joint DAS with CRP (DAS28-CRP) remission (<2.3) after >2 years of abatacept treatment in a phase II study and its long-term extension entered this 52 week, multicentre, non-blinded, prospective, observational study. At enrolment, the patients were offered the option to continue abatacept or not. The primary endpoint was the proportion of patients who remained biologic-free at 52 weeks after discontinuation. Clinical, functional and structural outcomes were compared between those who continued and those who discontinued abatacept.

Results. Of 51 patients enrolled, 34 discontinued and 17 continued abatacept treatment. After 52 weeks, 22 of the 34 patients (64.7%) remained biologic-free. Compared with the continuation group, the discontinuation group had a similar remission rate (41.2% *vs* 64.7%, $P=0.144$) although they had a significantly higher mean DAS28-CRP score at week 52 (2.9 *vs* 2.0, $P=0.012$). The two groups were also similar with regard to mean HAQ Disability Index (HAQ-DI) score (0.6 for both, $P=0.920$), mean change in total Sharp score (ΔTSS; 0.80 *vs* 0.32, $P=0.374$) and proportion of patients in radiographic remission ($\Delta TSS \leqslant 0.5$) at the endpoint (64.3% *vs* 70.6%, $P=0.752$). Those attaining DAS28-CRP <2.3 or <2.7 without abatacept at the endpoint had significantly lower HAQ-DI score and/or CRP at enrolment. Non-serious adverse events occurred in three patients who continued or resumed abatacept.

Conclusion. Biologic-free remission of RA is possible in some patients after attaining clinical remission with abatacept. Lower baseline HAQ-DI or CRP may predict maintenance of remission or low disease activity after discontinuation of abatacept.

Trial registration: UMIN Clinical Trials Registry, http://www.umin.ac.jp/ctr/ (UMIN000004137).

Key words: rheumatoid arthritis, abatacept, biologic-free remission, observational study.

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Introduction

RA is a systemic inflammatory disease characterized by polyarthritis and progressive joint destruction. In RA, synovial monocyte-/macrophage-like cells and dendritic cells serve as antigen-presenting cells (APCs) due to their expression of antigen–MHC class II complexes and co-stimulatory molecules such as CD80 and CD86 [1]. Activated $CD4^+$ T cells expressing CD28 significantly infiltrate into the synovial membrane of affected joints and exacerbate synovitis and joint destruction by secreting inflammatory cytokines and activating synovial cells and osteoclasts [2–4]. The activation of $CD4^+$ T cells is therefore an important stage in the development of rheumatic synovitis, with the CD28-mediated co-stimulatory signal being required for full T cell activation and playing a major role in the immunopathological process of RA.

Abatacept is a genetically engineered humanized fusion protein consisting of the extracellular domain of human cytotoxic T lymphocyte-associated molecule 4 (CTLA-4) connected to a modified Fc region (hinge-CH2-CH3 domain) of human immunoglobulin G-1. Abatacept is a novel anti-rheumatic drug that acts by modulating the activation of naive T cells through the competitive binding of co-stimulation molecules expressed on APCs (CD80 and CD86) and blockade of $CD4^+$ T cell co-stimulation via CD28 [5].

Abatacept has been reported to control disease activity, prevent or delay joint destruction and improve quality of life [6–12]. Further, abatacept exhibits similar efficacy in Japanese MTX-intolerant patients with active RA, achieving clinical remission [28-joint DAS with CRP (DAS28-CRP) <2.6] in 24.6% of patients after 24 weeks [7]. Due to the high cost of biologic DMARDs and concerns regarding their long-term safety, the potential for biologic-free remission has been identified as an issue for further investigation [13, 14]. No previous studies have addressed this potential therapeutic application of abatacept despite evidence of its ability to suppress $CD4^+$ T cell activation in autoimmune diseases such as RA.

Thus we conducted the present study in Japanese RA patients who had completed a phase II study of abatacept [7] and its long-term extension in order to determine whether clinical remission attained with the drug was sustained following its discontinuation.

Methods

Before enrolment in this study, written informed consent was obtained from each participating patient according to the Declaration of Helsinki (updated 2008). Prior to the start of the study, the institutional review board of each centre reviewed and approved the study.

Study design and patients

In the previous phase II study [7], 194 Japanese RA patients received double-blind treatment with abatacept or placebo for 24 weeks in addition to prior MTX therapy and 174 of them entered its long-term extension and received open-label abatacept for a mean of 37.7 months (range 3.6–45.1). Those who had completed the phase II study [7] and its long-term extension were eligible for this multicentre, non-blinded, prospective, observational study if they were in clinical remission (DAS28-CRP <2.3) and not receiving any other biologic therapy at enrolment. Inclusion criteria for the phase II study were age $\geqslant$20 years; fulfilment of the 1987 ACR criteria for the diagnosis of RA with a functional status of class I, II or III; previous treatment with MTX at 6–8 mg/week for at least 12 weeks and one or more of the following: $\geqslant$10 swollen joints (66-joint count), $\geqslant$12 tender joints (68-joint count) or CRP $\geqslant$ 1.0 mg/dl.

Procedures

At enrolment, patients were offered the option to continue or discontinue abatacept during the study. Those who discontinued abatacept treatment (discontinuation group) were periodically followed up for disease activity. Those who chose to continue abatacept (continuation group) were treated with the drug every 4 weeks at its approved dosage and received similar follow-up. Abatacept could be restarted at a fixed dose of 10 mg/kg in response to a sign of relapse (DAS28-CRP >2.7 at two consecutive visits) or at the investigator's discretion. If restarted after an interval of $\leqslant$12 weeks, administration was every 4 weeks, whereas if started after an interval of >12 weeks, the first two doses were administered every 2 weeks and subsequent doses every 4 weeks.

During the study, dose modifications of non-biologic DMARDs (e.g. MTX) and glucocorticoids were allowed at the investigator's discretion. Concomitant administration of NSAIDs was permitted, but that of biologic agents was not.

Efficacy outcomes

The primary outcome measure of this study was the proportion of patients who remained biologic-free at 52 weeks after discontinuation of abatacept. Secondary and tertiary outcomes were efficacy and safety, respectively.

RA disease activity was assessed in terms of DAS28-CRP and DAS28-ESR at weeks 0, 4, 12, 24, 36 and 52. If a patient resumed abatacept treatment, this assessment was made at the time of resumption as well as after 12 and 24 weeks.

In accordance with DAS28-CRP scores, disease activity was classified as remission (<2.3), low ($\leqslant$2.3 to <2.7), moderate ($\leqslant$2.7 to <4.1) or high ($\geqslant$4.1) [15]. The proportion of patients in each disease activity class at each specified time and the proportion of patients in DAS28-CRP remission (<2.3) at week 52 were calculated.

Similarly, disease activity was classified by DAS28-ESR as remission (<2.6), low (LDA; $\leqslant$2.6 to <3.2), medium (MDA; $\leqslant$3.2 to <5.1) or high (HAD; $\geqslant$5.1) [15]. To assess disease impact on a patient's level of functional ability, the HAQ Disability Index (HAQ-DI) was determined at weeks 0, 4, 12, 24, 36 and 52.

Radiographic progression of joint destruction was assessed in terms of van der Heijde-modified total Sharp score (mTSS) [16, 17] at weeks 0 and 52 or at the time of withdrawal from the study, where possible. Changes from baseline in TSS (ΔTSS), joint erosion (ΔJE) score and joint space narrowing (ΔJSN) score at week 52 were determined. The proportion of patients with no (ΔTSS $\leqslant$ 0), little (ΔTSS $\leqslant$ 0.5; defined as radiographic remission) and rapid radiographic progression (RRP; ΔTSS $\geqslant$5) [18] was calculated.

Time to abatacept treatment resumption

The mean time to resumption of abatacept treatment was determined in the discontinuation group.

Safety

Patients remaining on abatacept were monitored for adverse events (AEs) throughout the study period. In the discontinuation group, AE monitoring was done only if and after abatacept was resumed following relapse. To investigate the relationship between the immunogenicity of abatacept and its tolerability, the anti-abatacept antibody titre in blood was measured at the time of discontinuation, time of resumption and 24 weeks after resumption of abatacept, if applicable.

Statistical analysis

Missing data were imputed by linear extrapolation (radiographic assessments) or last observation carried forward (LOCF) (other efficacy variables). Continuous metric data were summarized in terms of descriptive statistics and were expressed as the mean (S.D.). Data between the two groups were compared using Wilcoxon's rank sum test (demographic and baseline characteristics, DAS28, HAQ-DI, ΔTSS, ΔJE and ΔJSN) or Fisher's exact test (proportion of patients in DAS28-CRP remission at week 52 and the proportions of patients with ΔTSS $\leqslant$0, $\leqslant$0.5 and $\geqslant$5).

Results

Patient disposition and baseline characteristics

Fifty-one consenting patients were enrolled and chose to either discontinue ($n=34$) or continue ($n=17$) abatacept. Nine of the 34 patients from the discontinuation group restarted abatacept at the investigator's discretion ($n=8$) or due to relapse ($n=1$). Six patients from the discontinuation group (with an additional patient withdrawn after resumption) and two from the continuation group dropped out of the study, leaving a total of 28 and 15 patients, respectively. Nineteen patients from the discontinuation group remained biologic-free at week 52 (Fig. 1). The demographic and baseline characteristics of the 51 patients enrolled are summarized in Table 1. The two groups had comparable baseline characteristics, except for significantly shorter disease duration and significantly less joint damage in terms of JSN and TSS in those who discontinued abatacept at enrolment ($P<0.05$ for all comparisons).

Efficacy outcomes

Of the 34 patients who discontinued abatacept at enrolment, 22 patients from an intention-to-treat (ITT) analysis (64.7%) remained biologic-free after 52 weeks. While the mean DAS28-CRP score remained constant in the continuation group, it gradually increased over time in the discontinuation group, leading to a significant difference between the groups at week 52 (2.9 *vs* 2.0, $P=0.012$).

This was also true when the subgroup of discontinuing patients who remained in the study and never restarted

Fig. 1 Patient disposition

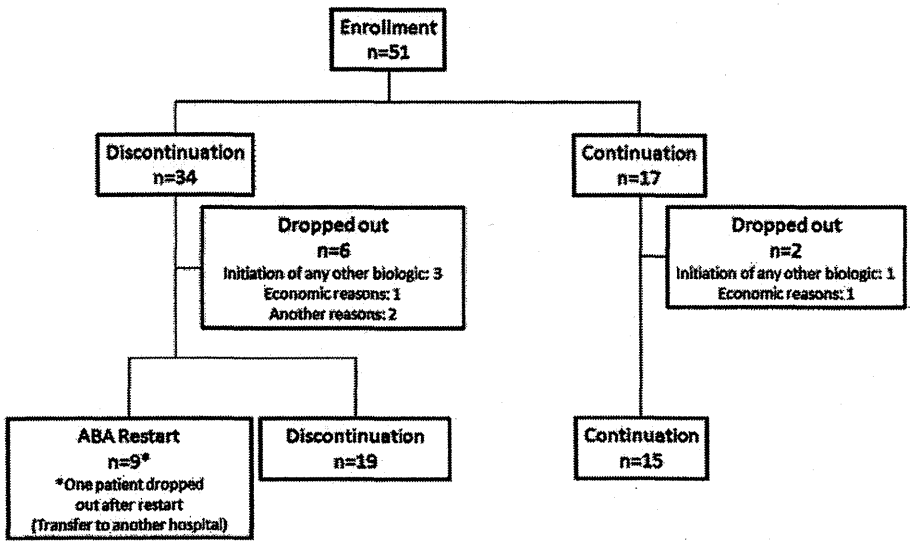


TABLE 1 Patient characteristics

	Discontinuation ($n=34$)	Continuation ($n=17$)	*P*-value
Age, mean (S.D.), years	56.9 (11.4)	60.9 (9.5)	0.195[a]
Male, *n* (%)	5 (14.7)	4 (23.5)	0.443[b]
Female, *n* (%)	29 (85.3)	13 (76.5)	
RA disease duration, mean (S.D.), years	9.6 (5.2)	15.3 (10.5)	0.018[a]
DAS28-CRP, mean (S.D.)	1.8 (0.4)	1.7 (0.5)	0.803[a]
Tender joint count (0–28), mean (S.D.)	0.3 (0.6)	0.1 (0.5)	0.788[a]
Swollen joint count (0–28), mean (S.D.)	0.5 (0.8)	0.6 (0.9)	0.429[a]
HAQ-DI, mean (S.D.)	0.5 (0.5)	0.5 (0.5)	0.356[a]
CRP, mean (S.D.), mg/dl	0.3 (0.5)	0.2 (0.2)	0.285[a]
ESR, mean (S.D.), mm/h	18.7 (9.5)	17.6 (8.5)	0.790[a]
DAS28-ESR, mean (S.D.)	2.4 (0.5)	2.3 (0.6)	0.705[a]
MMP-3, mean (S.D.), ng/ml	79.5 (63.3)[c]	75.3 (46.3)[d]	0.707[a]
RF, mean (S.D.), IU/ml	72.8 (128.5)[c]	50.7 (76.1)[e]	0.822[a]
RF positive, *n* (%)	14 (48.3)[c]	6 (60.0)[e]	0.394[b]
PGA (0–100 mm VAS), mean (S.D.)	12.7 (10.7)	17.4 (15.2)	0.363[a]
Erosion, mean (S.D.)	29.9 (37.9)[f]	62.0 (58.4)	0.015[a]
Joint space narrowing, mean (S.D.)	28.6 (27.2)[f]	55.5 (41.2)	0.020[a]
TSS (0–448), mean (S.D.)	58.5 (64.1)[f]	117.5 (97.7)	0.016[a]
Concomitant use of MTX, *n* (%)	19 (55.9)	12 (70.6)	1.000[a]
MTX dose, mean (S.D.), mg/week	6.7 (2.2)[g]	8.7 (2.3)[h]	0.211[a]
Concomitant use of PSL, *n* (%)	12 (35.3)	8 (47.1)	0.372[a]
PSL dose, mean (S.D.), mg/day	4.0 (2.8)[i]	3.9 (2.8)[j]	0.538[a]

PGA: patient's global assessment of disease activity; VAS: visual analogue scale; RF: rheumatoid factor; TSS: total Sharp score; PSL: prednisolone. [a]Wilcoxon's rank sum test; [b]Fisher's exact test; [c]$n=29$; [d]$n=14$; [e]$n=10$; [f]$n=28$; [g]$n=17$; [h]$n=12$; [i]$n=9$; [j]$n=8$.

abatacept ($n=19$) were compared with the continuing patients remaining in the study ($n=15$; 2.8 *vs* 2.1, $P=0.036$).

Fig. 2 shows the proportion of patients in each RA disease activity class at specified times. In the discontinuation group there was a tendency towards a decrease in the proportion of patients in DAS28-CRP remission and an increase in the proportion of those with HDA as follow-up progressed. At week 52 (LOCF), the proportion of patients in remission was 41.2% in the discontinuation group compared with 64.7% in the continuation group ($P=0.144$). Sixteen of the 17 continuing patients (94.1%) experienced no disease flare (DAS28-CRP < 2.7), while 20 of the 34 discontinuing patients (58.8%) were in remission or maintained LDA. Compared with the 14 patients who failed to do so, these 20 patients had significantly lower baseline HAQ-DI scores and CRP ($P=0.036$ and $P=0.048$, respectively). Of the 19 patients who went without abatacept for 52 weeks, 7 were in remission at the endpoint and 12 were not. These two subgroups had comparable baseline characteristics, except that more patients in remission than not in remission at the endpoint were in functional remission (HAQ-DI ⩽ 0.5) at enrolment (100% *vs* 41.7%, $P=0.016$). The mean time-averaged DAS28-CRP (TA-DAS28-CRP) [19, 20] was 1.9 (S.D. 0.4) for those who maintained LDA compared with 3.0 (S.D. 0.7) for those who failed to do so ($P<0.0001$).

In contrast to consistently low (<2.6) scores in the continuation group, the mean DAS28-ESR score in the discontinuation group increased slightly, from 2.4 at baseline to 2.7 at week 4, 3.1 at week 12, 3.3 at week 24, 3.5 at week 36 and 3.6 at week 52. According to the endpoint DAS28-ESR scores, 24.2% of the discontinuing *vs* 47.1% of the continuing patients were in remission, 30.3% *vs* 35.3% had LDA, 27.3% *vs* 17.6% had MDA and 18.2% *vs* 0% had HDA. The mean HAQ-DI scores for the two groups followed similar time courses and were 0.6 for both groups at week 52 ($P=0.920$; Fig. 3).

The TSS at weeks 0 and 52 was similar in the discontinuation and continuation groups, but the baseline TSS was higher for the continuation group (Fig. 4A). Mean ΔTSS (0.80 *vs* 0.32, $P=0.374$) and ΔJE (−0.02 *vs* 0.32, $P=0.466$) were similar for the two groups, while mean ΔJSN was significantly greater in the discontinuation group (0.82 *vs* 0, $P=0.035$; Fig. 4B). After correction by linear extrapolation, the proportion of patients in radiographic remission (ΔTSS ⩽ 0.5) was 64.3% in the discontinuation group compared with 70.6% in the continuation group ($P=0.752$; Fig. 4C). No radiographic progression was seen in 42.9% and 47.1% of patients, while RRP was seen in 14.3% and 0% of patients in the discontinuation and continuation groups, respectively (Fig. 4C). The four patients who showed RRP after discontinuation had significantly higher CRP at enrolment in this study and lower RF in the previous phase III study compared with the 24 patients who did not show RRP in this group ($P=0.034$ and $P=0.020$, respectively).

FIG. 2 Proportion of disease activity

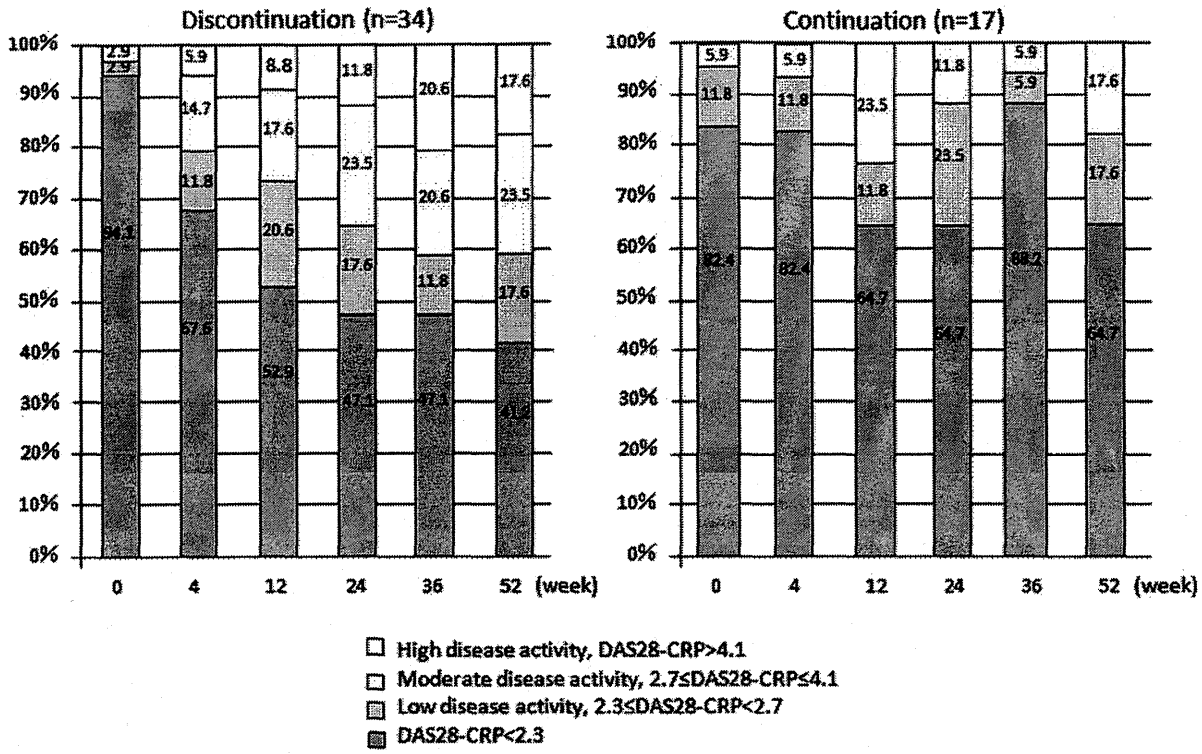
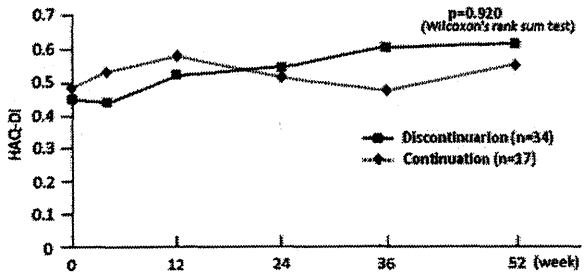


FIG. 3 Transition diagram of HAQ-DI



DI: Disability Index.

In the discontinuation group, 10 of the 14 patients in DAS28-CRP remission at week 52 were evaluable for ΔTSS, of whom 7 (70%) were in radiographic remission. In the continuation group, all 11 patients in DAS28-CRP remission at week 52 were evaluable for ΔTSS and 7 (63.6%) were in radiographic remission.

Resumption of abatacept treatment

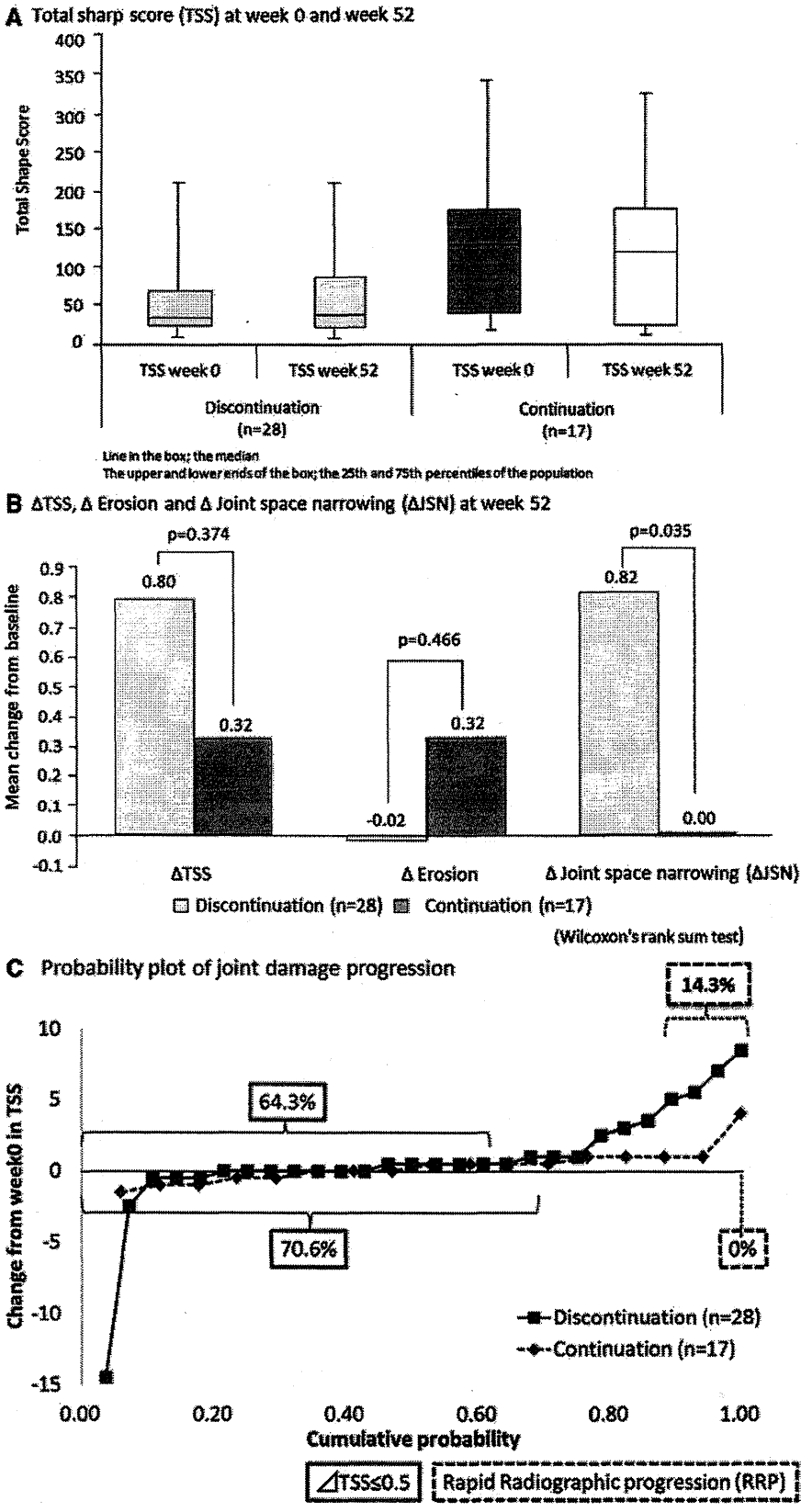
Nine patients resumed abatacept treatment after a mean interval of 149.6 days (S.D. 34.5). After resumption, the mean DAS28-CRP score steadily decreased, from 5.0 (S.D. 1.1) to 3.7 (S.D. 1.6) at 12 weeks and to 3.7 (S.D. 1.7) at 24 weeks, as was observed in the previous phase II/III study [from 4.8 (S.D. 0.8) at baseline to 3.0 (S.D. 0.9) at week 12 and to 2.8 (S.D. 0.9) at week 24; not significant by Wilcoxon's rank sum test].

In the previous study, time to remission in those who resumed ($n=9$) and did not resume ($n=25$) abatacept was similar ($P=0.643$; log rank test); clinical remission was achieved in 2 of 9 (22.2%) *vs* 13 of 25 (52.0%) patients at week 24 and in 88.9% *vs* 96.0% of patients at the endpoint, respectively. The two populations also had comparable demographic and baseline characteristics.

Safety

Non-serious AEs occurred in one patient who resumed abatacept (acute upper respiratory tract infection) and two patients who continued the drug (acute bronchitis in one and low back pain, cystitis, constipation, common cold and left scapulohumeral periarthritis in the second). No serious AEs were reported. Anti-abatacept antibody titre was measured in 26 of the 34 patients upon discontinuation of abatacept, as well as in 7 of 9 and 6 of 9 patients immediately and at 24 weeks after resumption. Positive titres were recorded in four patients (15.4%) upon discontinuation, in two patients (28.6%) immediately after resumption and in no patients at 24 weeks after resumption. Two of the four patients with positive titres upon discontinuation restarted abatacept. Both patients had positive titres again upon resumption, but not after 24 weeks. None of the patients with positive anti-abatacept antibody titre developed AEs or responded poorly to abatacept.

FIG. 4 Total Sharp score



Discussion

Accumulating evidence suggests that $CD4^+$ T cells play a key role in RA-associated inflammation [21–23], although the extent to which they contribute to this disease is not fully understood. Abatacept, which blocks a T cell co-stimulation pathway, has been shown to have favourable efficacy and tolerability profiles in Japanese and non-Japanese MTX-intolerant, TNFinhibitor-intolerant or MTX-naive [early (<2 years)] RA patients [7–12].

The ACR and European League Against Rheumatism treatment recommendations propose that remission or LDA should be the primary target for treatment of RA [24]. Combined therapy with currently available biologic and non-biologic DMARDs can help attain current treatment targets in the majority of RA patients. Nonetheless, the high costs of biologic agents have encouraged ongoing efforts to reduce the economic burden upon patients, including trials to discontinue biologic therapy in patients in sustained clinical remission. While existing data support the potential for biologic-free remission following intensive treatment with TNFinhibitors [25–28], definitive evidence for this potential following discontinuation of abatacept is limited. One study suggested that there was no further radiographic or MRI progression of joint destruction after discontinuation of abatacept in patients with undifferentiated inflammatory arthritis or very early RA [29]. Here we determined the potential of abatacept in promoting biologic-free remission in RA patients already in clinical remission.

At week 52, 64.7% of the patients who discontinued abatacept in an ITT population remained biologic-free (primary endpoint). In a drug-free follow-up of 102 RA patients (mean disease duration 5.9 years) who attained LDA with infliximab [25], 55% of the patients maintained LDA and 39 of the 83 patients (47%) who had achieved remission (DAS28 < 2.6) at enrolment remained in remission for 1 year. In a similar study for adalimumab [28], 14 of 22 patients (64%) maintained LDA (DAS28-CRP < 2.7) without the drug for 1 year. On comparison with these TNF inhibitors, abatacept seems to have a similar potential in the induction of biologic-free remission.

After discontinuation of abatacept, the mean DAS28-CRP score gradually increased and reached a level significantly higher than in the continuation group at week 52. This was also true when the mean endpoint DAS28-CRP score was compared between the 19 patients who went without abatacept and the 15 patients who continued the drug for 52 weeks. In the discontinuation group, the number of patients in DAS28-CRP remission decreased and the number of patients with HDA increased. HAQ-DI and CRP are two baseline parameters that were significantly different between those with ($n = 20$) and without ($n = 14$) LDA at week 52. In addition, HAQ-DI is the only baseline parameter that was significantly different between those in remission ($n = 7$) and those not in remission ($n = 12$) without abatacept at week 52. These findings suggest that the HAQ-DI or CRP immediately before discontinuation of abatacept may predict the probability of subsequent maintenance of remission or LDA. According to TA-DAS28-CRP data, those with LDA at the endpoint maintained LDA throughout the period of follow-up. Comparison between the discontinuation and continuation groups showed similar proportions of patients in clinical remission at week 52 and similar changes in the HAQ-DI over time, indicating that the effects of abatacept on clinical and functional outcomes are durable even after discontinuation.

In RA, joint destruction progresses over time, causing significant disability, which imposes an enormous social burden. Although the recently introduced biologic agents, including abatacept, can prevent or delay joint destruction in a proportion of patients, it is not known if they prevent disease relapse following discontinuation. In the present study, radiographic assessment of joint destruction showed no significant difference between those who discontinued and those who continued abatacept with regard to mean ΔTSS or the percentage of patients with ΔTSS $\leqslant 0$, $\leqslant 0.5$ or $\geqslant 5$. These data confirm that abatacept exerts a sustainable effect in preventing or delaying joint damage and thus keeps patients in radiographic remission even after discontinuation. These radiographic benefits of abatacept appear to be comparable to those of infliximab and adalimumab (in early RA), as evidenced by 67% [25] and 81% [27] of patients with LDA remaining in radiographic remission after discontinuation of those drugs.

As a proportion of RA patients have to suspend their biologic therapy for economic or other reasons, we also assessed the efficacy and safety of re-treatment with abatacept after relapse. Re-treatment with abatacept was effective in controlling disease activity but may be less effective than the initial treatment with abatacept, which was evaluated in the previous phase II study [7].

Abatacept was well tolerated after resumption and during extended use, with only non-serious AEs being reported in three patients. Regarding the immunogenicity of abatacept, two of the limited number of patients assessed were positive for anti-abatacept antibody at the resumption of treatment but were negative after 24 weeks. The disappearance of anti-abatacept antibody after resumption of abatacept treatment may reflect the immunomodulatory effect of the drug.

The present study has several limitations. First, this was an exploratory study about the possibility of biologic-free remission after attaining clinical remission with abatacept. This study had no hypothesis to be tested because no data were available about this possibility with any other biologic DMARDs when we planned this study. Second, this was a small, non-randomized, observational study. Only Japanese RA patients who had completed a phase II study of abatacept [7] and its long-term extension and were in DAS28-CRP remission (<2.3) were enrolled, and for ethical reasons they were offered the option to continue abatacept or not at enrolment. As an expected consequence, the two groups were not well matched at baseline; those who chose to discontinue the drug were at an earlier stage of RA and had less progressive joint damage. Therefore data comparing the two groups

should be interpreted cautiously. Third, we imputed missing data for non-radiographic efficacy variables using LOCF, a less favoured method than multiple imputation. This might introduce uncertainly about the reliability of the disease activity data and compromise their interpretation. Despite these limitations, the results are informative, as they indicate that the clinical remission achieved after abatacept treatment is potentially maintained following discontinuation of the drug in some of the patients, particularly in those who have also achieved a low HAQ-DI score and/or low CRP after the treatment. Given that the decision to continue or discontinue abatacept after attaining clinical remission was made by individual patients and their physicians, this finding will also be helpful for implementing the treat-to-target principle in RA practice.

Rheumatology key messages

- The effects of abatacept on clinical, functional and structural outcomes in RA continue after its discontinuation.
- Biologic-free remission of RA can be maintained after attaining sustained clinical remission with abatacept.
- Lower HAQ DI or CRP may predict maintenance of RA remission or low disease activity after discontinuation of abatacept.

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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, Akira Nomura and the MUSASHI Study Investigators

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

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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:
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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

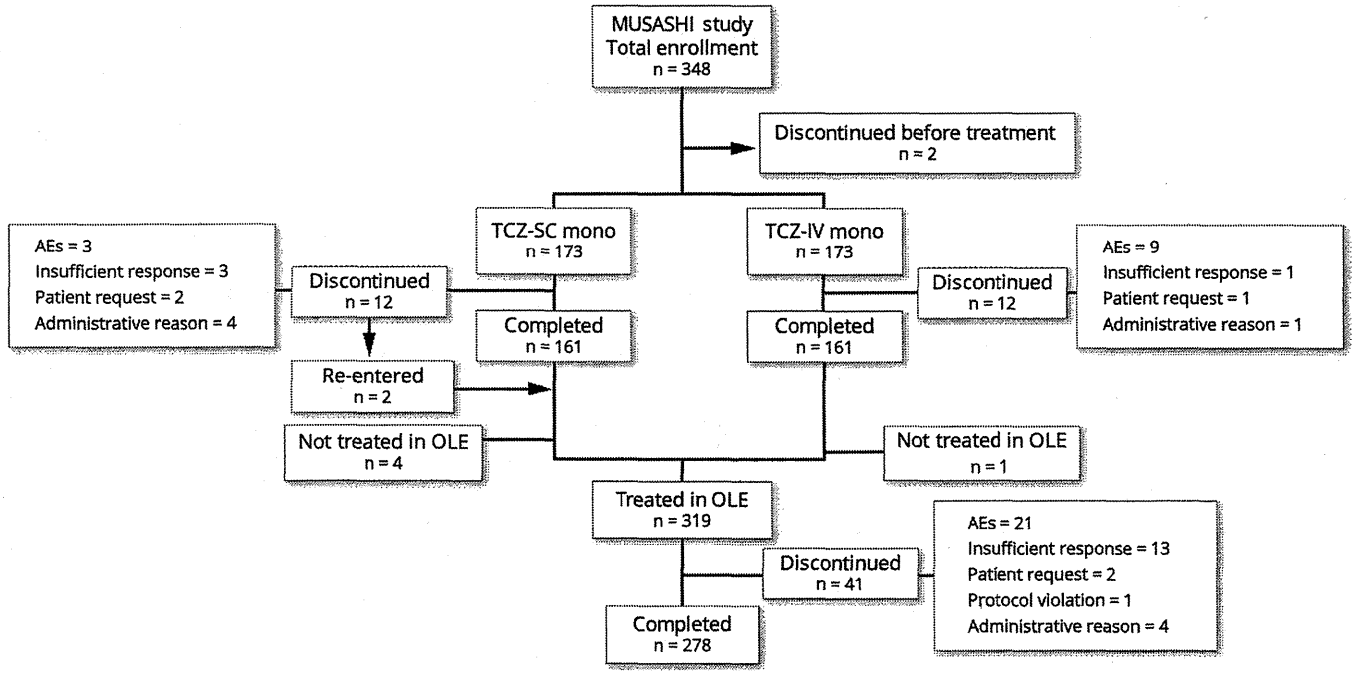

Figure 1. Patient disposition. AE: adverse event; OLE: open-label extension; TCZ-IV-mono: intravenous tocilizumab monotherapy; TCZ-SC-mono: subcutaneous TCZ monotherapy.

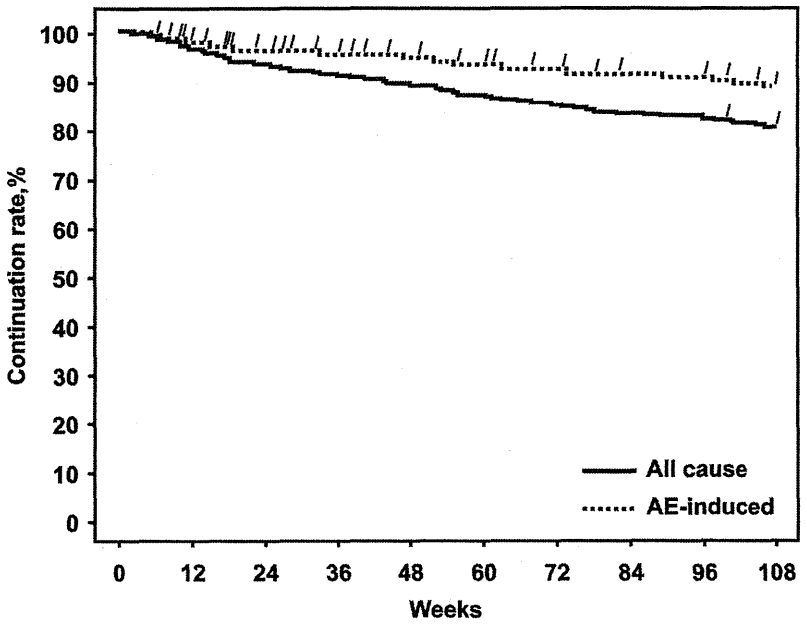

Figure 2. Kaplan-Meier plot of discontinuations over 108 weeks. AE: adverse events.

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.

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.

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 montherapy.

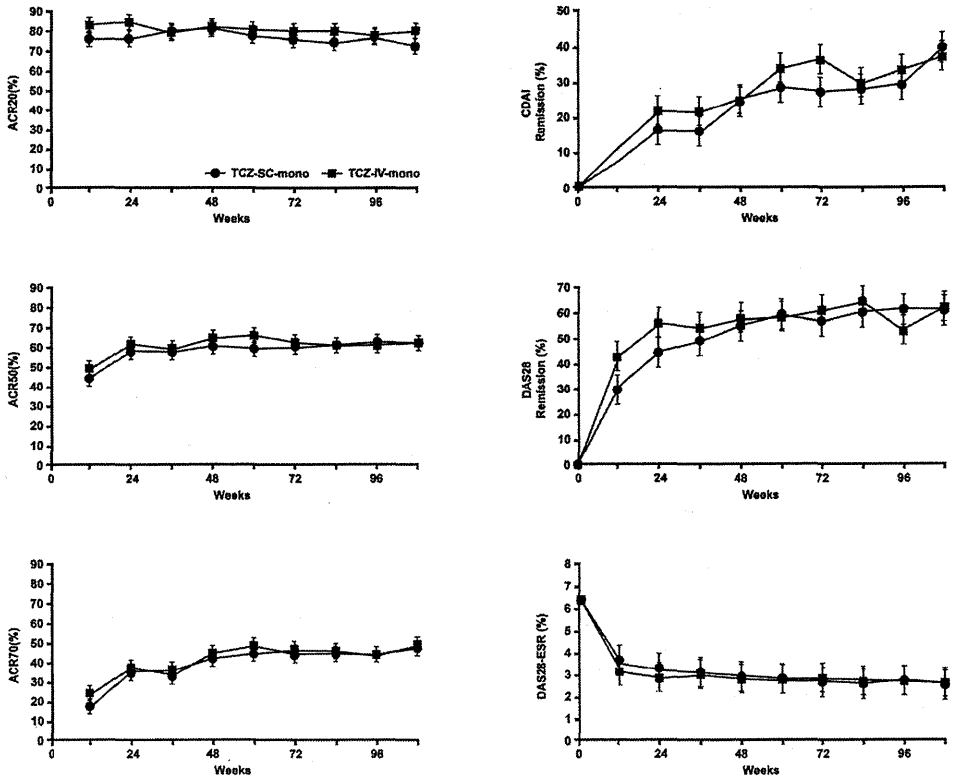

Figure 3. Efficacy of the open-label extension period (weeks 24–108) between patients who received TCZ-SC-mono or TCZ-IV-mono in the double-blind periods (weeks 0–24). American College of Rheumatology (ACR) response rate of 20% (ACR20), 50% (ACR50), and 70% (ACR70), Clinical Disease Activity Index (CDAI) 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