

Pharmacokinetics and Pharmacodynamics of Subcutaneous Sarilumab and Intravenous Tocilizumab Following Single-Dose Administration in Patients With Active Rheumatoid Arthritis on Stable Methotrexate

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Abstract

We assessed pharmacokinetics (PK), pharmacodynamics (PD), and PK/PD relationships of interleukin-6 (IL-6), soluble IL-6 receptor, and C-reactive protein (CRP) in serum, and absolute neutrophil count (ANC) in blood following single doses of subcutaneous sarilumab versus intravenous tocilizumab (NCT02097524) from patients with rheumatoid arthritis (RA) who are inadequate responders to methotrexate (MTX) and on a stable dose of MTX. Patients with RA randomized (1:1:1:1) to single-dose sarilumab (150 or 200 mg subcutaneously) or tocilizumab (4 or 8 mg/kg intravenously) were included (n = 101), and PK, PD, and PK/PD relationships and safety were assessed over 6 weeks postdose. PK profiles for both drugs are described by parallel linear and nonlinear target-mediated clearance pathways. PD markers showed similar onset of effect during the first week postdose, regardless of dose or route of administration. CRP and ANC decreased, with median postdose nadirs at 7–15 days for CRP and 3–5 days for ANC. Both drugs at low and high doses achieved the same nadir for ANC and a similar return toward baseline within 2 weeks postdose, suggesting a saturation of effect. Safety profiles of sarilumab and tocilizumab were generally similar. In conclusion, despite differences in PK, the onset of the decrease in CRP (efficacy) and ANC (safety) after a single dose were similar for subcutaneous sarilumab and intravenous tocilizumab. PD effects and safety were consistent with previous studies.

Keywords

sarilumab, tocilizumab, pharmacokinetics, interleukin-6, neutrophils, C-reactive protein

Approximately 20 million people worldwide are affected by rheumatoid arthritis (RA), a chronic, systemic inflammatory autoimmune disease, that primarily targets the diarthrodial joints, leading to bone and cartilage destruction, deformation, and disability.¹

Interleukin (IL)-6 plays a critical role in the systemic manifestations of RA and is known to drive inflammation and promote articular destruction.^{2–4} In response to infection or injury, IL-6 increases to mediate the induction of acute-phase reactants such as C-reactive protein (CRP) via binding to the IL-6 receptor (IL-6R) in its membrane-bound (mIL-6R) and soluble (sIL-6R) forms.^{3,5} In autoimmune conditions such as RA, IL-6 is persistently elevated and can contribute to chronic inflammation, disease progression, and joint damage.⁶ IL-6 in serum has been shown to correlate with RA disease activity.⁷

Sarilumab is an immunoglobulin G1 (IgG1) human monoclonal antibody that blocks IL-6 from bind-

ing to the alpha subunit of mIL-6R and sIL-6R (sIL-6R α), thereby inhibiting IL-6-mediated cis- and trans-signaling.^{8–11} Tocilizumab is a humanized IgG1 monoclonal antibody that also blocks IL-6 from binding to mIL-6R and sIL-6R α .¹² Both sarilumab and tocilizumab are approved for the treatment of adults

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with moderately to severely active RA.¹³⁻¹⁶ Decreased absolute neutrophil count (ANC) appears to be a function of inhibiting IL-6 signaling. However, clinical trials for sarilumab have not revealed any increase in the incidence of infections.^{8-10,17} In fact, during IL-6R inhibition, neutrophil function is preserved,¹⁸ and it has been postulated that “margination” of functioning neutrophils from the circulation occurs.¹⁹

The present analysis was conducted to investigate the pharmacokinetics (PK) and pharmacodynamics (PD) after a single dose of subcutaneous sarilumab 150 or 200 mg or intravenous tocilizumab 4 or 8 mg/kg in patients with RA on a stable dose of methotrexate (MTX). A key feature of this analysis was frequent sampling in the early postdose period to investigate the onset of PD effects by anti-IL-6R drugs and to describe margination of neutrophils. In addition, the time course of exploratory biomarkers of IL-6-mediated matrix metalloproteinase (MMP) degradation of CRP (CRP metabolite [CRPM]) and collagen (fragments C1M and C3M) were described. The primary objective was to describe the PD of key biomarkers of IL-6R α blockade: IL-6, sIL-6R, CRP, and ANC for subcutaneous sarilumab and intravenous tocilizumab.

Methods

Study NCT02097524 (6R88-RA-1309) was conducted in accordance with the principles laid down in the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice. All protocols and amendments were approved by the appropriate ethics committees/institutional review boards. Informed consent was obtained from all patients prior to any study-related procedures. Patient eligibility criteria have been described previously.²⁰ In brief, this was a phase 1b multicenter, randomized, open-label, parallel-group 6-week study to assess the PK, PD, and safety of single doses of subcutaneous sarilumab and intravenous tocilizumab in adults (≥ 18 years of age) with RA on a stable dose of MTX. Patients were randomized 1:1:1:1 to receive a single dose of either subcutaneous sarilumab 150 mg (low dose) or 200 mg (high dose) or intravenous tocilizumab 4 mg/kg (low dose) or 8 mg/kg (high dose). The sarilumab and tocilizumab doses used in this comparison study were consistent with approved prescribing information. The recommended sarilumab dose is 200 mg subcutaneously once every 2 weeks, with reduction to 150 mg once every 2 weeks if required to manage laboratory abnormalities.^{14,15} The recommended intravenous tocilizumab dose is 4 mg/kg every 4 weeks, with an increase to 8 mg/kg every 4 weeks based on clinical response.¹³

Assessments

Blood samples for PK, PD biomarkers (IL-6, total sIL-6R, high-sensitivity CRP [hereafter termed CRP], and ANC), and exploratory PD biomarker (CRPM, C1M, and C3M) analyses were collected according to the schedule shown in Figure 1. For a better understanding of the onset of IL-6 inhibition on PD markers on single-dose administration, this PK/PD analysis used a richer sampling schedule than previous reports.²¹

Bioanalytic Analyses

Concentrations of functional sarilumab (ie, sarilumab with either one or both binding sites available for binding IL-6R) in serum were measured using a validated enzyme-linked immunosorbent assay (ELISA), with lower level of quantification (LLOQ) of 0.313 ng/mL. Concentrations of functional tocilizumab in serum were measured using a qualified ELISA method (LLOQ, 0.294 mg/L) of similar design to that for sarilumab by Regeneron Pharmaceuticals, Inc. (Tarrytown, New York). Descriptive statistics of concentrations were reported by nominal time. For descriptive statistics and linear plots, concentrations below the LLOQ were set to zero; for semilogarithmic plots, concentrations below the LLOQ were set to LLOQ/2.

Values of IL-6 and total sIL-6R (free and complexed to drug) in serum were measured using a validated enzyme immunoassay (LLOQ, 3.12 pg/mL; Quantikine IL-6) by Covance (Princeton, New Jersey) and with a validated ELISA method (LLOQ, 15 ng/mL), respectively. CRP values in serum were measured using a high-sensitivity immunonephelometry assay (LLOQ, 0.020 mg/dL; Siemens BNII Nephelometer) by Covance. The ANC was derived by multiplying the percent of bands and segmented neutrophils by the total leukocyte count in blood.

Values of CRPM (LLOQ, 0.814 ng/mL), C1M (LLOQ, 7.228 ng/mL), and C3M (LLOQ, 1.963 ng/mL) in serum were measured using a validated ELISA by Synarc Laboratory (Newark, California). Intra- and interassay variability (coefficients of variation) was $< 14.2\%$ for CRPM, $< 13.8\%$ for C1M, and $< 19.8\%$ for C3M.

End Points

The following PK end points were assessed: concentration-time profiles; maximum quantifiable concentrations (C_{\max}); time to C_{\max} (t_{\max}); area under the curve (AUC) from time 0 to day 28, last positive (quantifiable) concentration, and infinity (AUC_{0-28 day}, AUC_{0-last}, and AUC_{0- ∞} , respectively); and clearance (CL for intravenous tocilizumab or CL/F for subcutaneous sarilumab, where F is the absolute bioavailability).

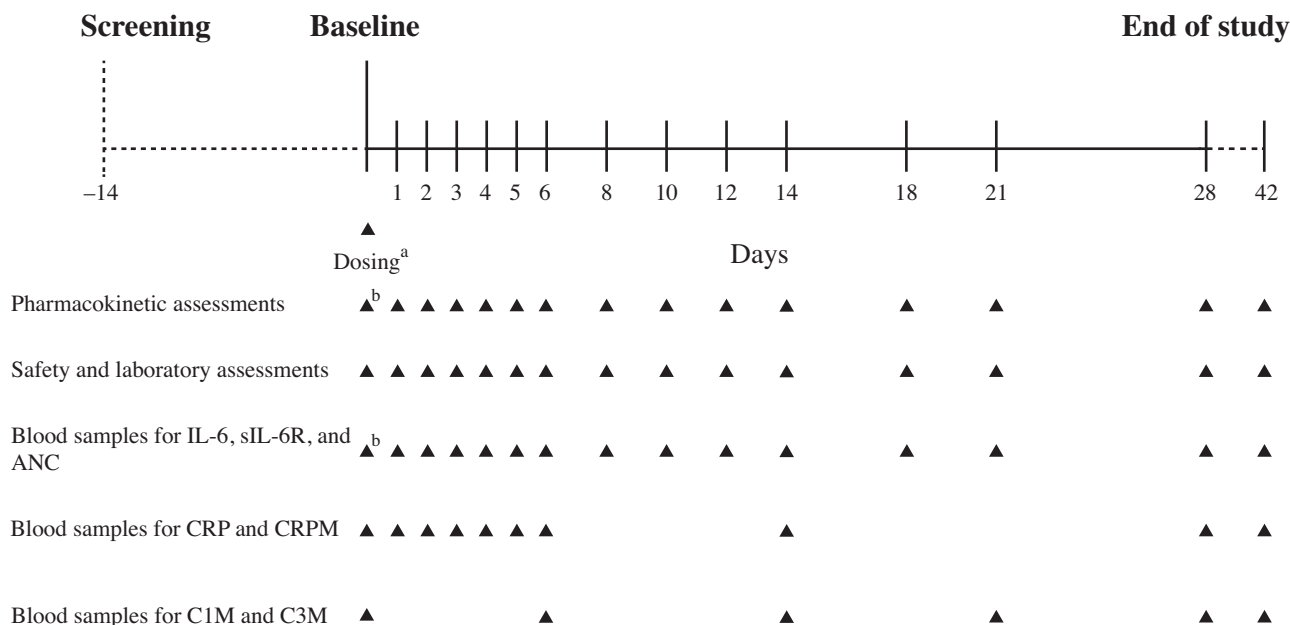


Figure 1. Study visit schedule. ANC, absolute neutrophil count; C1M, degradation fragments of collagen I; C3M, degradation fragment of collagen III; CRP, C-reactive protein; CRPM, C-reactive protein metabolite; IL-6, interleukin-6; PD, pharmacodynamics; sIL-6R, soluble interleukin-6 receptor. ^aPatients received a single open-label dose of subcutaneous sarilumab 150 mg, subcutaneous sarilumab 200 mg, intravenous tocilizumab 4 mg/kg, or intravenous tocilizumab 8 mg/kg. ^bSamples taken predose and 1, 4, and 8 hours postdose.

The following PD end points were assessed and reported for IL-6, sIL-6R, CRP, and ANC: measurement of value-time profiles and maximal effect (peak or nadir); time to maximal effect (described in the text according to the clinical assessment schedule); AUC; mean/median change from baseline; and percent change from baseline. For the exploratory PD biomarkers CRPM, C1M, and C3M, values were measured, and changes from baseline in week 4 and at the end of the study were reported.

Safety was monitored through adverse event reporting, physical examination, clinical laboratory tests (biochemistry, hematology, urinalysis, and liver function tests), and vital sign measurement and has been reported previously.²⁰ Safety and tolerability were assessed according to the percent of patients with a treatment-emergent adverse event (TEAE) from baseline through the end of the study (day 43).

Data Analysis

As a phase 1b PK/PD study with no formal hypothesis testing, the sample size was based on practical considerations and clinical judgment. The safety population included all randomized patients who received a study drug (either sarilumab or tocilizumab). The PK and PD populations included all randomized patients receiving a study drug with at least 1 nonmissing postbaseline measurement of drug concentration with or without a PD measurement, respectively.

PK parameters for individual patients were determined by noncompartmental analysis using Phoenix WinNonlin (version 6.3; Certara, L.P.) models 200-202 for extravascular dose (subcutaneous sarilumab) or intravenous infusion (tocilizumab). Actual time was used in the PK analysis. For the determination of mean values, individual drug concentrations in serum that were below the LLOQ were set to zero for linear plots and to LLOQ/2 for semilog plots.

The exploratory assessment of the PK/PD relationships for subcutaneous sarilumab or intravenous tocilizumab initially compared the PK concentration-time and PD value-time profiles. Direct PK/PD correlations for individual patient data across dose groups were then performed between individual PK (in terms of C_{max} and $AUC_{0-28 \text{ day}}$) and PD (in terms of maximal effect on PD values, as median/mean, change, or percent change from baseline). Paired mean PK and PD data were also plotted in chronological order (sequenced over time) to explore the temporal relationship between drug effect on the PD marker values and drug concentrations. Individual temporal PK/PD relationships were performed to verify that these were well represented by the mean \pm SD temporal PK/PD relationships. A hysteresis is observed when a temporal delay in drug effect occurs with respect to the circulating drug concentrations; the hysteresis is counterclockwise for a positive effect (stimulation [or inhibition of a negative regulator] or induction) and clockwise for a

Table 1. Summary of PK Parameters of Subcutaneous Sarilumab and Intravenous Tocilizumab in Serum by Group (PK Populations)

Parameter, Mean (SD)	Subcutaneous Sarilumab 150 mg (n = 26)	Subcutaneous Sarilumab 200 mg (n = 26)	Intravenous Tocilizumab 4 mg/kg (n = 25)	Intravenous Tocilizumab 8 mg/kg (n = 24)
C_{max} (mg/L)	13.9 (9.3)	21.6 (11.7)	138 (21.8)	256 (48.3)
t_{max} (day)	3.6 (1.1)	3.7 (1.1)	0.2 (0.1)	0.2 (0.1)
C_{last} (mg/L) ^a	0.7 (0.3)	1.0 (0.9)	2.2 (1.6)	5.3 (3.9)
t_{last} (day)	13.6 (4.3)	16.2 (3.7)	25.3 (5.3)	34.1 (7.3)
AUC _{0-28 day} (mg·day/L)	107 (92.2)	171 (105)	765 (210)	1688 (334)
AUC _{0-last} (mg·day/L)	106 (91.9)	169 (105)	766 (219)	1758 (403)
AUC _{0-∞} (mg·day/L)	108 (92.2)	173 (105)	778 (222)	1807 (404)
Dose normalization				
$C_{max}/dose$ (1/L)	0.09 (0.06)	0.11 (0.06)	–	–
$C_{max}/dose$ (kg/L)	–	–	34.4 (5.5)	32.0 (6.0)
AUC _{0-28 day} /dose ^b	0.7 (0.6)	0.9 (0.5)	191 (52.5)	211 (41.8)
AUC _{0-last} /dose ^b	0.7 (0.6)	0.8 (0.5)	192 (54.8)	220 (50.4)
AUC _{0-∞} /dose ^b	0.7 (0.6)	0.9 (0.5)	194 (55.5)	226 (50.5)
Clearance				
CL/F (L/day)	4.3 (5.9)	2.3 (4.6)	–	–
CL (L/day/kg)	–	–	0.006 (0.001)	0.005 (0.001)

AUC_{0-28 day}, area under the concentration-time curve from day 0 to day 28; AUC_{0-last}, area under the concentration-time curve from day 0 to last assessment; AUC_{0-∞}, area under the concentration-time curve from day 0 to infinity; C_{last} , last concentration; C_{max} , maximum concentration; CL, clearance; CRP, C-reactive protein; F, function of bioavailability; IL-6, interleukin-6; LLOQ, lower level of quantification; PK, pharmacokinetic; SD, standard deviation; sIL-6R, soluble interleukin-6 receptor; t_{last} , time at last concentration; t_{max} , time at maximum concentration.

^aLLOQ for sarilumab, 6.25 ng/mL in the assay, 0.313 ng/mL in serum; LLOQ for tocilizumab, 5.88 ng/mL in the assay, 0.294 mg/L in serum.

^bSarilumab day/L, tocilizumab kg·day/L.

negative effect (inhibition). A proteresis is observed when, in the temporal delay between the changing drug concentration and the PD effect, the maximal effect precedes the maximal drug concentration, which could occur with drug tolerance. The proteresis is clockwise for a positive effect (stimulation or induction) and counterclockwise for a negative effect (inhibition).²² The absence of a loop suggests a direct relationship between drug effect and systemic drug concentration and thus no temporal delay between effect and drug concentration.

Results

Study Population

A total of 105 patients were enrolled in the study from 24 sites in the United States, of whom 4 patients were randomized but not treated. Therefore, the PK/PD analysis included 101 patients (26 receiving low-dose sarilumab, 26 high-dose sarilumab, 25 low-dose tocilizumab, and 24 high-dose tocilizumab). Demographics have previously been reported and were similar across the groups.²⁰ Most patients were white (83.2% [84 of 101]) and female (86.1% [87 of 101]), with mean \pm SD age of 55 ± 11.7 years and disease duration of 10.6 ± 11.6 years. Body weight was balanced across the 4 groups, with means of 82.3-83.4 kg.

Pharmacokinetics

Of 936 serum samples to be collected in 52 patients for functional sarilumab concentration assessment, 925

were available for analysis, of which 571 (61.7%) had quantifiable concentrations (LLOQ, 0.313 mg/L). Of the 354 samples with functional sarilumab concentrations below the LLOQ, 52 were collected predose, and 302 were collected up to 1 month postdose. Of 882 serum samples to be collected in 49 patients for functional tocilizumab concentration assessment, 874 were available for analysis, of which 775 (88.7%) had quantifiable concentrations (LLOQ, 0.294 mg/L). Of the 99 samples with functional tocilizumab concentrations below the LLOQ, 49 were collected predose, and 50 were collected up to 1 month postdose.

The concentration-time profiles for sarilumab in serum after subcutaneous administration consisted of an initial absorption phase followed by a short beta-elimination phase and a terminal target-mediated elimination phase, which predominated in this profile at low concentrations (Figure 2; Table 1).

The concentration-time profile for functional tocilizumab after intravenous administration (1-hour infusion) consisted of an initial distribution phase followed by biphasic elimination, which also consisted of a concentration-independent elimination phase and a terminal target-mediated elimination phase, in which the rate of clearance increased as concentration declined (Figure 2; Table 1). After intravenous dosing of tocilizumab, C_{max} was generally observed shortly after the completion of the 1-hour infusion. After subcutaneous dosing of sarilumab, C_{max} was observed at 3.6-3.7 days (t_{max}).

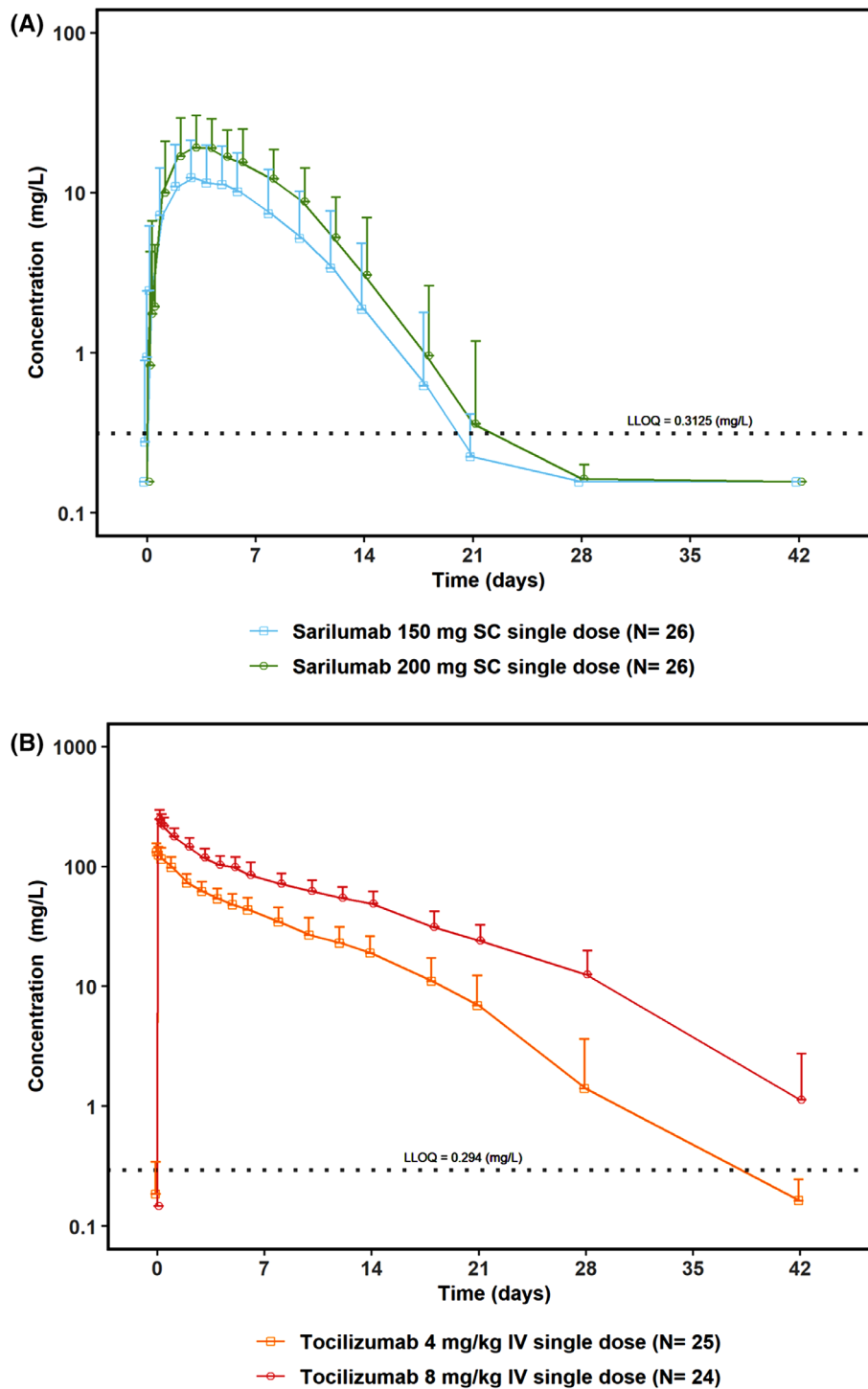


Figure 2. Mean drug concentration-time profiles for (A) sarilumab (concentrations below the LLOQ [horizontal dotted line, 0.313 mg/L] are imputed as LLOQ/2, 0.156 mg/L) and (B) tocilizumab (concentrations below the LLOQ [horizontal dotted line, 0.294 mg/L] are imputed as LLOQ/2, 0.147 mg/L) in log scale. Error bars indicate standard deviation. IV, intravenous; LLOQ, lower limit of quantitation; SC, subcutaneous.

Drug exposure for both C_{max} and AUC was about 10-fold higher for intravenous tocilizumab compared with subcutaneous sarilumab (Table 1). Mean C_{max} for sarilumab was 13.9 and 21.6 mg/L, at low and high doses, respectively; C_{max} for intravenous tocilizumab

was 138 and 265 mg/L at low and high doses, respectively. Mean $AUC_{0-28 \text{ day}}$ for subcutaneous sarilumab was 107 and 171 mg·day/L at low and high doses, respectively; $AUC_{0-28 \text{ day}}$ for intravenous tocilizumab was 765 and 1688 mg·day/L at low and high doses,

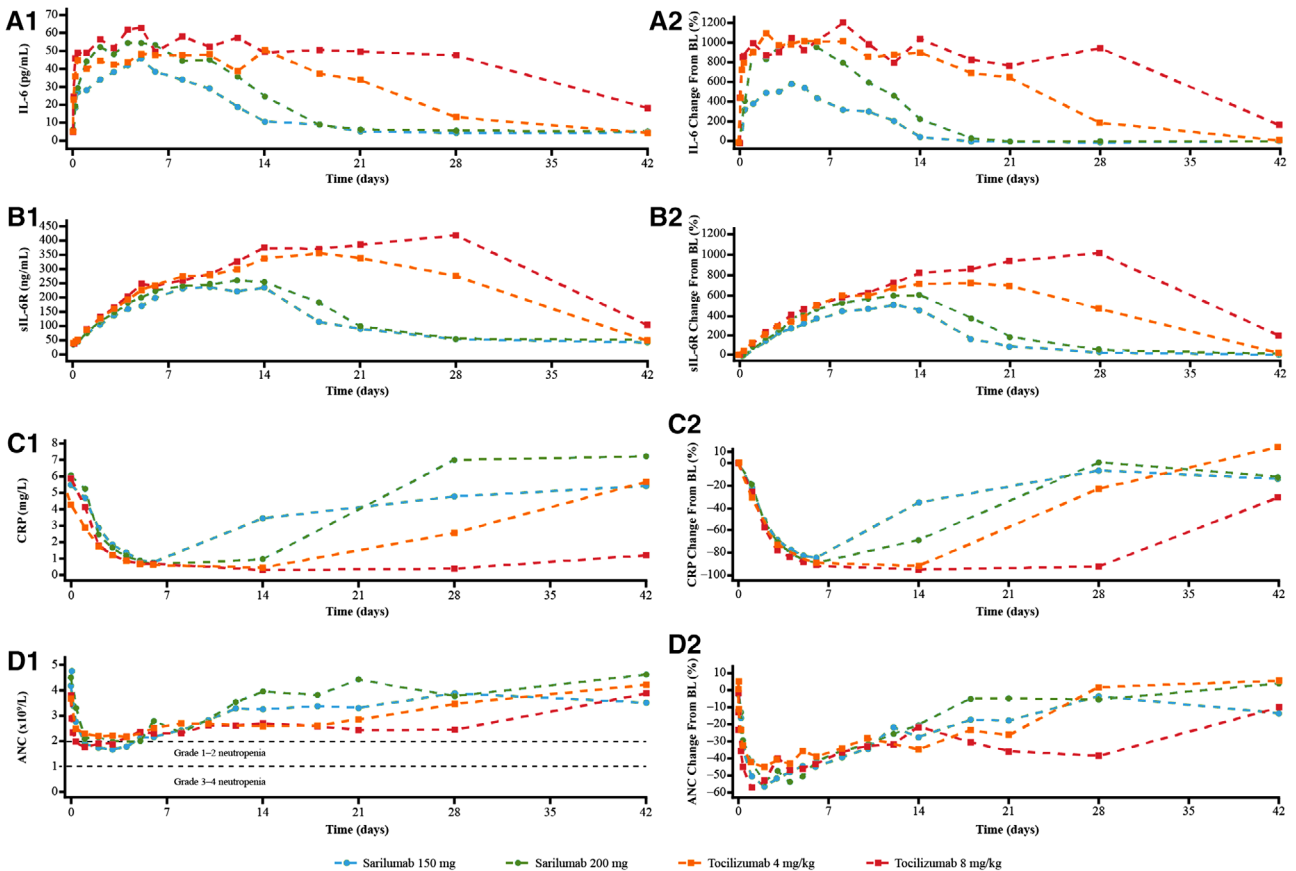


Figure 3. Biomarker (PD) value-over-time profiles for (A) serum IL-6, (B) serum total sIL-6R, (C) serum CRP, and (D) blood ANC displayed as median values (left-hand side) and percent change from BL (right-hand side). ANC, absolute neutrophil count; BL, baseline; CRP, C-reactive protein; IL-6, interleukin-6; IV, intravenous; sIL-6R, soluble interleukin-6 receptor. ANC < 2.0–1.5, < 1.5–1.0, < 1.0–0.5, and < 0.5 × 10⁹/L correspond with neutropenia grades 1, 2, 3, and 4, respectively.

respectively. After a single dose, sarilumab was detectable in serum up to 2.5 weeks at low dose and up to 3 weeks at high dose. Tocilizumab was detectable in serum up to 4 weeks at low dose and >6 weeks at high dose (Figure 2).

Dose-normalized exposure (AUC_{inf}/dose) between the low and high doses was marginally higher (1.4-fold) for subcutaneous sarilumab over a 1.33-fold increase in dose from 150 to 200 mg and was similar (1.1-fold) for intravenous tocilizumab over a 2-fold increase in dose from 4 to 8 mg/kg, reflecting limited contributions of nonlinear PK to their overall PK profiles (Table 1).

Pharmacodynamics

PD concentration–time profiles (Figure 3) are presented to allow for PK and PD comparison with the concentration–time profiles (Figure 2). In addition, temporal PK/PD relationships for direct PK/PD comparison are presented in Figure 4. PK/PD relationships are best described over a wide range of drug concentrations, particularly at low drug concentrations for which saturation of effect has not yet occurred. Hence, PK/PD

relationships are more informative after subcutaneous administration in which drug concentrations increase progressively than after intravenous administration, in which maximal concentration is reached immediately. This difference is particularly relevant for change in ANC, which is characterized by a very rapid decrease followed by an immediate increase, a pattern described as tolerance.

The temporal PK/PD relationships for mean ± SD PD (Figure 4) represented the individual temporal PK/PD relationships well (Figure S1).

IL-6. Although mean baseline IL-6 values differed 2- to 3-fold, median baseline IL-6 values were generally well balanced across groups (4.7–5.9 pg/mL; Table 2). IL-6 values increased over time, with generally similar times to peak of 4.5–5.0 days for the subcutaneous sarilumab groups and 6.0–6.5 days for the intravenous tocilizumab groups (Figure 3A1). Peak IL-6 was 60.0–94.3 pg/mL for subcutaneous sarilumab and 68.4–88.2 pg/mL for intravenous tocilizumab (Table 2). The increase in IL-6 as change from baseline (data not shown) and percent change from baseline (Figure 3A2)

Table 2. Baseline Values and Change in PD Parameters by Group

	Subcutaneous Sarilumab 150 mg (n = 26)	Subcutaneous Sarilumab 200 mg (n = 26)	Intravenous Tocilizumab 4 mg/kg (n = 25)	Intravenous Tocilizumab 8 mg/kg (n = 24)
IL-6				
Baseline				
Mean ± SD (pg/mL)	21.91 ± 58.39	9.86 ± 10.46	7.33 ± 11.14	22.14 ± 45.45
Median (range)	5.87 (1.56-299.03)	5.85 (1.56-40.39)	4.74 (1.56-57.52)	4.83 (1.56-202.19)
Peak ^a				
Mean ± SD (pg/mL)	159.28 ± 356.08	177.14 ± 234.19	142.75 ± 169.01	183.12 ± 245.76
Median (range)	60.00 (21.72-1844.40)	94.27 (17.07-1079.49)	68.39 (22.87-644.45)	88.17 (24.89-1095.16)
Median time to peak, study day ^b	4.0 [5.0]	3.5 [4.5]	5.0 [6.0]	5.5 [6.5]
Total sIL-6R				
Baseline				
Mean ± SD (ng/mL)	42.86 ± 11.94	42.91 ± 13.69	43.30 ± 14.45	43.81 ± 15.72
Median (range)	42.31 (22.12-61.75)	42.61 (19.54-67.83)	44.56 (19.54-71.43)	40.56 (22.83-75.70)
Peak ^a				
Mean ± SD (ng/mL)	274.11 ± 72.71	313.79 ± 72.53	414.97 ± 109.03	480.68 ± 119.97
Median (range)	286.92 (124.65-405.77)	305.29 (158.77-442.16)	416.06 (229.57-602.71)	443.81 (339.72-704.09)
Median time to peak, study day ^b	10.0 [11.0]	12.0 [13.0]	18.0 [19.0]	21.0 [22.0]
CRP				
Baseline				
Mean ± SD (mg/L)	13.08 ± 18.69	8.87 ± 8.50	7.07 ± 7.74	12.39 ± 14.13
Median (range)	5.50 (0.30-82.70)	6.05 (0.75-30.60)	4.28 (0.61-31.40)	5.87 (0.61-46.50)
Nadir ^a				
Mean ± SD (mg/L)	1.31 ± 1.87	0.81 ± 1.14	0.51 ± 0.46	0.37 ± 0.32
Median (range)	0.67 (0.10-8.82)	0.49 (0.10-5.13)	0.43 (0.10-1.73)	0.31 (0.10-1.35)
Median time to nadir, study day ^b	6.0 [7.0]	6.0 [7.0]	14.0 [15.0]	14.0 [15.0]
ANC				
Baseline				
Mean ± SD, × 10 ⁹ /L	4.32 ± 1.53	4.72 ± 1.96	4.04 ± 1.36	4.52 ± 2.48
Median (range)	4.15 (1.94-7.28)	4.50 (1.96-9.64)	3.63 (1.55-7.40)	3.84 (1.70-13.16)
Nadir ^a				
Mean ± SD, × 10 ⁹ /L	1.55 ± 0.56	1.76 ± 1.04	1.78 ± 0.60	1.64 ± 0.89
Median (range)	1.43 (0.61-3.07)	1.58 (0.21-3.97)	1.77 (0.96-2.92)	1.43 (0.69-4.51)
Median time to nadir, study day ^b	2.5 [3.5]	3.0 [4.0]	4.0 [5.0]	2.0 [3.0]
CRPM				
Baseline				
Mean ± SD (ng/mL)	10.86 ± 4.28	12.48 ± 5.92	9.09 ± 2.85	13.37 ± 5.40
Median (range)	9.72 (4.67-21.95)	11.44 (7.56-37.93)	9.37 (3.52-15.68)	11.69 (3.90-25.40)
Nadir				
Mean ± SD (ng/mL)	9.04 ± 3.19	10.47 ± 4.80	7.34 ± 2.29	9.39 ± 5.63
Median (range)	8.98 (3.42-17.65)	9.75 (5.44-30.83)	7.30 (3.08-11.38)	9.39 (5.20-28.20)
CIM				
Baseline				
Mean ± SD (ng/mL)	85.20 ± 69.27	78.60 ± 46.57	66.78 ± 38.15	81.69 ± 50.04
Median (range)	59.46 (14.83-271.45)	69.85 (25.65-195.31)	54.55 (23.94-162.61)	58.16 (23.04-171.21)
Nadir				
Mean ± SD (ng/mL)	40.47 ± 22.33	36.82 ± 10.52	31.24 ± 5.04	28.64 ± 9.47
Median (range)	33.83 (17.26-111.86)	34.56 (17.17-59.32)	30.04 (24.48-43.68)	28.53 (11.43-51.40)
C3M				
Baseline				
Mean ± SD (ng/mL)	17.43 ± 6.04	19.64 ± 7.16	17.49 ± 4.84	19.03 ± 6.73
Median (range)	16.00 (9.36-31.43)	18.93 (5.36-45.38)	17.48 (10.04-29.32)	17.93 (9.76-41.01)
Nadir				
Mean ± SD (ng/mL)	15.04 ± 4.74	17.41 ± 6.86	14.23 ± 3.64	15.36 ± 6.09
Median (range)	15.01 (7.65-27.95)	17.01 (5.04-42.10)	14.15 (8.47-23.88)	13.45 (9.50-32.78)

ANC, absolute neutrophil count; CIM, degradation fragment of collagen I; C3M, degradation fragments of collagen III; CRP, C-reactive protein; CRPM, C-reactive protein metabolite; IL-6, interleukin-6; PD, pharmacodynamics; SD, standard deviation; sIL-6R, soluble interleukin-6 receptor.

^aTime to nadir or peak values was calculated based on the study point at which individual patients achieved their lowest or highest value and then determining the mean or median value.

^bTimes to peak and nadir are presented based on the PK/PD time, which starts on Day 0, time 0, followed in square brackets by the time according to the clinical assessment schedule, which starts on Day 1.

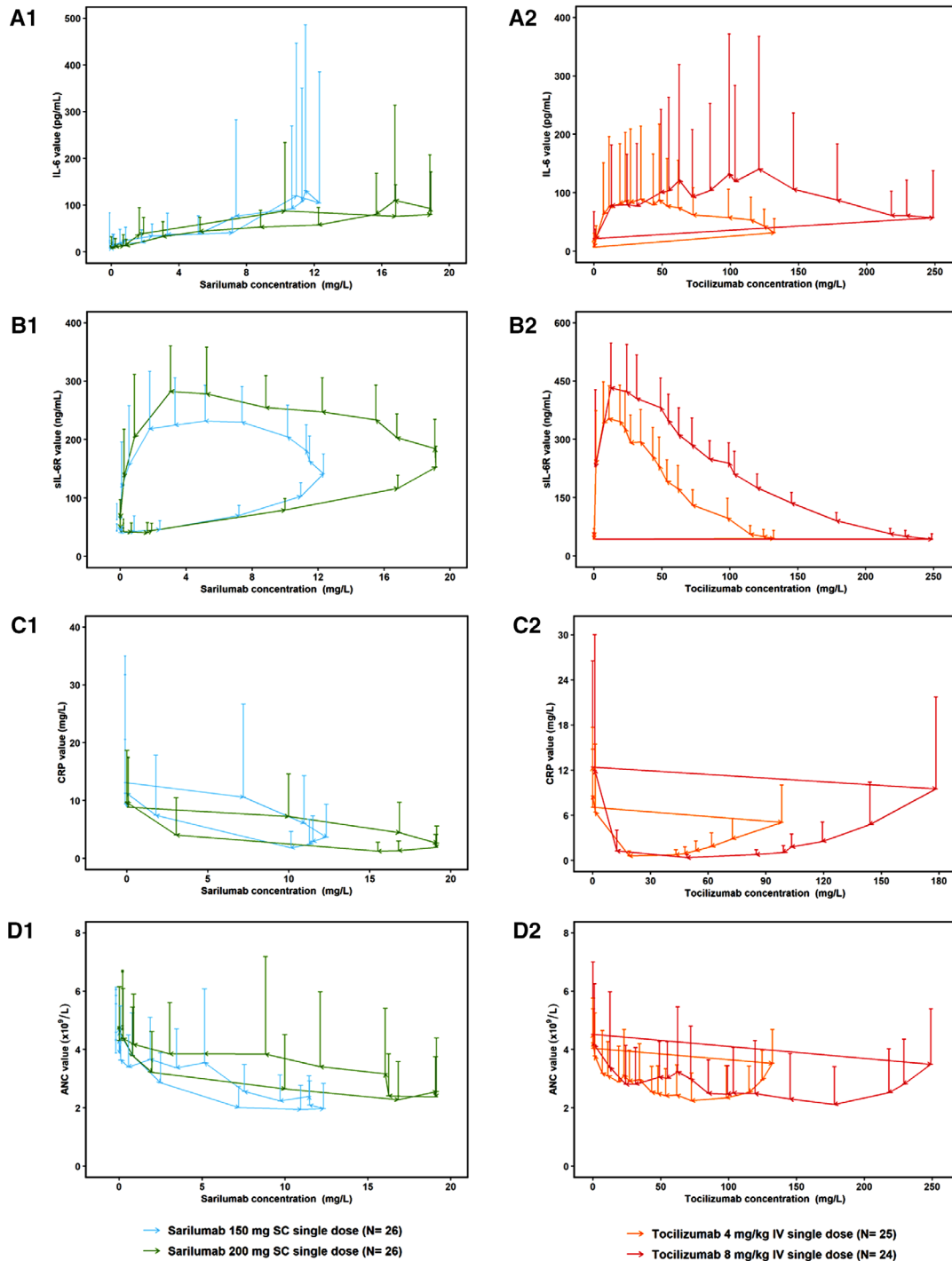


Figure 4. Temporal PK/PD relationships, where mean \pm SD biomarker values of (A) IL-6, (B) total sIL-6R, (C) CRP, and (D) ANC are plotted against mean serum sarilumab and tocilizumab concentrations over time.* *Representative individual temporal PK/PD relationships (1 patient with the 4 biomarkers per treatment group) are provided in Figure S1. ANC, absolute neutrophil count; CRP, C-reactive protein; IL-6, interleukin-6; PD, pharmacodynamic; PK, pharmacokinetic; SE, standard error; sIL-6R, soluble interleukin-6 receptor.

followed a similar pattern over time as the IL-6 values. The time to onset of the increase in IL-6 was rapid and similar across groups, whereas the effect lasted longer with intravenous tocilizumab compared with subcutaneous sarilumab. IL-6 had returned to baseline

by day 14 after subcutaneous low-dose sarilumab and by day 20 after high-dose subcutaneous sarilumab (Figure 3A1). Following a single intravenous dose of tocilizumab, IL-6 returned to baseline by day 28 after intravenous low-dose tocilizumab but had not returned

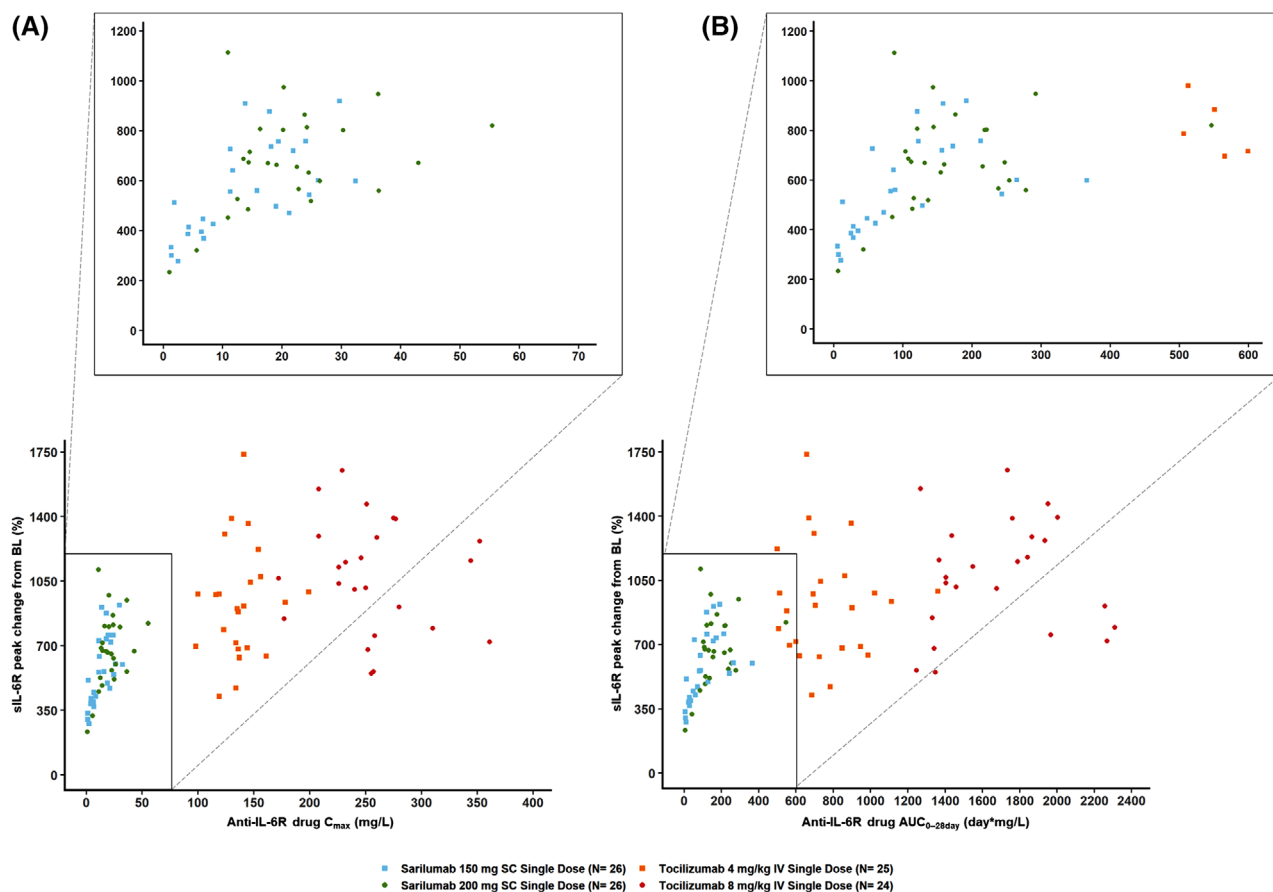


Figure 5. PK/PD relationship for individual total sIL-6R peak percent change from BL versus sarilumab or tocilizumab C_{max} (A), and $AUC_{0-28 \text{ day}}$ (B) in serum. AUC, area under the concentration-time curve; BL, baseline; C_{max} , maximum concentration; anti-IL-6R, anti-interleukin 6 receptor; PD, pharmacodynamic; PK, pharmacokinetic; sIL-6R, soluble interleukin-6 receptor.

to baseline by day 42 (end of study) after intravenous high-dose tocilizumab, reflecting the relatively high tocilizumab concentration at the end of the study.

Although no PK/PD relationship was observed between individual peak drug concentration and individual IL-6 peak value in serum (data not shown), the temporal PK/PD relationship for sarilumab concentrations and IL-6 levels showed a flat hysteresis loop (clockwise, counterclockwise, or twisted), suggestive of a direct concentration-effect relationship (Figure 4A1). Because the highest tocilizumab concentrations occurred immediately after intravenous tocilizumab, maximal IL-6 values were observed while the drug concentrations were in the initial distribution phase (Figure 4A2), not allowing for further interpretation of this temporal PK/PD relationship.

sIL-6R. Baseline mean and median serum sIL-6R values were generally comparable across groups. The time to onset of increase in sIL-6R was similar across groups, with a shorter duration of effect with subcutaneous sarilumab compared with intravenous tocilizumab. Time-to-peak for total sIL-6R was earlier with sarilumab than with tocilizumab and

ranged from 11 to 13 days with sarilumab and 19-22 days with tocilizumab (Table 2; Figure 3B1). Total sIL-6R median values were generally lower with sarilumab than with tocilizumab and higher with high- versus low-dose sarilumab. The mean change from baseline (data not shown) and mean percent change from baseline in sIL-6R (Figure 3B2) were also lower with subcutaneous sarilumab than with intravenous tocilizumab. With subcutaneous sarilumab at both doses, total sIL-6R values remained elevated through day 14 and decreased back to baseline by day 21. With intravenous tocilizumab, total sIL-6R values on day 28 remained elevated at the high dose and had begun to decrease with the low dose (Figure 3B2).

Individual total sIL-6R peak (value, change, and percent change from baseline) appeared to be associated with sarilumab C_{max} , with a trend toward a plateau at a C_{max} above 25 mg/L as well as with sarilumab $AUC_{0-28 \text{ day}}$ (Figure 5). No such correlations were observed for intravenous tocilizumab (Figure 5).

As anticipated, the increase in total sIL-6R occurred after maximal drug concentrations had been reached. This was indicated by a counterclockwise hysteresis

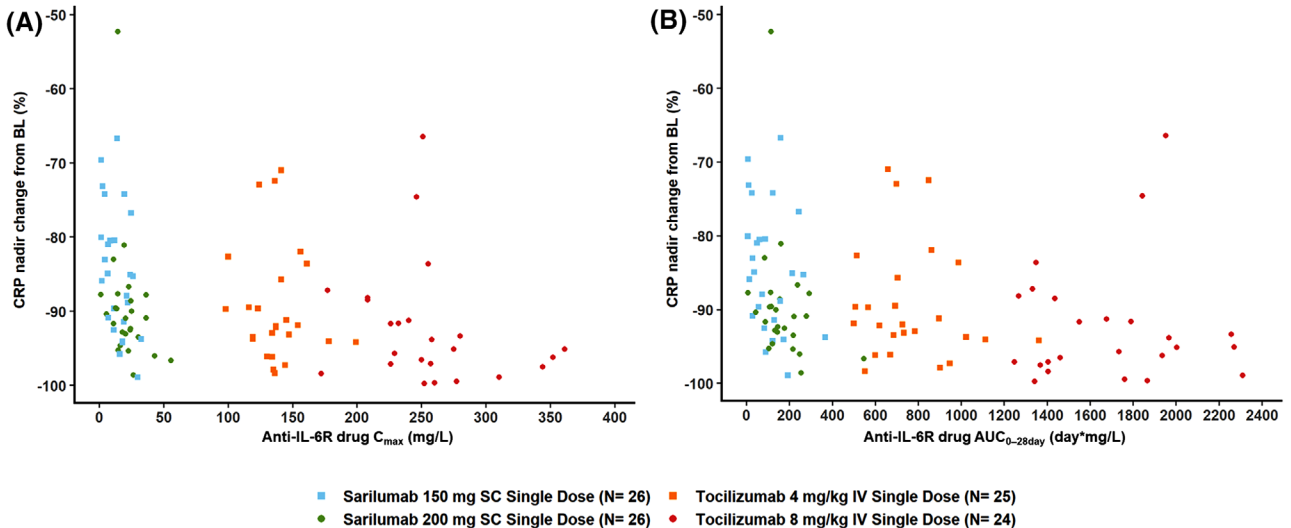


Figure 6. PK/PD relationships for individual CRP nadir percent change from BL versus sarilumab or tocilizumab C_{max} (A) or $AUC_{0-28 \text{ day}}$ (B) in serum. AUC, area under the concentration-time curve; BL, baseline; C_{max} , maximum concentration; CRP, C-reactive protein; IL-6R, interleukin 6 receptor; PD, pharmacodynamic; PK, pharmacokinetic.

loop on the temporal PK/PD relationship for sarilumab or tocilizumab concentrations and total sIL-6R values (Figure 4B1,2). Maximal increase in total sIL-6R was achieved and remained high as drug concentrations had already declined. The maximal increase in total sIL-6R appeared slightly higher with the high dose compared with the low dose of the anti-IL-6R drugs.

CRP. As expected, individual baseline CRP values in serum were not normally distributed in the patient population, and therefore median values are reported. Median baseline CRP did not differ across the groups (Table 2). Following both subcutaneous sarilumab and intravenous tocilizumab, a decrease in CRP was observed by 4 hours postdose, reaching a nadir for both subcutaneous sarilumab doses on day 7 and for both intravenous tocilizumab doses on day 14 (Figure 3C1). The decrease in CRP values, as change from baseline (data not shown) and percent change from baseline (Figure 3C2), followed a similar pattern as the absolute values. Although the onset in decrease was similar across all groups, a difference in the rate of return to baseline was observed, with CRP returning toward baseline beginning by day 14 with subcutaneous sarilumab at both doses, by day 28 with low-dose intravenous tocilizumab, and with remaining suppression on day 28 after high-dose intravenous tocilizumab (Figure 3C1).

Overall, there was no clear trend toward a PK/PD relationship between PK parameters (C_{max} or $AUC_{0-28 \text{ day}}$) of anti-IL-6R drugs and individual CRP nadir (as absolute value [data not shown], change [data not shown], and percent change from baseline [Figure 6]).

In agreement with the direct PK/PD relationship described above, the temporal PK/PD relationship for sarilumab concentrations/CRP values (Figure 4C1) indicated that CRP values decreased over time with increasing sarilumab concentrations before returning to baseline as the drug concentrations decreased. A clockwise hysteresis loop indicated a time delay between the decrease in CRP with increasing drug concentrations. Because the highest drug concentrations for intravenous tocilizumab occurred immediately, maximal decrease in CRP values was observed as tocilizumab concentrations already had declined (Figure 4C2).

ANC. Baseline mean and median ANC were generally comparable across groups (Table 2). The onset of the decrease in ANC was immediate, within a few hours of administration, and similar across groups, whereas the effect lasted longer with intravenous tocilizumab compared with subcutaneous sarilumab (Figure 3D1). The median time to nadir was comparable between groups and was reached by day 3-5 (Table 2). Following the nadir, ANC began to return toward baseline at similar rates through day 14. From day 14 onward, ANC generally increased in accordance with drug concentration (Figure 3D1,2). Thus, rate of return of ANC to baseline was faster with the lower doses of sarilumab and tocilizumab. By day 14, ANC had increased in the sarilumab groups, although it did not return to baseline values. ANC values had essentially returned to baseline on day 28 in the intravenous low-dose tocilizumab group but were still suppressed in the intravenous high-dose tocilizumab group, with recovery toward baseline observed at the subsequent assessment on day 42.

The decrease in ANC that occurred immediately (first sampling point) following IL-6R α inhibition with sarilumab was similar regardless of drug concentrations, indicating an immediate effect that already occurred at very low drug concentrations and suggesting that saturation of the decrease in ANC may occur. This was immediately followed by a slow increase in ANC, even before the maximal sarilumab concentrations in serum had been reached, suggesting that tolerance to the decrease in ANC may occur. The overall duration of the decrease in ANC differed across groups and was \approx 14 days (2 weeks) for both low-dose subcutaneous sarilumab and intravenous tocilizumab and \approx 28 days (1 month) with high-dose intravenous tocilizumab (Figure 3D1), consistent with their PK profiles.

As suggested by the similar onset of effect on ANC, no PK/PD correlations were apparent between individual C_{\max} or $AUC_{0-28 \text{ day}}$ for subcutaneous sarilumab, or intravenous tocilizumab and individual ANC nadir (as absolute value, change from baseline, or percent change from baseline; data not shown). The temporal PK/PD relationship for mean sarilumab concentration/ANC (Figure 4D1) indicated that ANC decreased immediately and to the same extent regardless of drug concentration, indicating saturation of the decrease in ANC. The maximal inhibitory effect (ANC nadir) preceding the maximal drug concentration is shown with sarilumab subcutaneously as a counterclockwise proteresis. The saturation of the inhibitory effect is indicated by the horizontal position of the proteresis along the x axis (Figure 4D1).

Exploratory biomarkers. Baseline values of each of the exploratory biomarkers (CRPM, C1M, and C3M) were similar across groups. CRPM, C1M, and C3M values decreased transiently postdose (Table 2) and returned toward baseline values by day 42. The median time to nadir for CRPM occurred on days 6 and 7 for low- and high-dose sarilumab, respectively, and days 7 and 15 for low- and high-dose tocilizumab, respectively. The nadir for CRPM was more pronounced with the high dose compared with the low dose of either drug. For C1M and C3M (Table 2), the nadir occurred somewhat earlier with the low dose of sarilumab (day 7 for both) and somewhat later with the high dose of tocilizumab (day 14 for C1M and day 28 for C3M). The nadir for both C1M and C3M was more pronounced with high doses of either drug.

Safety

Overall safety findings following a single dose of subcutaneous sarilumab or intravenous tocilizumab have been previously described for this study.²⁰ The incidence of TEAEs was similar with sarilumab and tocilizumab, with a higher number of events observed for the high-dose groups. The most common TEAE was neutrope-

nia (15.4%, 26.9%, 12.0%, and 25.0% of patients treated with low- and high-dose sarilumab and low- and high-dose tocilizumab, respectively). Per protocol, grade 3 (ANC ≥ 0.5 - $1.0 \times 10^9/L$) or grade 4 neutropenia (ANC $< 0.5 \times 10^9/L$) were to be reported as TEAEs. TEAEs of neutropenia were all grade 3 except for 1 patient (3.8%) in the sarilumab 200-mg group, who had grade 4 neutropenia. Laboratory changes were consistent with IL-6R signaling blockade and included decreases in neutrophil and platelet counts and increases in transaminases and lipids.²⁰ The observed decrease in ANC and platelet counts was not associated with any apparent increase in the incidence of infections or bleeding events, respectively.

Discussion

This phase 1b study assessed the PK and PD parameters of IL-6R blockade with single-dose subcutaneous sarilumab 150 mg (low dose) or 200 mg (high dose), or single-dose intravenous tocilizumab 4 mg/kg (low dose) or 8 mg/kg (high dose) in patients with RA on a stable dose of MTX. Frequent sampling times in the early postdose period were unique to this analysis and allowed for a comprehensive understanding of the onset of IL-6 inhibition on PD markers and the relationship between individual PD markers for IL-6 blockade and the anti-IL-6R drug concentrations in serum. In addition, the time course of exploratory biomarkers of IL-6-mediated MMP degradation (CRPM, C1M, and C3M) were described.

Consistent with previous PK evaluations of sarilumab²³ and tocilizumab,²⁴ concentration-time profiles observed following a single subcutaneous or intravenous dose were described by parallel linear and nonlinear target-mediated clearance pathways. At the doses studied, the linear component was dominant, as suggested by the similarity in dose-normalized PK parameters. Because of the different dosing regimens and routes of administration, further comparisons between sarilumab and tocilizumab PK are not relevant.

sIL-6R blockade by anti-IL-6R drugs causes an increase in total sIL-6R and a delay in the elimination of sIL-6R because of formation of the anti-IL-6R drug/sIL-6R complex, the clearance of which is slower than that of sIL-6R.²¹ By blocking the natural target-mediated binding and elimination pathway of sIL-6R, a reflex feedback mechanism may occur that results in enhanced IL-6 production without a biologic consequence, as the receptor has been blocked. Nishimoto et al also showed that anti-IL-6R drugs actually generate an increase in IL-6 values in serum and proposed that this results from inhibition of IL-6R-mediated consumption of IL-6 by unbound

(drug-free) sIL-6R.²¹ Therefore, the increased free IL-6 values observed during anti-IL-6R treatment are unable to trigger downstream signaling and are therefore unlikely to closely reflect actual endogenous IL-6 production and thus disease activity.²¹ In the absence of anti-IL-6R therapy, elevated IL-6 enhances signaling in hepatocytes to promote production of acute-phase reactants such as CRP, an established marker of both systemic inflammation and disease activity in RA.²⁵ However, when complexed by anti-IL-6R therapy, sIL-6R and mIL-6R effectively block IL-6 activities because they block IL-6 signaling.²¹ Hence, decreases in CRP following anti-IL-6R therapy reflect the clinically desired anti-inflammatory drug response and therefore improve disease control.²⁵ An additional PD effect of anti-IL-6R therapy is a reduction in circulating white blood cells (measured as ANC in blood), which has not been associated with an increased risk of infection.^{8-10,17}

Overall, following single-dose administration of subcutaneous sarilumab (150 or 200 mg) or intravenous tocilizumab (4 or 8 mg/kg), IL-6, sIL-6R, and CRP values, and ANC in blood or serum demonstrated a similar onset of anti-IL-6R effect during the first week postdose across all groups, characterized by an increase in sIL-6R and IL-6 values and a nadir in CRP and ANC. IL-6 increased to a lesser extent at the subcutaneous sarilumab low dose but, as described above, is of no clinical relevance in the presence of IL-6R α blockade. Total sIL-6R values in serum rose to a plateau in which saturation of effect was reached. This suggests that maximal drug effect on sIL-6R, CRP, and ANC was achieved for subcutaneous sarilumab, in agreement with its high affinity for the IL-6R at 10-fold lower anti-IL-6R drug concentrations compared with intravenous tocilizumab.²⁶ Aligned with the concentration-time profiles, return of PD parameters toward baseline values occurred faster with subcutaneous sarilumab (both doses) and with low-dose intravenous tocilizumab than with high-dose intravenous tocilizumab, for which the effect lasted for a longer period. IL-6R α inhibition resulted in an immediate decrease in CRP values from day 1, reaching close to nadir by day 7 for both subcutaneous sarilumab and intravenous tocilizumab and lasting through day 15 for intravenous tocilizumab at both low and high doses.

Despite the similar onset of PD effect across all anti-IL-6R drug doses and the absence of a clear PK/PD relationship between individual C_{\max} of anti-IL-6R drugs in serum, the maximal effect on sIL-6R (peak; % increase) and CRP (nadir; % decrease) and a trend toward a PK/PD relationship could be perceived at low anti-IL-6R drug concentrations (subcutaneous sarilumab), more so for the sIL-6R peak than for CRP nadir. Temporal PK/PD relationships showed a

hysteresis loop that was counterclockwise for sIL-6R and clockwise for CRP.

CRPM (CRP degradation product) and C1M and C3M (collagen degradation products) are released from chronically inflamed tissue when CRP and collagen are degraded by proteases such as MMPs.^{27,28} IL-6 has been shown to upregulate MMPs, and in this single-dose study, dose-dependent decreases in circulating markers of joint inflammation (CRPM, C1M, and C3M) were observed. Similar findings have been shown in previous analyses following subcutaneous sarilumab multiple dosing in phase 3 studies.^{29,30} In 1 retrospective analysis, sarilumab 150 or 200 mg every 2 weeks with MTX significantly reduced values of markers of joint inflammation and collagen degradation compared with MTX alone.²⁹ A rapid dose-dependent reduction in several MMP-generated biomarkers was observed as early as 2 weeks after initiation of subcutaneous sarilumab and was sustained for ≥ 24 weeks. In another exploratory analysis, subcutaneous sarilumab 150 or 200 mg every 2 weeks with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) also significantly and dose-dependently reduced values of markers of joint inflammation by week 2 compared with csDMARDs alone.³⁰ Together, these data suggest that 1 mechanism driving the accumulation of CRP and collagen degradation products may be IL-6-mediated upregulation of MMPs. However, given that the maximal reduction of CRPM occurred on day 15 in tocilizumab-treated patients, which was also the nadir for CRP, the reduction in CRPM could alternatively be driven by a reduction in CRP values. Our findings add to the previous data, showing early effects on these biomarkers for joint inflammation, which reached a maximum effect within 2-3 weeks after a single dose.

In the present study, a similar onset of the effect on ANC was observed within the first 2 weeks after a single low or high dose of subcutaneous sarilumab or intravenous tocilizumab. A mean ANC nadir ranging from 1.55 to $1.78 \times 10^9/L$ across all groups occurred 3 to 5 days postdose, with an immediate increase toward baseline. ANC returned to baseline after 2 weeks for subcutaneous sarilumab and around 1 month for intravenous tocilizumab postdose.

The temporal PK/PD relationship between sarilumab concentrations in serum and ANC is represented by a proteresis in which maximal drug effect (decrease in ANC) precedes the maximum circulating drug concentrations. Data suggest that maximum reduction in ANC is already achieved at very low sarilumab concentrations and that the effect of sarilumab on ANC is saturable, as can be observed from the maximal effect that remains around $2 \times 10^9/L$ despite higher circulating drug concentrations. The rapid and similar onsets in decreases in ANC with subcutaneous

sarilumab and intravenous tocilizumab reflect an immediate and saturable effect, irrespective of the dose and the route of administration of the anti-IL-6R drug. The minimum concentration of tocilizumab to produce a maximum decrease in ANC is unknown but is expected to be low and could not be observed, as intravenous administration immediately resulted in very high tocilizumab concentrations at which saturation of effect had already occurred. In addition to saturation of effect, ANC returned toward baseline while sarilumab concentrations were still increasing. That the decrease in ANC preceded the maximal drug concentrations and ANC returned toward baseline while anti-IL-6R drug concentrations remained high translated into a counterclockwise temporal PK/PD proteresis loop. This indicates a phenomenon of pharmacologic “tolerance” to the anti-IL-6R drug, whereby the immediate effect on the decrease in ANC is relatively short lasting.

Overall, the findings suggest a phenomenon of IL-6-mediated redistribution of the white blood cells (neutrophils) from the vascular compartment into the vascular wall or other tissues (such as bone marrow), which is referred to as “margination of neutrophils,” without changing their functionality and while remaining available in case of an infection (demargination).¹⁸ Margination and demargination of neutrophils with preservation of the functionality of neutrophils is supported by clinical experience with sarilumab, with which decreases in ANC have not been associated with an increased risk of infection.^{8-10,14,17}

Safety has been reported in more detail previously.²⁰ Aligned with the ANC observations, neutropenia was the most commonly reported TEAE in this single-dose study and is consistent with what has been observed with administration of repeat doses of sarilumab.¹⁴ The rates of TEAEs were comparable in the sarilumab and tocilizumab groups and numerically higher for the higher doses compared with the lower doses of sarilumab and tocilizumab.

Study of the relationships between drug concentrations and PD marker values allows a better understanding of the phenomena involved in IL-6R blockade on single-dose treatment and is also relevant in the clinical multiple-dose setting. At the time when this study was designed, tocilizumab was approved only for intravenous administration. Therefore, subcutaneous tocilizumab was not investigated in this study, and PK and PD relationships for subcutaneous tocilizumab cannot be directly extrapolated from data generated after intravenous administration. However, PK and PD data collected after intravenous tocilizumab provide additional insights on the PK/PD relationships for anti-IL-6R drugs in general. In addition, PK and PD effects (on IL-6, sIL-6R, CRP, and ANC) following single-dose subcutaneous tocilizumab compared with

subcutaneous sarilumab have recently been reported in Japanese patients.³¹ Observations for the PD biomarkers evaluated here confirm that the return to baseline in PD response is faster with subcutaneous sarilumab and subcutaneous tocilizumab compared with intravenous tocilizumab, which is consistent with the approved dosing regimens (once every 2 weeks for subcutaneous sarilumab, once every 2 weeks or weekly for subcutaneous tocilizumab, and once every 4 weeks for intravenous tocilizumab).

Conclusions

In summary, the drug concentration-time profiles following single doses of subcutaneous sarilumab (150 and 200 mg) and intravenous tocilizumab (4 and 8 mg/kg) were indicative of target-mediated drug disposition and concentration-dependent elimination. Maximal drug effect on the PD biomarkers (IL-6, sIL-6R, CRP, and ANC) was achieved at the low and high doses evaluated here. The PK and PD data provide support for the elevation in IL-6 and sIL-6R values in serum as being a secondary effect of IL-6R blockade because of loss of IL-6R-mediated clearance. Overall, despite differences in PK, the onset of the increases in IL-6 and sIL-6R was similar for subcutaneous sarilumab and intravenous tocilizumab. A rapid decrease in CRP and in ANC occurred, with an onset that was similar regardless of the dose and route of administration of the anti-IL-6R drug. Maximal decrease in CRP (indicator of efficacy) correlated with circulating drug concentrations, while there was maximal decrease in ANC saturated with drug concentrations. The effect on ANC is in agreement with the hypothesis that anti-IL-6R drugs promote neutrophil margination from the systemic circulation to the vascular walls or other tissue. Exploratory markers for joint inflammation (CRPM, C1M, and C3M) decreased in a dose-dependent manner. The effect of both anti-IL-6R drugs, subcutaneous sarilumab and intravenous tocilizumab, on PD biomarkers and safety is consistent with previous study results of RA patients administered an IL-6 inhibitor.

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Conflicts of Interest

A.J.P., P.K., J.P., A.B., J.D.D., and A.T.D. are employees of Regeneron Pharmaceuticals, Inc., and may hold stock and/or stock options in the company. C.X. and H.v.H. are employees of Sanofi Genzyme, and may hold stock and/or stock options in the company. T.I. has received research grants and/or consulting fees from GlaxoSmithKline and Janssen, and speakers' bureau for Asahi, AbbVie, Astellas, Chugai, Daiichi-Sankyo, Eisai, Janssen, Mitsubishi-Tanabe, Ono, Pfizer, Sanofi, Takeda, Teijin, UCB, and Kasei Pharma.

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Data Sharing

Qualified researchers may request access to patient-level data and related study documents including clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and data set specifications. Patient-level data will be anonymized and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data-sharing criteria, eligible studies, and process for requesting access can be found at <https://www.clinicalstudydatarequest.com>.

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Supplemental Information

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