Pharmacokinetic and Pharmacodynamic Analysis of Subcutaneous Tocilizumab in Patients With Rheumatoid Arthritis From 2 Randomized, Controlled Trials: SUMMACTA and BREVACTA

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Abstract

Tocilizumab is a humanized anti–interleukin-6 receptor antibody for treating rheumatoid arthritis. Pharmacokinetic/pharmacodynamic analysis was performed on the 24-week double-blind parts of 2 randomized, controlled trials: SUMMACTA and BREVACTA. SUMMACTA compared subcutaneous tocilizumab 162 mg every week to intravenous tocilizumab 8 mg/kg every 4 weeks, whereas BREVACTA evaluated 162 mg subcutaneous tocilizumab every 2 weeks versus placebo. In addition to noncompartmental analysis, a 2-compartment population pharmacokinetic model, with first-order absorption (for subcutaneous) and linear and Michaelis–Menten elimination was used. Mean observed steady-state predose tocilizumab concentrations in week 24 were 40 and 7.4 μg/mL for subcutaneous every-week and every-2-week dosing, respectively, and 18 μg/mL for intravenous dosing. In the population PK model, body weight was an important covariate affecting clearance and volume of distribution. Mean $\pm$ SD population-predicted predose concentration for patients $\geq$100 kg was 23.0 $\pm$ 13.5 μg/mL for subcutaneous tocilizumab every week and 1.0 $\pm$ 1.6 μg/mL for every 2 weeks. Efficacy was lowest with subcutaneous every-2-week dosing in patients > 100 kg, reflecting lower exposure. The subcutaneous every-2-week regimen is not recommended for these patients. Pharmacodynamic responses were comparable for the every-week subcutaneous and every-4-week intravenous regimens and less pronounced with the every-2-week subcutaneous regimen. No trend was observed for increased adverse events with increasing tocilizumab exposure. The results of this analysis are consistent with the noninferiority of efficacy of the every-week subcutaneous regimen to the every-4-week intravenous regimen and the superiority of the every-2-week subcutaneous regimen to placebo. These results support the label recommendations for subcutaneous dosing of tocilizumab in rheumatoid arthritis patients.

Keywords

rheumatoid arthritis, tocilizumab, subcutaneous, pharmacokinetics

Biologic disease-modifying antirheumatic drugs (bDMARDs) are recommended for the treatment of patients with rheumatoid arthritis (RA) who do not respond to nonbiologic DMARDs (nbDMARDs), such as methotrexate, or as initial treatment in combination with methotrexate in patients with poor prognoses.[1,2] Currently available bDMARDs for the treatment of RA are administered either as intravenous infusion or subcutaneous injection.[3,4]

Tocilizumab (Actemra, RoActemra) is a recombinant humanized monoclonal antibody that binds to the interleukin-6 receptor (IL-6R), blocking IL-6 inflammatory signaling.[5,6] It is currently approved for the treatment of patients with RA who have had inadequate responses to DMARDs[7,8] or were not previously treated with methotrexate.[8] Tocilizumab is available as intravenous infusion and subcutaneous injection.

The route of administration may be an important factor influencing adherence to bDMARDs.[9] A subcutaneous formulation offers improved patient choice and potential for self-administration,[10,11] and many patients prefer subcutaneous over intravenous administration.[12,13] The subcutaneous formulation of tocilizumab provides patients with RA with an alternative and more convenient route of administration, which could be self-administered in a home setting, negating the requirement for and associated health care costs of intravenous access and frequent clinic visits.

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The safety and efficacy of subcutaneous tocilizumab in combination with background nbDMARDs have been demonstrated in 2 randomized, double-blind, controlled phase 3 trials, SUMMACTA and BRE-VACTA, which have been presented separately.[14,15] The 2 studies were designed to constitute a comprehensive strategy to bridge intravenous to subcutaneous dosing in the 2 main world regions, the European Union and the United States, where the approved intravenous tocilizumab starting doses are different. In European Union countries, the approved starting dose is 8 mg/kg every 4 weeks, which could be reduced to 4 mg/kg every 4 weeks to address safety concerns.[8] The US label, on the other hand, recommends a starting dose of 4 mg/kg every 4 weeks, followed by an increase to 8 mg/kg every 4 weeks based on clinical response. In the SUM-MACTA study, the efficacy and safety of tocilizumab 162 mg subcutaneously every week was compared with tocilizumab 8 mg/kg intravenously every 4 weeks, whereas in BREVACTA, tocilizumab 162 mg subcu-taneously every 2 weeks were tested against placebo. SUMMACTA showed safety and noninferior efficacy comparable to tocilizumab 162 mg subcutaneously every week compared with tocilizumab 8 mg/kg intra-venously every 4 weeks, whereas BREVACTA showed that tocilizumab 162 mg subcutaneously every 2 weeks was superior to placebo. The results of the 2 stud-ies were the basis for approval of the subcutaneous formulation and the dosing recommendations in the European Union and the United States.[7,8] Consistent with the respective intravenous labels, the approved starting dose for subcutaneous tocilizumab is 162 mg every week in the European Union, with a possible decrease to every 2 weeks for safety, and 162 mg every 2 weeks in the United States, with a possible increase to every week based on clinical response.

The pharmacokinetics (PK) and pharmacodynamics (PD) of intravenous tocilizumab have been reviewed extensively,[16] whereas the PK/PD of subcutaneous tocilizumab in patients with RA has only been de-scribed in a small open-label study in 29 patients without a control treatment.[17] Therefore, an analysis was performed to compare the PK, PD, and exposure-efficacy and exposure-safety relationships of subcuta-neous tocilizumab 162 mg administered every week or every 2 weeks with those of tocilizumab 8 mg/kg intravenously every 4 weeks or placebo, using data from the SUMMACTA and BREVACTA studies.

Methods

All patients signed informed consent documents that were approved by an independent ethics committee or institutional review board, and the studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Data were pooled from SUMMACTA (NCT01194414) and BREVACTA (NCT01232569), 2 phase 3 randomized, controlled, parallel-arm trials in patients with RA who had inad-equate responses to DMARDs (this may have included ≥1 antitumor necrosis factor agent, but the proportion of patients who had an inadequate response to these agents was capped at 20%). Both trials had a 24-week double-blind period followed by a 72-week open-label extension. PK/PD results are presented for the 24-week double-blind periods.

Inclusion and exclusion criteria for the studies were published previously.[14,15] Briefly, the studies included adult patients (≥ 18 years old) with moderate to severe RA of at least 6 months' duration who had been receiv-ing nbDMARDs at a stable dose for at least 8 weeks before baseline and had discontinued bDMARDs for a suitable washout period before randomization.

Tocilizumab was administered as a subcutaneous injection of 162 mg via a prefilled syringe or by intravenous infusion at 8 mg/kg. Patients in SUM-MACTA received tocilizumab 162 mg subcutaneously every week plus placebo intravenously every 4 weeks or placebo subcutaneously every week plus tocilizumab 8 mg/kg intravenously every 4 weeks for 24 weeks in combination with nbDMARDs. Per US and EU labels, patients weighing ≥ 100 kg received a flat dose of 800 mg every 4 weeks. Patients in BREVACTA received tocilizumab 162 mg subcutaneously or placebo subcu-taneously every 2 weeks for 24 weeks in combination with nbDMARDs; during this period, patients with <20% improvement from baseline in swollen joint count and tender joint count could escape to open-label rescue therapy with tocilizumab 162 mg subcutaneously every week from week 12.

In both studies, predose serum samples were taken from all patients in the PK/PD population to measure PK and PD parameters (patients from whom at least 1 blood sample was collected: SUMMACTA, n = 1262; BREVACTA, n = 437; total number of samples, 13 642). Patients could also enter an optional PK/PD substudy in which more intense serum samples were collected. Noncompartmental analysis, in addition to the population PK analysis, was also performed on samples from patients in the substudies. The serum samples for PK/PD analysis (tocilizumab, IL-6, and soluble IL-6R [sIL-6R] for SUMMACTA; tocilizumab and sIL-6R for BREVACTA) were collected before tocilizumab administration at baseline; in weeks 1, 2, and 4; and then every 4 weeks thereafter until week 24 in the double-blind period of SUMMACTA, and at baseline and every 2 weeks until week 8 and then every 4 weeks until week 24 in the double-blind period of BREVACTA. Patients' C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were assessed at

baseline, in weeks 2 and 4, and every 4 weeks thereafter until week 24 in the double-blind period of both studies. Antitocilizumab antibodies were assessed at baseline and in week 12 and week 24 in the double-blind period of both studies. Additional sequential serum samples were taken for the PK/PD substudy following the day 1 and week 20 doses for SUMMACTA and following the day 1 and week 12 doses for BREVACTA.

The effect of body weight on systemic drug exposure at steady state was assessed using noncompartmental analysis and confirmed by the population PK analysis. Patients from BREVACTA who escaped to rescue therapy were included up to the time of escape, after which they were classed as withdrawn and excluded. Nonlinear mixed-effects modeling (NONMEM 7.2)[18] was used to analyze the concentration–time data for tocilizumab from intravenous and subcutaneous dosing simultaneously. The population PK model previously developed using data from the intravenous formulation was used as a starting point of the analysis.[19] Structural model refinement was driven by the data and was based on various goodness-of-fit indicators, plausibility of the parameter estimates, precision of the parameter estimates, the minimum objective function value, and the number of parameters. Covariates such as body weight, sex, age, creatinine clearance, and rheumatoid factor were tested. Steady-state secondary PK parameters (area under the concentration curve [AUC], maximum concentration [C_{max}], trough concentration [C_{trough}]) were computed using Bayesian post hoc estimates obtained for each patient. The PD analysis included IL-6 levels (SUMMACTA only) and sIL-6R, CRP, and ESR levels (both studies). PD markers are presented using descriptive summary statistics.

Immunogenicity was assessed as serum levels of antitocilizumab antibodies measured using a bridging enzyme-linked immunosorbent assay (ELISA), as described previously,[20] in samples collected at baseline, every 12 weeks, and at study completion or early withdrawal. Samples that tested positive in an initial screening assay were analyzed by a confirmation assay to confirm specificity. If the confirmation assay was positive, an inhibition ELISA was performed to evaluate the neutralizing potential of the antitocilizumab antibody.[14,15] The effect of antitocilizumab antibodies on the PK of tocilizumab and the effect of neutralizing antitocilizumab antibodies on the PK/PD relationship between tocilizumab concentration and 28-joint Disease Activity Score (DAS28) was investigated.

The relationship between exposure to tocilizumab and efficacy was assessed using American College of Rheumatology (ACR) 20/50/70 responses in week 24, summarized by tocilizumab observed C_{trough} exposure quartiles in week 24. Graphical analyses using logistic regression were also performed for ACR20/50/70.

Patients from BREVACTA who escaped to rescue therapy after week 12 were treated as ACR20/50/70 nonresponders, and the last C_{trough} value before escape was used in the analysis. The relationship between exposure to tocilizumab and safety was assessed by summarizing laboratory abnormalities and adverse events (AEs) up to week 24 by tocilizumab observed C_{trough} exposure quartiles in week 24. Patients from BREVACTA who escaped to rescue therapy were not included in the exposure–safety analysis.

Results

Baseline demographics and disease characteristics were similar for patients in the safety populations (all patients who received ≥1 dose of the study drug and had ≥1 postdose safety assessment) across the 2 studies and across treatment arms, except for a slightly heavier mean weight and larger proportion ≥100 kg for patients in SUMMACTA and longer disease duration in BREVACTA (11.1 years) than in SUMMACTA (8.7 years); see Supplementary Table S1. The data set used for the population PK analysis and noncompartmental analysis included 1759 patients from both SUMMACTA and BREVACTA.

Pharmacokinetics

Based on observed data in the PK/PD population, the mean predose tocilizumab concentrations with 8 mg/kg intravenous every-4-week administration increased from baseline to week 16 and appeared to reach steady state thereafter (Figure 1). There was an approximately 2-fold increase in mean predose concentration from week 4 to week 24. Steady-state predose tocilizumab concentration in week 24 was approximately 18 μg/mL, with every-4-week intravenous dosing. Following subcutaneous every-week administration, tocilizumab concentrations increased from baseline to week 12 and appeared to reach steady state thereafter. There was approximately a 5-fold increase in mean predose tocilizumab concentration from week 1 to week 24. Steady-state predose tocilizumab concentration in week 24 was approximately 40 μg/mL. Subcutaneous dosing of tocilizumab 162 mg every 2 weeks resulted in increasing predose concentrations from baseline to week 20 and appeared to reach steady state thereafter (Figure 1). There was an approximately 4-fold increase in mean predose tocilizumab concentrations from week 2 to week 24. Steady-state predose tocilizumab concentration in week 24 was approximately 7.4 μg/mL. Results from the PK substudies are also included in Supplementary Tables S2 and S3.

The population PK model developed for this analysis had a structure similar to the model previously developed based only on intravenous data[19]; it was
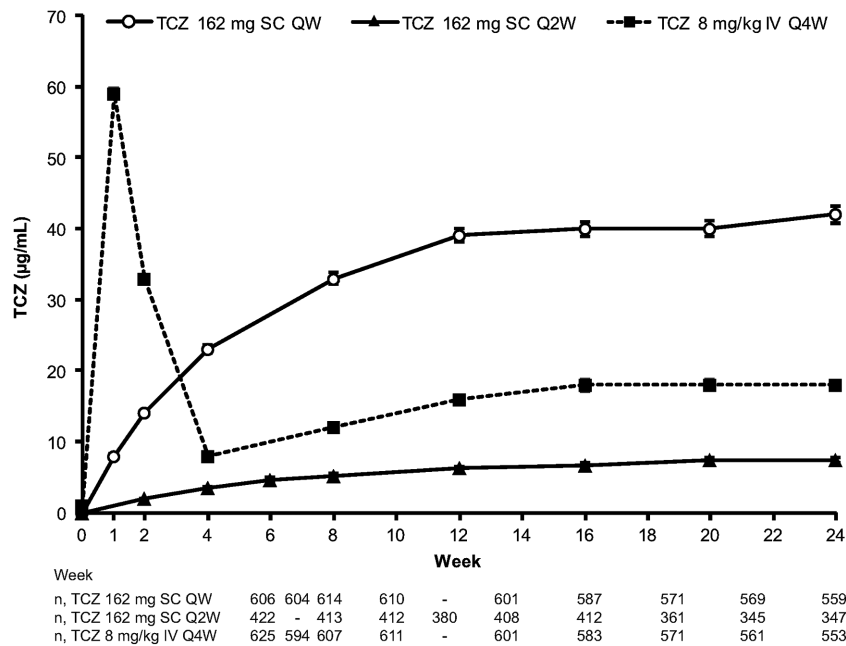
Figure 1. Mean observed predose tocilizumab concentrations for SC QW, SC Q2W, or IV Q4W dosing. Error bars show standard error. IV, intravenous; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, weekly; SC, subcutaneous; TCZ, tocilizumab.

Table 1. Parameter Estimates From the Final PK Model: (A) Primary Parameters and (B) Secondary Parameters

A. Primary Parameters				
Parameter		Estimate	% RSE	95%CI
CL (mL/day)	$\theta 1$	216	1.2	211–221
V2 (L)	$\theta 2$	4.5	1.6	4.4–4.7
Q (mL/day)	$\theta 3$	274	2.2	262–285
V3 (L)	$\theta 4$	2.8	1.7	2.7–2.9
V_M (mg/L/day)	$\theta 5$	1.9	1.0	1.8–1.9
K_M (μg/mL)	$\theta 6$	0.34	2.5	0.33–0.36
ka (1/day)	$\theta 7$	0.23	2.7	0.22–0.25
F_{SC}	$\theta 8$	0.80	1.1	0.79–0.81

B. Secondary Parameters[a] (Mean $\pm$ SD)								
	162 mg SC QW			162 mg SC Q2W			8 mg/kg IV Q4W		
Tocilizumab Dose	First Dosing Interval	Steady State	R_{AC}	First Dosing Interval	Steady State	R_{AC}	First Dosing Interval	Steady State	R_{AC}
AUC_τ, μg·h/mL	1243 $\pm$ 689	8254 $\pm$ 3833	6.8	1210 $\pm$ 940	3460 $\pm$ 2530	2.7	28 824 $\pm$ 7704	39 216 $\pm$ 14 304	1.36
C_{max}, μg/mL	9.3 $\pm$ 5.1	51.3 $\pm$ 23.2	5.5	5.8 $\pm$ 4.1	13 $\pm$ 8.3	2.1	136 $\pm$ 34	154 $\pm$ 42	1.13
C_{trough}, μg/mL	7.0 $\pm$ 4.1	45.3 $\pm$ 22.2	6.4	1.0 $\pm$ 1.5	5.9 $\pm$ 6.3	5.6	7.7 $\pm$ 6.7	18.7 $\pm$ 15.3	2.43

CL, linear clearance; V2, central volume of distribution; Q, intercompartmental clearance; V3, peripheral volume of distribution; V_M, maximum target-mediated elimination rate; K_M, Mechaelis–Menten constant; Ka, absorption rate constant; F_{SC}, absolute bioavailability following SC dosing; RSE, relative standard error, RSE, 100·SE/parameter estimate; 95%CI, 95% confidence interval; AUC_τ, area under the concentration curve within the dosing interval; C_{max}, maximum concentration; C_{trough}, predose trough concentration; PK, pharmacokinetic; Q2W, every 2 weeks; QW, weekly; R_{AC}, accumulation ratio; SC, subcutaneous.
[a]Data are from simulations performed for 5000 subjects.

a 2-compartment PK model with parallel linear and Michaelis–Menten eliminations. In addition, the model contained a first-order absorption process to describe subcutaneous administration. Diagnostic plots for the model are provided in Supplementary Figure 1, and the parameter estimates are listed in Table 1A, along with their corresponding relative standard errors and 95%

confidence intervals (CI). The absolute bioavailability of tocilizumab following subcutaneous administration was estimated to be 79.5%, with a 95% confidence interval of 77.9%–81.1%. The following parameters estimates (95% CI) were obtained for tocilizumab, which were in good agreement with those of the previous model[19]: linear clearance, 216 mL/day (95%CI,
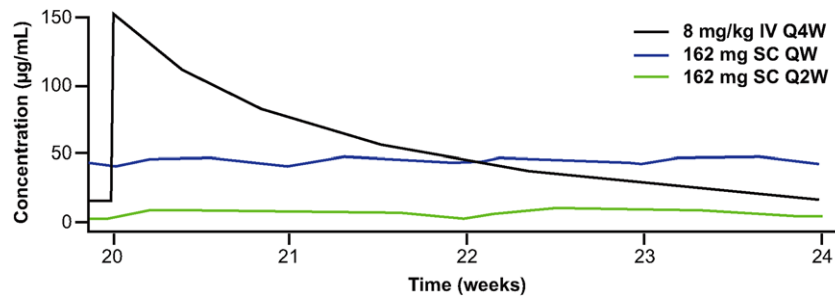
Figure 2. Simulated tocilizumab serum concentrations over time at steady state. Black line, tocilizumab 8 mg/kg IV Q4W; blue line, tocilizumab 162 mg SC QW; green line, tocilizumab 162 mg SC Q2W. IV, intravenous; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, weekly; SC, subcutaneous; TCZ, tocilizumab.

211–221 mL/day); central volume of distribution, 4.5 L (94%CI, 4.4–4.7 L); peripheral volume of distribution, 2.8 L (95%CI, 2.7–2.9 L); K_M (Michaelis–Menten constant), 0.34 μg/mL (95%CI, 0.33–0.36 μg/mL); and V_M (maximum target-mediated elimination rate), 1.9 mg/L/day (95%CI, 1.8–1.9 mg/L/day). Model-predicted secondary PK parameters for the every-week, every-2-week, and intravenous regimens are shown in Table 1B. The predicted mean ± SD steady-state AUC within the dosing interval (AUC_τ) values for tocilizumab 162-mg subcutaneous every-week and every-2-week dosing were 8254 ± 3833 and 3460 ± 2530 μg·h/mL, respectively. The mean steady-state pre-dose C_{trough} and C_{max} were 7.7-fold and 3.9-fold higher, respectively, for every-week versus every-2-week dosing (Table 1 and Figure 2).

Effect of Body Weight on Tocilizumab Exposure and PK Parameters

Based on observed data in the PK/PD population, increase in body weight was associated with lower tocilizumab predose concentration with both every-week and every-2-week subcutaneous dosing (Table 2 and Supplementary Figure S2).

Among all identified covariate relationships in the population PK analysis, the only strong covariate dependence was the influence of weight on tocilizumab clearance and volume parameters. Increase of clearances and volumes with weight was described by the power function CL ~ $(WT/70)^{CLWT}$ and V ~ $(WT/70)^{VWT}$, with power coefficients estimated at 0.51 (95%CI, 0.47–0.56) and 0.68 (95%CI, 0.63–0.74), respectively. Clearance terms of patients with weight of 40 and 140 kg (values close to the extreme values of weight in the study population) decreased and increased, respectively, by 25% and 47%, and volumes decreased and increased, respectively, by 32% and 61% compared with the CL of a patient weighing 70 kg.

The predicted mean ± SD tocilizumab C_{trough} values for patients weighing ≥100 kg were lower with tocilizumab subcutaneous every-2-week dosing (1.0 ±

1.6 μg/mL) than with subcutaneous every-week dosing (23 ± 14 μg/mL) or intravenous every-4-week dosing (31 ± 24 μg/mL); a similar trend was observed for predicted AUC_τ, average observed concentration, and C_{max} in patients ≥100 kg (Table 2).

Pharmacodynamics

IL-6 and sIL-6R levels were comparable with tocilizumab 162-mg subcutaneous every-week and tocilizumab 8 mg/kg intravenous every-4-week dosing in SUMMACTA (Figure 3A,B). In the BREVACTA study, tocilizumab 162-mg subcutaneous every-2-week dosing also resulted in rapid increases in sIL-6R, whereas sIL-6R values were unchanged with placebo (Figure 3B). CRP and ESR levels were comparable with tocilizumab 162-mg subcutaneously every-week and tocilizumab 8-mg/kg intravenous every-4-week dosing (Figure 3C,D). CRP and ESR levels decreased rapidly following tocilizumab 162-mg subcutaneous every-2-week dosing and continued to drop to week 24, remaining below the upper limit of normal (ULN). CRP and ESR levels also decreased slightly following treatment with placebo subcutaneously, but were higher than in patients treated with tocilizumab and did not fall below the ULN.

Immunogenicity

In the safety populations, 5 of 631 patients (0.8%) receiving tocilizumab 162 mg subcutaneously every week, 5 of 631 patients (0.8%) receiving tocilizumab 8 mg/kg intravenously every 4 weeks, 7 of 437 patients (1.6%) receiving tocilizumab 162 mg every 2 weeks, and 3 of 218 patients (1.4%) receiving placebo developed antitocilizumab antibodies in the confirmation assay by week 24. Of these patients, all 5 receiving tocilizumab 162 mg subcutaneously every week, all 5 receiving tocilizumab 8 mg/kg intravenously every 4 weeks, 6 of 7 patients receiving tocilizumab 162 mg every 2 weeks, and 1 of 3 patients receiving placebo also developed antibodies with neutralizing potential. None of the patients with positive antitocilizumab antibodies in the confirmation assay had serious or clinically significant

Table 2. Tocilizumab Exposure in Week 24 (Observed) and at Steady State (Predicted) by Baseline Body Weight Categories

Body Weight	TCZ 162 mg SC QW		TCZ 162 mg SC Q2W		TCZ 8 mg/kg IV Q4W	
	Observed	Model Predicted	Observed	Model Predicted	Observed	Model Predicted
C_{trough} (µg/mL)						
<60 kg	62.1 ± 30.5 (59.0: 0–151) n = 105	62.6 ± 22.1 (59.8: 17.3–145.2) n = 143	11.70 ± 7.91 (11.5: 0–37.4) n = 90	10.2 ± 6.9 (10.6: 0.2–34.4) n = 136	15.2 ± 11.4 (12.0: 0–50.0) n = 116	13.2 ± 11.4 (10.6: 0.1–61.5) n = 146
60 to <100 kg	41.5 ± 24.7 (37.6: 0–154) n = 325	42.4 ± 19.0 (40.5: 1.3–123.4) n = 420	6.16 ± 6.74 (4.90: 0–35.5) n = 238	4.6 ± 5.3 (2.6: 0.1–28.3) n = 346	19.8 ± 14.5 (17.6: 0–86.3) n = 322	18.8 ± 12.7 (16.4: 0.1–68.3) n = 416
≥100 kg	21.6 ± 14.5 (17.6: 0.7–61.7) n = 47	23.0 ± 13.5 (19.7: 2.2–61.2) n = 58	2.03 ± 2.82 (0.288: 0–8.95) n = 19	1.0 ± 1.6 (0.2: 0.0–5.8) n = 27	20.8 ± 13.0 (18.4: 3.7–52.5) n = 42	31.0 ± 23.5 (24.3: 0.2–158.7) n = 67
AUC_τ (µg·day/mL)						
<60 kg		470.5 ± 157.2 (452.6: 129.0–1038.0) n = 143		220.4 ± 113.1 (212.0: 34.1–607.5) n = 136		1338.8 ± 461.7 (1260.1: 461.4–3199.0) n = 146
60 to <100 kg		323.7 ± 135.7 (311.5: 16.3–905.4) n = 420		121.7 ± 88.1 (92.6: 8.8–467.5) n = 346		1649.3 ± 493.8 (1585.2: 648.8–3498.6) n = 416
≥100 kg		178.8 ± 97.3 (154.0: 25.4–447.8) n = 58		48.3 ± 37.1 (40.8: 3.0–154.5) n = 27		2282.3 ± 928.1 (2146.7: 766.0–7296.5) n = 67
C_{mean} (µg/mL)						
<60 kg		67.2 ± 22.5 (64.7: 18.4–148.3) n = 143		15.7 ± 8.1 (15.1: 2.4–43.4) n = 136		47.8 ± 16.5 (45.0: 16.5–114.3) n = 146
60 to <100 kg		46.2 ± 19.4 (44.5: 2.3–129.3) n = 420		8.7 ± 6.3 (6.6: 0.6–33.4) n = 346		58.9 ± 17.6 (56.6: 24.5–124.9) n = 416
≥100 kg		25.5 ± 13.9 (22.0: 3.6–64.0) n = 58		3.5 ± 2.6 (2.9: 0.2–11.0) n = 27		81.5 ± 33.1 (76.7: 27.4–260.6) n = 67
C_{max} (µg/mL)						
<60 kg		69.7 ± 22.7 (68.0: 19.1–150.1) n = 143		19.0 ± 8.9 (17.9: 4.0–48.7) n = 136		129.8 ± 31.1 (126.3: 64.1–248.6) n = 146
60 to <100 kg		48.3 ± 19.7 (46.4: 2.9–132.6) n = 420		11.2 ± 6.9 (9.3: 1.1–37.9) n = 346		152.9 ± 34.7 (152.6: 69.2–266.9) n = 416
≥100 kg		26.9 ± 14.2 (23.2: 4.4–65.6) n = 58		5.2 ± 3.3 (5.0: 0.4–14.5) n = 27		201.8 ± 59.5 (200.6: 99.1–492.0) n = 67

Data are mean ± SD (median: min–max). AUC_τ, area under the concentration curve within the dosing interval; C_{max}, maximum observed concentration; C_{mean}, average observed concentration; C_{trough}, predose trough concentration; IV, intravenous; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, weekly; SC, subcutaneous; TCZ, tocilizumab.

hypersensitivity reactions or withdrew because of insufficient therapeutic response. Overall, antitocilizumab antibodies had no impact on the PK of tocilizumab. In the limited numbers of patients who had confirmed antitocilizumab antibodies, there was no apparent trend for reduced tocilizumab concentrations when evaluating their PK profiles with individual dosing records and actual sampling times (data not shown). Furthermore, in the population PK analysis, antitocilizumab antibod-

ies were not identified as a covariate that influenced the PK of tocilizumab.

Exposure–Efficacy and Exposure–Safety Relationships

Clinical response (proportions of patients with ACR20/50/70 responses) increased with increasing tocilizumab C_{trough} exposure quartiles after subcutaneous administration, but this was not observed with intravenous administration (Table 3). Exposure

Panel A data:

Week									
n, TCZ 162 mg SC QW	524 602 614	605	596	582	566	564	552
n, TCZ 8 mg/kg IV Q4W	539 591 605	603	588	570	561	551	537

Panel B data:

Week									
n, TCZ 162 mg SC QW	573 551 557	520	–	431	351	255	188	132
n, TCZ 162 mg SC Q2W	422 – 403	416	380	409	413	364	348	346
n, TCZ 8 mg/kg IV Q4W	564 546 539	511	–	444	349	265	198	143
n, Placebo	215 – 205	210	194	202	207	148	130	123

Panel C data:

Week									
n, TCZ 162 mg SC QW	557	549	616	543	538	527	524	516
n, TCZ 162 mg SC Q2W	428	426	423	413	419	366	353	345
n, TCZ 8 mg/kg IV Q4W	536	522	532	519	518	511	507	498
n, Placebo	217	217	217	210	209	145	128	124

Panel D data:

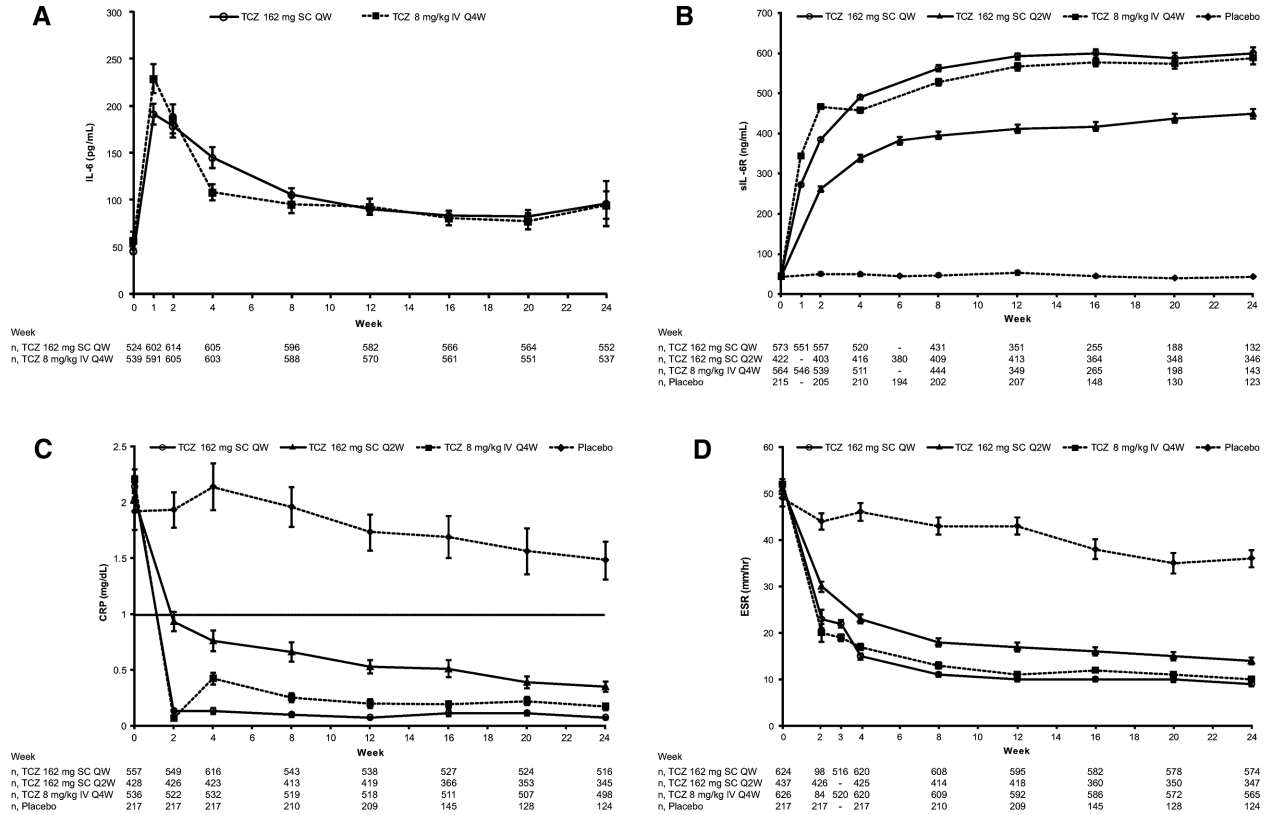| Week									
n, TCZ 162 mg SC QW	624	98 516 620	608	595	582	578	574
n, TCZ 162 mg SC Q2W	437	426 – 425	414	418	360	350	347
n, TCZ 8 mg/kg IV Q4W	626	84 520 620	609	592	586	572	565
n, Placebo	217	217 – 217	210	209	145	128	124

Figure 3. Mean IL-6 (A), sIL-6R (B), CRP (C), and ESR (D) levels following treatment with SC or IV tocilizumab. Error bars show standard error. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin 6; IV, intravenous; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, weekly; SC, subcutaneous; sIL-6R, soluble IL-6 receptor; TCZ, tocilizumab.

quartiles showed a clearer gradation in response with the subcutaneous every-2-week regimen compared with the subcutaneous every-week regimen, in which the efficacy parameters showed a plateau past the first quartile. Logistic regressions for the subcutaneous every-2-week regimen and for the combined every-2-week and every-week regimens demonstrated almost identical relationships between tocilizumab exposure and ACR responses (Supplementary Figure S3).

There was no apparent association between increasing tocilizumab exposure and occurrence of AEs, including infections and infestations, for any of the dosing schedules (Table 4). The occurrence of serious AEs (SAEs) was low and similar with tocilizumab subcutaneous every-week (26 of 631, 4.1%), subcutaneous every-2-week (15 of 437, 3.4%), and intravenous every-4-week (26 of 631, 4.1%) dosing. However, quartile analysis was not feasible because of the low numbers of SAEs. Neutrophil counts decreased with increasing tocilizumab exposure quartiles; there was increased incidence of grade 1 and grade 2 neutropenia with increasing tocilizumab exposure (Table 4), which was not temporally associated with serious infections. There was no clear trend for increased alanine aminotrans-

ferase elevations with increasing tocilizumab exposure quartiles (Table 4).

Discussion

As expected, fluctuation of tocilizumab concentration at steady state was small for the subcutaneous every-week and every-2-week regimens compared with intravenous administration over the dosing interval. Mean C_{trough} values were higher with 162-mg subcutaneous every-week dosing than with 8 mg/kg intravenous every-4-week dosing. Tocilizumab 162-mg subcutaneous every-2-week dosing consistently resulted in the lowest C_{trough} values. Tocilizumab 162 mg subcutaneous every week showed noninferior efficacy and comparable safety to the 8 mg/kg intravenous every-4-week regimen. Consistent with the clinical results, the 2 regimens exhibited similar PD responses (IL-6, sIL-6R, CRP, and ESR). CRP and ESR suppression compared with the 162-mg subcutaneous every-2-week regimen, suggesting greater inhibition of IL-6-mediated activation of the acute-phase response.

A 2-compartment PK model with parallel linear and Michaelis–Menten elimination and first-order

Table 3. Proportion of Patients With ACR Responses in Week 24 by Observed Tocilizumab C_{trough} Exposure Quartiles

	TCZ 162 mg SC QW				TCZ 162 mg SC Q2W				TCZ 8 mg/kg IV Q4W			
	Q1 (n = 131)	Q2 (n = 129)	Q3 (n = 130)	Q4 (n = 129)	Q1 (n = 98)	Q2 (n = 98)	Q3 (n = 98)	Q4 (n = 97)	Q1 (n = 134)	Q2 (n = 135)	Q3 (n = 134)	Q4 (n = 131)
ACR20 responders, n (%)	82 (63)	99 (76)	95 (73)	106 (82)	41 (43)	63 (64)	70 (71)	71 (73)	101 (75)	110 (81)	108 (81)	102 (78)
ACR50 responders, n (%)	51 (39)	67 (52)	69 (53)	69 (53)	24 (24)	40 (41)	48 (49)	50 (52)	78 (58)	69 (51)	77 (57)	59 (45)
ACR70 responders, n (%)	26 (20)	37 (28)	36 (28)	35 (27)	8 (8)	16 (16)	29 (30)	25 (26)	46 (34)	40 (30)	43 (32)	33 (25)
Mean (median) C_{trough}, $\mu g/mL$	14.6 (15.4)	32.7 (33.1)	47.9 (47.7)	80.1 (72.5)	0.1 (0.1)	2.6 (2.4)	7.6 (7.5)	17.4 (16.5)	4.1 (4.1)	12.2 (12.0)	20.2 (19.8)	38.9 (36.9)

Q1–Q4 refer to C_{trough} exposure quartiles (lowest to highest). ACR, American College of Rheumatology; C_{trough}, predose trough concentration; IV, intravenous; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, weekly; SC, subcutaneous; TCZ, tocilizumab.

absorption could best describe the PK of the tocilizumab subcutaneous formulation. Body weight had the most significant influence on tocilizumab clearance and volume parameters. The power coefficients of the effect of body weight on clearance and volume terms of the structural model (0.51 and 0.68, respectively) were lower than the allometric coefficients of 0.75 for clearance and 1 for volume,[21] but consistent with the previous analysis for tocilizumab (in which CL depended on BSA with a power coefficient of 0.67 approximately corresponding to a coefficient of 0.50 for dependence on weight).[19]

Unlike intravenous dosing, the tocilizumab subcutaneous dosing regimens use a fixed dose (162 mg) over a wide range of body weights. It was important, therefore, to investigate the influence of body weight on tocilizumab PK. In both SUMMACTA and BREVACTA, patients were stratified by body weight category (<60, 60 to <100, and ≥100 kg) for efficacy and safety analysis. These analyses are summarized elsewhere.[14,15] We summarize here observed and model-predicted PK parameters using the same body weight categories (Table 2). Tocilizumab exposure provided by the subcutaneous regimens was inversely correlated with body weight. Patients in the highest body weight category (≥100 kg) obtained little or no benefit from the every-2-week subcutaneous regimen,[15] which resulted in C_{trough} concentrations considered subefficacious.[6] In these patients, the ACR response scores were numerically similar to placebo. The every-week regimen resulted in clinical response (ACR scores) in patients weighing >100 kg, comparable to the 8 mg/kg every-4-weel intravenous regimen.[14] On the other hand, patients in the lightest body weight category (<60 kg), who typically show the highest exposure from the subcutaneous every-week regimen, did not show increased incidence of AEs. Examination of total AEs, infections, neutropenia, and liver enzyme elevation by exposure quartiles (Table 4) reinforced the safety profile of subcutaneous tocilizumab. Although there was a higher incidence of grade 1 or 2 neutropenia with higher tocilizumab exposure, the incidence of grade 3 or 4 neutropenia was low and comparable for the tocilizumab subcutaneous every-week and intravenous regimens, and there was no association between grade 3 or 4 neutropenia and the development of serious infections.

Although the starting-dose recommendation for tocilizumab is different in the United States (162 mg subcutaneously every 2 weeks) and the European Union (162 mg subcutaneous every week), regulatory authorities in both regions allow for dose adjustment up (United States) or down (European Union) to optimize the risk:benefit ratio for individual patients, based on well-established efficacy scores, such as ACR

Table 4. Neutropenia, ALT Elevations, and Adverse Events to Week 24 by Observed Tocilizumab C_{crough} Exposure Quartiles

	TCZ 162 mg SC QW				TCZ 162 mg SC Q2W				TCZ 8 mg/kg IV Q4W			
	Q1 (n = 131)	Q2 (n = 129)	Q3 (n = 130)	Q4 (n = 129)	Q1 (n = 81)	Q2 (n = 80)	Q3 (n = 80)	Q4 (n = 80)	Q1 (n = 134)	Q2 (n = 135)	Q3 (n = 134)	Q4 (n = 131)
Total patient-years	63.3	62.1	62.6	62.2	37.5	37.0	37.1	37.0	64.7	65.0	64.7	63.3
Total AEs, n (n per 100 PY: 95%CI)	388 (613: 553–677)	292 (471: 418–528)	373 (596: 537–660)	346 (556: 499–618)	177 (472: 405–547)	136 (367: 308–434)	139 (375: 315–442)	158 (427: 363–499)	349 (539: 484–599)	345 (531: 476–590)	367 (567: 510–628)	356 (563: 506–624)
Infection and infestation AEs, n (n per 100 PY: 95%CI)	68 (107: 83–136)	62 (100: 77–128)	75 (120: 94–150)	72 (116: 91–146)	40 (107: 76–145)	30 (81: 55–116)	25 (67: 44–99)	26 (70: 46–103)	61 (94: 72–121)	80 (123: 98–153)	76 (117: 93–147)	78 (123: 97–154)
Neutropenia grade 1, n (%)	20 (15)	24 (19)	33 (26)	26 (20)	5 (6)	3 (4)	12 (15)	18 (23)	5 (4)	9 (7)	19 (14)	17 (13)
Neutropenia grade 2, n (%)	9 (7)	17 (13)	12 (9)	27 (21)	0 (0)	4 (5)	5 (6)	9 (11)	5 (4)	9 (7)	19 (14)	17 (13)
Neutropenia grade 3, n (%)	1 (1)	2 (2)	5 (4)	2 (2)	1 (1)	2 (2)	4 (5)	1 (1)	3 (2)	2 (2)	3 (2)	7 (5)
ALT elevation grade 1, n (%)	69 (59)	59 (50)	68 (57)	49 (40)	24 (31)	28 (38)	32 (44)	30 (38)	55 (45)	52 (44)	65 (50)	44 (37)
ALT elevation grade 2, n (%)	4 (3)	8 (7)	4 (3)	1 (1)	1 (1)	3 (4)	2 (3)	0 (0)	5 (4)	5 (4)	5 (4)	4 (3)
ALT elevation grade 3, n (%)	2 (2)	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)	1 (1)	0 (0)	0 (0)
Mean (median) C_{crough}, μg/mL	14.6 (15.4)	32.7 (33.0)	47.9 (47.7)	80.1 (72.5)	0.2 (0.1)	3.5 (3.6)	8.2 (8.1)	17.9 (16.6)	4.1 (4.1)	12.2 (12.0)	20.2 (19.8)	38.9 (36.9)

Q1–Q4 refer to C_{crough} exposure quartiles (lowest to highest). There were no cases of grade 4 neutropenia observed. AE, adverse event; ALT, alanine aminotransferase; C_{crough}, predose trough concentration; IV, intravenous; PY, patient-years; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, weekly; SC, subcutaneous; TCZ, tocilizumab.

and DAS28, and objective laboratory tests, such as liver enzymes and neutrophil count.[7,8]

Conclusions

The results of this PK/PD analysis of subcutaneous and intravenous administration of tocilizumab in patients with RA demonstrate that the higher exposure obtained with subcutaneous every-week dosing compared with subcutaneous every-2-week dosing is associated with more pronounced PD effects and with greater clinical efficacy that is comparable to tocilizumab intravenous 8 mg/kg every-4-week dosing. Tocilizumab exposure was lowest in patients weighing >100 kg who received subcutaneous every-2-week dosing, supporting recommendations for subcutaneous every-week dosing in this body weight group. There was no trend for increasing AEs with increasing tocilizumab exposure.

Declaration of Conflicting Interests

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