Pharmacokinetics and pharmacodynamics of tocilizumab after subcutaneous administration in patients with rheumatoid arthritis

Xiaoping Zhang¹, Ya-Chi Chen¹, Scott Fettner¹, Lucy Rowell², Tatiana Gott¹, Paul Grimsey² and Adam Unsworth²

¹Hoffmann-La Roche Inc., Nutley, NJ, USA, and ²Roche Products Ltd., Welwyn Garden City, UK

**Key words**

**Abstract.** Objectives: To investigate the pharmacokinetics, pharmacodynamics, safety and efficacy of subcutaneous tocilizumab 162 mg weekly (QW) or every other week (Q2W) in rheumatoid arthritis patients on methotrexate. Methods: This was a multicenter, open-label, randomized, parallel-group study. Patients were randomly assigned to receive tocilizumab 162 mg subcutaneously QW or Q2W for 12 weeks. Pharmacokinetic and pharmacodynamic measurements were taken from baseline through to treatment end. Efficacy was assessed at baseline and Q4W thereafter. Safety and tolerability were monitored. Results: 29 patients received tocilizumab treatment for 12 weeks. After final QW and Q2W dosing, mean ± SD for Cₘₐₓ, Cₘᵦᵦ and AUC₀–₈₈₈₈ was 39.4 ± 18.1 and 10.7 ± 6.6 µg/ml, 27.9 ± 14.7 and 2.3 ± 3.2 µg/ml and 5,505 ± 2,632 and 2,332 ± 1,696 µg×h/ml. Median tₘₐₓ was 2 – 3 days. Mean soluble interleukin-6 receptor (sIL-6R) complex concentration increased within 1 week and plateaued (670 ± 211 (QW); 387 ± 194 ng/ml (Q2W)) by final dosing; median C-reactive protein (CRP) levels decreased to below upper limit of normal after first and third doses; mean ± SD (range) reduction in Disease Activity Score using 28 joints at Week 12 was similar between groups (–2.5 ± 1.2 (–4 to –1); –3.1 ± 1.1 (–5 to –2)). Patients experiencing ≥ 1 adverse event were comparable between groups (71% vs. 80%). Conclusions: Greater tocilizumab exposure and sIL-6R elevation and more rapid CRP level normalization occurred with QW than with Q2W dosing. Both regimens demonstrated clinical benefit and were well tolerated.

**Introduction**

Tocilizumab is a humanized monoclonal antibody that inhibits interleukin-6 (IL-6) from binding to the soluble (sIL-6R) and membrane-expressed forms of its receptor, thus inhibiting the IL-6–mediated signaling cascade that brings about the proinflammatory activity of the cytokine [1]. The efficacy and safety of tocilizumab, administered as an intravenous (i.v.) infusion, in the treatment of patients with rheumatoid arthritis (RA) were shown in randomized, controlled, phase 3 trials [2, 3, 4, 5, 6]. Tocilizumab is approved in many countries and regions of the world – among them the United States, the European Union and Japan – for the treatment of patients with moderate to severe active RA at a recommended i.v. dose of 8 mg/kg (not exceeding 800 mg per infusion) every 4 weeks (in the United States, the recommended starting dose is 4 mg/kg followed by an increase to 8 mg/kg based on clinical response) [7, 8, 9]. This dosing schedule necessitates regular visits to the clinic for infusion. Although a subcutaneous (s.c.) delivery method administered by the patient at home would appear preferable to repeated clinic visits, treatment delivery by s.c. injection has innate challenges, particularly because s.c. injection volumes are limited (e.g., 1 ml). Because of its limited solubility (180 mg/ml), tocilizumab cannot be delivered by the s.c. route at a dose (560 mg for a 70 kg patient) similar to that given by the i.v. route (8 mg/kg) using a 1 ml syringe. Therefore, more frequent dosing of tocilizumab is foreseen for the s.c. compared with the i.v. formulation. This is the first study evaluating the pharmacokinetics (PK), pharmacodynamics (PD), efficacy and safety of tocilizumab administered using the s.c. formulation for injection in patients with active RA. PK and PD results from this study were also compared with historical data obtained from tocilizumab i.v. studies.
Methods

Study drug

Tocilizumab for s.c. injection was supplied at a concentration of 180 mg/ml, in single-use vials, with a nominal 162 mg tocilizumab in 0.9 ml histidine-buffered solution (RO4877533/F10, Lot M8C21). The sterile, yellowish, preservative-free liquid solution, which had a pH of ~ 6.0, comprised tocilizumab, polysorbate 80, L-histidine and L-histidine monohydrochloride, L-arginine hydrochloride, L-methionine and water.

Patient population

29 subjects who satisfied the following eligibility requirements were enrolled in the study: RA of at least 6 months’ duration; diagnosis according to the revised 1987 American College of Rheumatology (ACR) criteria [10]; swollen joint count (SJC) ≥ 4 (66 joint count) and tender joint count (TJC) ≥ 6 (68 joint count); stable dose of methotrexate (7.5 – 25 mg/week); C-reactive protein (CRP) levels ≥ 0.7 mg/dl (or erythrocyte sedimentation rate (ESR) ≥ 28 mm/hour). All disease-modifying antirheumatic drugs (DMARDs), other than methotrexate, were withdrawn before baseline. Oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and nonsteroidal anti-inflammatory drugs (up to maximum recommended dose) were permitted if doses were given for at least 4 weeks before baseline.

Patients were excluded if any of the following applied: treatment with any investigational agent within 4 weeks (or 5 half-lives of investigational drug, whichever was longer) of screening; immunization with a live vaccine within 4 weeks; previous treatment with tocilizumab; history of severe allergic or anaphylactic reactions to human, humanized or murine monoclonal antibodies; serious uncontrolled concomitant cardiovascular, nervous system, pulmonary, renal, hepatic, endocrine or gastrointestinal (GI) diseases, including history of GI perforation; uncontrolled disease states such as asthma, psoriasis or inflammatory bowel disease, for which flares are commonly treated with oral or parenteral corticosteroids; active infection or history of recurrent bacterial, viral, fungal, mycobacterial or other infection; any major episode of infection requiring hospitalization or treatment with i.v. antibiotics within 4 weeks of screening or with oral antibiotics within 2 weeks of screening; diagnosis of rheumatic autoimmune disease other than RA, including systemic lupus erythematosus, mixed connective tissue disease, scleroderma, polymyositis or significant systemic involvement secondary to RA (e.g., vasculitis, pulmonary fibrosis, Felty syndrome).

All patients provided written informed consent before screening and enrollment in the study. The study was conducted in compliance with the Declaration of Helsinki and was approved by an Independent Ethics Committee at each center (Canada, Institutional Review Board Services; New Zealand, Upper South A Regional Ethics Committee; Spain, Comité Autonómico de Ensayos Clínicos).

Study design

In this multicenter, open-label, randomized, parallel-group study, patients with active RA were randomly assigned to receive a tocilizumab 162 mg s.c. injection once weekly (QW dosing group) or biweekly (Q2W dosing group) for 12 weeks. All patients received weekly methotrexate 7.5 – 25 mg (oral or parenteral) and at least 5 mg oral folic acid weekly throughout the study. Patients not entering a 1-year poststudy provisional care program offered by the study sponsor had a follow-up visit 3 weeks after the final treatment visit. The study was conducted at seven centers located in Canada (three centers), New Zealand (one center) and Spain (three centers).

Pharmacokinetic and pharmacodynamic assessments

The schedule for serum sample collection for assessment of CRP, tocilizumab PK and PD (IL-6 and sIL-6R) and anti-tocilizumab antibody measurement is provided in Table 1. Samples for CRP assessments were taken every other week for the QW group. In contrast, samples were taken between doses
In the Q2W dosing group given that CRP levels fluctuate during a dosing interval if the concentration of tocilizumab is not sufficient to block the IL-6R [11], CRP assessment was taken from safety laboratory tests. The CRP assay was performed at Covance Central Laboratory Services (multiple locations) by immunonephelometry using the BN II Nephelometer (Siemens Healthcare Diagnostics, Inc., Tarrytown, NY, USA).

### Sample analysis

Samples were analyzed using enzyme-linked immunosorbent methods for tocilizumab, IL-6, sIL-6R and anti-tocilizumab antibodies (QPS Netherlands BV, Gröningen, The Netherlands). The tocilizumab lower limit of quantification (LLQ) was 0.1 mg/ml, precision (% coefficient of variation (CV%)) was 8.6 – 13.2%, and overall accuracy was 102.5 – 105.4%. sIL-6R LLQ was 12.5 ng/ml (in native serum, sIL-6R concentrations reported are the total of three analytes: free sIL-6R, tocilizumab-bound sIL-6R and IL-6–bound sIL-6R), precision was 5.4 – 6.3%, and overall accuracy was 105.1 – 109.5%. IL-6 low-sensitivity assay LLQ was 3.12 pg/ml (native serum), precision was 6.9 – 9.7%, and overall accuracy was 102.6 – 108.8%. IL-6 high-sensitivity assay LLQ was 0.31 pg/ml (native serum), precision was 15.3 – 23.6%, and overall accuracy was 89.5 – 96.5%. Tests for antitocilizumab antibodies were performed according to the standard testing paradigm, which consists of a screening assay, a confirmation assay in patients with positive findings at screening, and further assessment for neutralizing antibodies in patients with positive findings in the confirmation assay. For screening and confirmatory assays, sensitivity was 7.81 ng·Eq/ml (native serum), precision was 8.1 – 12.6% (screening assay) and 8.0 – 11.8% (confirmatory assay), and overall accuracy was 93.4 – 95.8% (screening assay) and 93.7 – 99.4% (confirmatory assay). For neutralizing antibody assay, sensitivity of the assay was 211 ng·Eq/ml (native serum), precision was 0.4 – 6.6%, and overall accuracy was 76.8 – 94.4%. Values for CRP and ESR were taken from safety laboratory tests. The CRP assay was performed at Covance Central Laboratory Services (multiple locations) by immunonephelometry using the BN II Nephelometer (Siemens Healthcare Diagnostics, Inc., Tarrytown, NY, USA).

### Efficacy evaluations

Efficacy parameters included Disease Activity Score using 28 joints (DAS28) [12], categorical DAS28 responders (European League Against Rheumatism (EULAR) responders) [12] and ACR20, ACR50 and ACR70 responses [10]. Efficacy core components (SJC, TJC, pain on a visual analogue scale (VAS), patient and physician global assessment on using VAS, health assessment questionnaire (HAQ), CRP levels and ESR) were assessed predose at baseline and at Weeks 4, 8, and 12 for both groups. SJC and TJC were assessed by a skilled joint assessor experienced in arthritic joint assessment without access to any other patient data. Other efficacy evaluations were made by the investigator.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Dose</th>
<th>Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP assessment</td>
<td>QW</td>
<td>Pre</td>
</tr>
<tr>
<td></td>
<td>Q2W</td>
<td>Pre</td>
</tr>
<tr>
<td>Tocilizumab PK and PD (IL-6 and sIL-6R)</td>
<td>QW</td>
<td>Pre and posta</td>
</tr>
<tr>
<td></td>
<td>Q2W</td>
<td>Pre and posta</td>
</tr>
<tr>
<td>Anti-tocilizumab antibodies</td>
<td>QW</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Q2W</td>
<td>X</td>
</tr>
</tbody>
</table>

Table 1. Schedule for collection of serum samples.

B = baseline; CRP = C-reactive protein; FUP = follow-up period; IL-6 = interleukin-6; PD = pharmacodynamics; PK = pharmacokinetics; Pre = predose; Post = postdose; QW = weekly; Q2W = every 2 weeks; sIL-6R = soluble form of interleukin-6 receptor. a6, 24, 48, 72, 120 and 168 hours postdose. b6, 24, 48, 72, 120, and 168 hours postdose. c6, 24, 48, 72, 120, 168, 240 hours postdose.
Safety evaluations

The safety population included all patients who received at least one dose of study medication, regardless of whether they were prematurely withdrawn from the study. Adverse events (AEs) were recorded throughout the study. Injection site reactions (ISRs) were evaluated immediately after (0 – 2 hours) the first, second and last injections, and 24 hours after the first and last injections. Laboratory tests included blood chemistry and urinalysis (tested at baseline and at Week 12), hematology (tested at baseline and at Weeks 1, 2, 4, 6, 8 and 12), liver function (tested at baseline and at Weeks 1, 2, 4, 8 and 12) and lipid panel (tested at baseline and Weeks 1, 4, 8 and 12). All laboratory safety tests were performed at screening and follow-up visits.

Pharmacokinetic analysis

Serum tocilizumab concentration vs. actual sampling time after first and last tocilizumab s.c. dosing was analyzed by noncompartmental methods using WinNonlin (Professional version 5.2.1; Pharsight Corporation, Mountain View, CA, USA) to determine PK parameter estimates, which included maximum and minimum serum concentrations (C_{max} and C_{min}), time to maximum serum concentration (t_{max}), area under the serum tocilizumab concentration-time curve during the relevant dosing interval (AUC_{0–168h} (QW group) and AUC_{0–336h} (Q2W group)) and apparent terminal half-life (t_{1/2}). Accumulation ratios (R_{ac}) were calculated by PK exposure (AUC_{0–τ}, C_{max} and C_{min}) ratios following the last dose divided by the first dose.

Statistical analysis

All PK and PD parameters were summarized graphically and/or descriptively according to dose group. Proportions of patients with ACR20, ACR50 and ACR70 responses at Week 12 were calculated. DAS28 at Week 12 and its change from baseline were summarized. Numbers of patients who were categoric DAS28 responders (EULAR responders) at Week 12 are presented. AEs were described by frequency and were subdivided by system organ class. AEs were also classified according to intensity and causal relationship with treatment. Laboratory parameters were reported based on the grading system from Common Toxicity Criteria (CTC), version 3 [13].

Results

Patient disposition and demographics

All evaluable randomly assigned patients (n = 29) were included in PK, PD, efficacy and safety evaluations. In the QW group, one patient received an intra-articular corticosteroid injection on Day 22, and another patient received doxycycline on Day 20; both were excluded from subsequent efficacy evaluations. One patient in the Q2W group withdrew from the study on Day 36 (after three doses of tocilizumab) because of lack of efficacy. Patient characteristics were similar between groups except that the Q2W group included more women and had more severe baseline disease characteristics, including higher mean SJC and TJC, and higher scores on pain and on patient-
Pharmacokinetics

After s.c. administration of tocilizumab, serum concentrations increased and $t_{\text{max}}$ was reached between 48 and 72 hours across both dose cohorts and following the first or last dose. Mean trough tocilizumab concentration increased on multiple dosing in both groups (Figure 1A). In the QW group, exposure stabilized by the final dose; predose concentrations on Day 78 and Day 85 (7 days after the final dose) were similar (29.1 ± 15.9 µg/ml vs. 27.9 ± 14.7 µg/ml). In the QW group, ~5-fold accumulation for $\text{AUC}_{0-168\text{h}}$, $C_{\text{max}}$ and $C_{\text{min}}$ was observed (Table 3). In the Q2W group, steady state was reached by Week 9 (Figure 1A). Accumulation ratios for 162 mg Q2W were lower than those for 162 mg QW for the AUC and $C_{\text{max}}$ parameters (1.8 fold for AUC and 1.7 fold for $C_{\text{max}}$), but the accumulation ratio was greater for $C_{\text{min}}$ (9.0 fold) with Q2W dosing. Inter-subject variability for $C_{\text{max}}$ and $\text{AUC}_{0-\tau}$ ranged from 46% to 89% for both dose groups. Inter-subject variability for $C_{\text{min}}$ appeared larger for the Q2W (115 – 140%) group than for the QW group (53 – 88%). Mean $C_{\text{max}}$, $C_{\text{min}}$ and $\text{AUC}_{0-168\text{h}}$ values (multiplied by 2 for 2-week duration) were 3.7-fold, 12.3-fold and 4.7-fold higher for the QW group than for the Q2W group after the last dose (Table 3). After the last dose, tocilizumab $t_{1/2}$ was longer for QW dosing than for Q2W dosing (193 hours vs. 84 hours) (Table 3).

Pharmacodynamics

IL-6 levels increased after tocilizumab administration, reaching a maximum on day 4; levels then decreased slowly with repeated dosing for both groups (Figure 1B). After Day 8, IL-6 levels were lower in the Q2W group than in the QW group. Before the last dose on Days 78 and 71, respectively, IL-6 levels differed ~3-fold between groups (QW 71.2 ± 44.5 pg/ml vs. Q2W 23.7 ± 18.4 pg/ml).

Mean sIL-6R levels increased within the first week after tocilizumab administration.
Increased accumulation was evident with repeated dosing, reaching a plateau by Week 12 for both groups. After Day 8, when dosing differed between groups, sIL-6R levels were lower in the Q2W group than in the QW group. Before the last dose, on Days 78 and 71, respectively, sIL-6R levels were ~1.7-fold greater in the QW group than in the Q2W group (670 ± 211 ng/ml vs. 387 ± 194 ng/ml).

Median CRP levels decreased in both groups after the first dose of tocilizumab (Figure 1D). Median CRP levels remained below the upper limit of normal (ULN; 0.3 mg/dl) in the QW group. In the Q2W group, median CRP levels fluctuated after the first three doses, with elevations occurring after “off” dosing weeks; however, levels remained below ULN after ~3 doses.

### Efficacy

Mean DAS28 decreased from baseline to Week 12 in both groups. Change in mean ± standard deviation (SD) (range) from baseline to Week 12 was −2.5 ± 1.2 (−4 to −1) for the QW group and −3.1 ± 1.1 (−5 to −2) for the Q2W group.

By Week 12, 6 of 12 (50%) patients in the QW group had EULAR good response compared with 8 of 13 (61.5%) patients in the Q2W group. The number of patients who had no EULAR response at Week 12 in the Q2W group was 0 vs. 2 (16.7%) in the QW group. The proportion of patients with ACR20 response at Week 12 was 9 of 12 (75%) in the QW group and 9 of 14 (64.3%) in the Q2W group. In both groups, the proportion of patients with an ACR20 response had increased from Week 4 (QW, 5/12 (41.7%); Q2W, 6/15 (40.0%)). At Week 12, the proportion of patients with ACR50 response was 3 of 12 (QW, 25%) and 5 of 14 (Q2W, 35.7%), and the proportion of ACR70 response was 1 of 12 (QW, 8.3%) and 3 of 14 (Q2W, 21.4%).

### Safety

10 patients (71%) in the QW group and 12 patients (80%) in the Q2W group experienced AEs; most were mild in intensity. The most frequently reported AEs were gastrointestinal disorders (16 events in 11 patients). No serious AEs or deaths were reported, and no patient withdrew because of an AE.

A total of 252 injections were received by 29 patients in the study. Mean ± SD (range) injection time was 13.6 ± 10.0 (5 – 62) seconds. Eleven ISRs occurred in 7 patients (24% of the total; 4 in the QW group; 3 in
the Q2W group). Most ISRs were mild in intensity; the most common ISR (6 events in 5 patients) was erythema. Three patients tested positive for anti-tocilizumab antibodies in the screening assay; none tested positive in the confirmatory assay. All 3 patients who tested positive with the screening assay had positive findings at baseline. Positive screening assay results were not likely to be attributed to the s.c. administration of tocilizumab. One patient tested negative at baseline and during the study but positive for anti-tocilizumab antibodies at follow-up with screening and confirmatory assays. For this patient, the result in the neutralizing assay at follow-up was 211 ng·Eq/ml, which was equal to the assay detection limit.

Throughout the randomized treatment phase, mean white blood cell (WBC) counts remained within normal limits. Mean neutrophil counts decreased in both groups after the start of treatment but remained within normal limits. The only events ≥ CTC Grade 2 involved two patients with low lymphocyte counts, both CTC Grade 3 (one in the QW group and one in the Q2W group) but not clinically significant. In both cases, lymphocyte values were Grade 0 at baseline and had resolved by the following visit. Mean values for chemistry parameters remained within normal ranges throughout the randomized treatment phase of the study. Of the three liver function parameters measured in this study (total bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST)), three patients in the Q2W group had an ALT level > 2 – 3 × ULN, and 1 patient in the Q2W group had an AST level > 2× ULN.

Discussion

This is the first study evaluating PK and PD of tocilizumab following multiple-dose s.c. administration in patients with RA. Following i.v. administration, tocilizumab clearance was found to be concentration dependent and consisted of both linear and nonlinear clearances [11]; the nonlinear clearance pathway played a major role at low tocilizumab concentrations (< 25 µg/ml). A population PK model from tocilizumab i.v. data showed that for the nonlinear clearance pathway the estimated values for $K_m$ (Michaelis-Menten constant) and the mean $V_m$ (maximum elimination rate) were 2.7 µg/ml and 7.5 mg/day, respectively [14]. Once the nonlinear clearance pathway is saturated at higher tocilizumab concentrations, clearance is apparently linear. Consequently, the half-life of tocilizumab is also concentration dependent [11]. In the present study, after 162 mg Q2W, tocilizumab serum concentrations were within the nonlinear clearance range from first dose to last dose on Day 71 (Figure 1A). After 162 mg QW, tocilizumab serum concentrations were within the nonlinear clearance range up to Day 64 and within the linear clearance range afterward (Figure 1A). Concentration-dependent $t_{1/2}$ was observed in the present study after s.c. administration. Mean $t_{1/2}$ was 193 ± 72 hours for QW dosing and 84 ± 53 hours for Q2W dosing after the last dose (Table 3) because of the higher concentrations associated with the QW dosing regimen. Therefore, apparent $t_{1/2}$ should be considered specific to the regimen (162 mg QW or 162 mg Q2W) and time.

Outside the United States, the recommended dose for tocilizumab is 8 mg/kg i.v. every 4 weeks. In the United States, the recommended starting dose is 4 mg/kg i.v. every 4 weeks, which can be increased to 8 mg/kg depending on clinical response [7, 8, 9]. The purpose of the present study was to explore s.c. doses that would be comparable to the i.v. doses of 8 mg/kg and 4 mg/kg. The results of the study were to be compared to historic data from four i.v. studies [3, 4, 5, 15].

The assessment of sIL-6R and CRP as PD markers of tocilizumab i.v. activity in patients with RA has been reviewed elsewhere [11]. sIL-6R levels increase and CRP levels decrease after the administration of tocilizumab i.v. in patients with RA. Furthermore, increased tocilizumab exposure is associated with improvements in DAS28 and ACR criteria and with a decrease in inflammatory markers [16]. Here we compared changes in sIL-6R and CRP levels between s.c. data and historical data from i.v. studies. In addition, changes in DAS28 from baseline were compared. Levels of IL-6, another recognized PD marker of tocilizumab activity, were not compared because of the variability in levels between subjects.

In a dose-ranging study (CHARISMA) evaluating the safety, tolerability, PK and
PK, PD of subcutaneous tocilizumab in RA

Efficacy of repeat doses of tocilizumab administered alone or in combination with methotrexate in patients with RA [15], blood samples for PK measurement were taken predose, at the end of infusion for all four infusions at baseline, and at Weeks 4, 8 and 12. Samples were also taken between infusions at Weeks 2, 6, 10 and 14, with the last PK sample taken at Week 16. OPTION was a randomized, placebo-controlled, Phase 3 study that evaluated the safety and efficacy (reduction in signs and symptoms) of tocilizumab in combination with methotrexate in patients with moderate to severe active RA [5]. In this study, blood samples were taken for measurement of CRP levels at baseline, at Weeks 2, 4, 6, 8, 12, 14, 16, 20 and 24. In another randomized, placebo-controlled, Phase 3 study (TOWARD), the efficacy and safety of tocilizumab combined with conventional DMARDs were assessed [3]. In TOWARD, blood samples for CRP measurement were taken at baseline, at Weeks 2 and 4 and every 4 weeks thereafter until Week 24. Finally, LITHE, a randomized, placebo-controlled, Phase 3 study, evaluated the safety and efficacy (prevention of structural joint damage) of tocilizumab in combination with methotrexate in patients with moderate to severe active RA [4]. Blood samples for measurement of sIL-6R concentrations were taken at baseline, at Weeks 4, 8, 12, 16, 20 and 24 before infusion and between infusions at Weeks 2, 6 and 14. Data for sIL-6R have been reported elsewhere [11].

PK and PD profiles for 162 mg tocilizumab s.c. QW and 8 mg/kg tocilizumab i.v. Q4W are shown in Figure 2. sIL-6R–bound tocilizumab complex kinetics was similar or slightly higher with respect to onset and magnitude of the increase between 8 mg/kg tocilizumab i.v. Q4W after treatment compared with 162 mg tocilizumab s.c. QW (Figure 2A). CRP levels decreased rapidly.
and consistently in a similar pattern when
the 162 mg tocilizumab s.c. QW dose was
compared with the 8 mg/kg tocilizumab i.v.
Q4W dose (Figure 2B). Change from base-
line in DAS28 data after 162 mg tocilizumab
s.c. QW dosing parallels data after 8 mg/kg
tocilizumab i.v. Q4W dosing (Figure 2C).
In contrast, levels of IL-6R (Figure 2A) and
CRP (Figure 2B) as well as DAS28 data (Fig-
ure 2C) remained close to baseline through-
out 168 days of treatment with placebo.

Although total exposure for 8 mg/kg to-
cilizumab i.v. Q4W (35 ± 16 mg×h/ml) [14]
was 1.6-fold higher than for 162 mg tocili-
zumab s.c. QW (22 ± 10.5 mg×h/ml) during
a 4-week treatment period at steady state, C_{min}
at steady state for 162 mg tocilizumab
s.c. QW (27.9 ± 14.7 µg/ml) was comparable
to or higher than that for 8 mg/kg tocilizum-
ab i.v. Q4W (9.7 ± 11.0 µg/ml) (Figure 2D).

PK and PD profiles for 162 mg tocili-
zumab s.c. Q2W and 4 mg/kg tocilizumab
i.v. Q4W are shown in Figure 3 for com-
parison. sIL-6R levels were generally higher
with 162 mg tocilizumab s.c. Q2W than with
8 mg/kg tocilizumab i.v. Q4W in the pres-
ent study (Figure 3A), indicating more per-
sistent binding of tocilizumab to sIL-6R for
162 mg tocilizumab s.c. Q2W than for 4 mg/
kg tocilizumab i.v. Q4W. Tocilizumab s.c.
Q2W reduced CRP levels to a greater extent
than was observed with 4 mg/kg tocilizumab
i.v. Q4W; fluctuation patterns in CRP levels
were observed with both s.c. and i.v. admin-
istration (Figure 3B) [5]. Change from base-
line in DAS28 after 162 mg tocilizumab s.c.
Q2W parallels the data after 4 mg/kg tocili-
zumab i.v. Q4W (Figure 3C) [5]. Although
total exposure for 4 mg/kg tocilizumab i.v.
Q4W (13 ± 5.8 mg×h/ml) [14] was 2.5-fold
higher than for 162 mg tocilizumab s.c. Q2W
(4.66 ± 3.39 mg×h/ml) during a 4-week treat-
ment period at steady state, the C_{min}
at steady state for 162 mg tocilizumab s.c.
PK, PD of subcutaneous tocilizumab in RA

Q2W (2.26 ± 3.17 µg/ml) was comparable to or higher than that for 4 mg/kg tocilizumab i.v. Q4W (1.5 ± 2.1 µg/ml) (Figure 3D) [14]. Absolute PK and PD bioavailabilities of tocilizumab after s.c. administration have been preliminarily reported in healthy subjects [17]. Tocilizumab absolute PK bioavailability after a single 162-mg s.c. dose when compared with a single 162-mg i.v. dose was low (AUC_{inf} ratio (s.c./i.v.), 48.8%). It should be noted that due to the considerable non-linearity of tocilizumab clearance, absolute bioavailability estimates should be taken with caution. When the PD effects were used to estimate bioavailability, assuming the same PK/PD relationship with i.v. and s.c. dosing, greater bioavailability was suggested: AUC_{last} ratio (s.c./i.v.) for sIL-6R was 109% and AUC_{480h} ratio (s.c./i.v.) for CRP was 98.2%. These findings are consistent with the PK and PD data from the present study in patients with RA. Despite lower PK exposures in the present study, PD profiles were comparable to historical i.v. data.

The safety profile after multiple-dose administration of tocilizumab s.c., as observed in the present study, was similar to that reported after i.v. administration in previous Phase 3 studies [11]. As expected for an s.c. formulation, several patients reported ISRs (24%), most of which were mild in intensity.

Conclusions

Tocilizumab exposure was higher with 162 mg tocilizumab s.c. QW than with 162 mg tocilizumab s.c. Q2W. Greater elevation of sIL-6R levels and more rapid normalization of CRP levels were observed with the QW regimen than with the Q2W schedule. Both tocilizumab s.c. regimens demonstrated clinical benefit and were well tolerated by RA patients.

Acknowledgments

The authors thank the following for their contributions to the clinical conduct of the study: Majed Khraishi (Nexus Clinical Research, St. John’s, Newfoundland, Canada), Rafat Faraawi (K-W Musculoskeletal Research, Kitchener, Ontario, Canada), Frédéric Morin (Clinique Rhumatologie Centre du Québec, Trois-Rivières, Quebec, Canada), Jean-Luc Tremblay (Centre de Recherche Musculo-Squelettique, Trois-Rivières, Quebec, Canada), Richard Robinson (Christchurch Clinical Studies Trust, Christchurch, New Zealand), John O’Donnell (Christchurch Clinical Services Trust, Christchurch, New Zealand), Juan Jesús Gómez Reino (Hospital Clínico Universitario, Santiago de Compostela, Spain), Federico Navarro-Sarabia (Hospital Universitario Virgen de la Macarena, Seville, Spain) and Francisco Blanco (Hospital Juan Canalejo, La Coruña, Spain).

Conflicts of interest

Xiaoping Zhang, Ya-Chi Chen, Scott Fettner and Tatiana Gott have been employees of Hoffmann-La Roche, Nutley, New Jersey, USA, and have owned stock options in Hoffmann-La Roche in the previous 3 years. Lucy Rowell, Paul Grimsey and Adam Unsworth have been employees of Roche Products, Welwyn Garden City, United Kingdom, in the previous 3 years. There are no other relationships or activities that could appear to have influenced the submitted work.

Funding

This study was funded by Roche. Third-party writing assistance for this manuscript was provided by Maribeth Bogush, PhD, and Sara Duggan, PhD, and was supported by F. Hoffmann-La Roche Ltd.

References


[8] Roche Registration Limited. RoActemra® (tocilizumab) Summary of product characteristics. Welwyn Garden City, UK; Roche Registration Limited; 2011.


学霸图书馆
www.xuebalib.com

本文献由“学霸图书馆-文献云下载”收集自网络，仅供学习交流使用。

学霸图书馆（www.xuebalib.com）是一个“整合众多图书馆数据库资源，提供一站式文献检索和下载服务”的24小时在线不限IP图书馆。

图书馆致力于便利、促进学习与科研，提供最强文献下载服务。

图书馆导航：

图书馆首页 文献云下载 图书馆入口 外文数据库大全 疑难文献辅助工具