Population Pharmacokinetics (PK) of Tocilizumab Following Intravenous (IV) and Subcutaneous (SC) Administration to Patients With Rheumatoid Arthritis (RA)

W-026

Leonid Gibiansky,[1] Nicolas Frey,[2] Joy C. Hsu[3]

[1]QuantPharm LLC, North Potomac, Maryland; [2]F. Hoffmann-La Roche Ltd., Pharma Research and Early Development, Roche Innovation Center, Basel, Switzerland; [3]Roche TCRC, Inc., Pharma Research and Early Development, Roche Innovation Center, New York, New York

INTRODUCTION

- Tocilizumab (TCZ; RO4877533) is a recombinant, humanized, antihuman interleukin-6 receptor (IL-6R) monoclonal antibody that specifically inhibits the binding of human interleukin-6 (IL-6) to its receptor (soluble and membrane-bound forms)
- TCZ, in IV and SC formulations, was shown to be effective in the treatment of RA. The population PK model that describes TCZ concentrations after IV doses was developed earlier.[1] The present data analysis addresses the development of the population PK model that describes TCZ concentrations after SC and IV doses using data from studies WA22762 (SUMMACTA)[2] and NA25220 (BREVACTA)[3]
- The population PK analysis of the IV data that included data from 1820 RA patients completely characterized the TCZ PK and covariate relationships after IV administration. Therefore, this analysis aimed to confirm the previously developed PK model and to describe TCZ properties (absorption rate and bioavailability) related to SC administration

OBJECTIVES

- The objectives of the present analysis were
  - To establish a predictive population model that describes the PK of TCZ after IV and SC administration
  - To identify covariate factors that may influence TCZ disposition
  - To determine whether the presence of confirmatory anti-TCZ antibodies affects the PK of TCZ after IV and SC administration
  - To perform model-based simulations of clinically important dosing regimens

METHODS

- PK data from two phase 3 studies, WA22762 (**Figure 1**) and NA25220 (**Figure 2**), were analyzed using NONMEM 7.2.0

Figure 1. WA22762 study design.

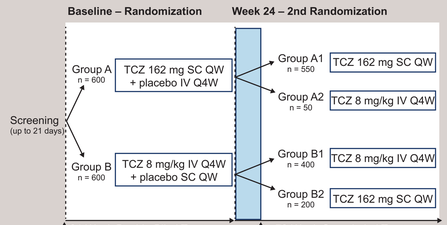
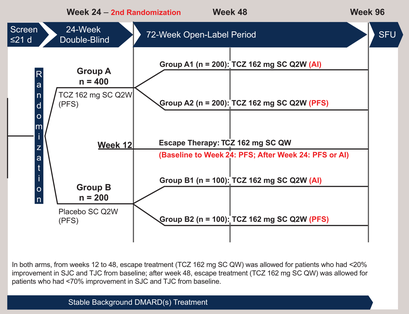


Figure 2. NA25220 study design.



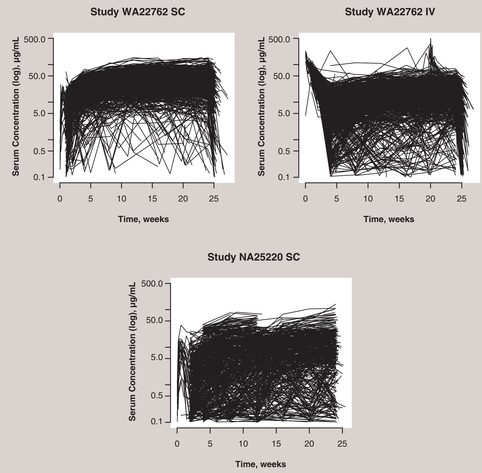
AI, autoinjector; DMARD(s), disease-modifying antirheumatic drug(s); PFS, prefilled syringe; SFU, study follow-up; SJC, swollen joint count; TJC, tender joint count.

- TCZ PK were described by a 2-compartment linear model with parallel linear and Michaelis-Menten elimination supplemented by the first-order absorption to describe SC administration. A full-model approach was implemented for development of the covariate model
- Selection of the covariates for the investigation was based on previous knowledge of the typical covariate relationships for monoclonal antibodies and the previously developed TCZ population PK model for the IV data
- After the full model was developed, small (clinically insignificant) and precisely estimated effects were excluded to arrive at a parsimonious model. Covariate effects not supported by the data (effects close to null value and/or with high relative standard error and/or with 95% confidence intervals [CIs] that included the null value) were also excluded
- Extensive model evaluation using diagnostic plots and various visual predictive check (VPC) procedures was performed

RESULTS

- The data set included 13,642 samples from 1759 patients. Among those, 10,364 PK samples were from 1250 patients in study WA22762 and 3278 PK samples were from 509 patients in study NA25220
- Individual serum concentration-time profiles for patients whose data were included in the analysis are shown in **Figure 3**

Figure 3. Individual TCZ serum concentration-time profiles, semi-log scale.



Observed serum concentrations (µg/mL) versus time (weeks).

- The final PK model included the effects of weight and high-density lipoprotein (HDL)-cholesterol on clearance (CL); weight, total protein, and albumin on central and peripheral volumes; normalized creatinine clearance on V_M; age and study on k_a; and injection site on bioavailability
- Estimates of the final model are provided in **Table 1**

Table 1. Parameter Estimates for the Final PK Model

Parameter	Estimate	% RSE	Parameter	Estimate	% RSE
CL (L/day)	0.216	1.18	$V_{M,CRCLN}$	0.229	7.43
V_2 (L)	4.51	1.61	$k_{a,age}$	–0.442	17.2
Q (L/day)	0.274	2.2	$k_{a,study}$	0.61	3.54
V_3 (L)	2.77	1.7	$F_{SC,thigh}$	1.11	0.712
V_M (mg/L/day)	1.85	1.04	σ_{study}	1.94	3.1
K_M (µg/mL)	0.343	2.49	ω^2_{CL}	CV = 27.6	4.49[a]
k_a (1/day)	0.233	2.68	$\omega^2_{V_2}$	CV = 22.5	5.04[a]
F_{SC}	0.795	1.05	$R\omega_{V_2}\omega_{V_3}$	R = 0.661	8.26[a]
CL_{WT}, QW_T	0.512	4.36	$\omega^2_{V_3}$	CV = 30.3	7.22[a]
$V_{2,WT}$, $V_{3,WT}$	0.683	3.86	$\omega^2_{k_a}$	CV = 46.5	6.3[a]
CL_{HDL}	–0.256	10.9	ω^2_{EPS}	CV = 53.8	3.72[a]
$V_{albumin}$	–0.672	9.38	σ^2	CV = 20.7	3.99[a]
$V_{protein}$	0.728	12.2			

RSE, relative standard error of estimate.
[a]% RSE for the estimate of variance.

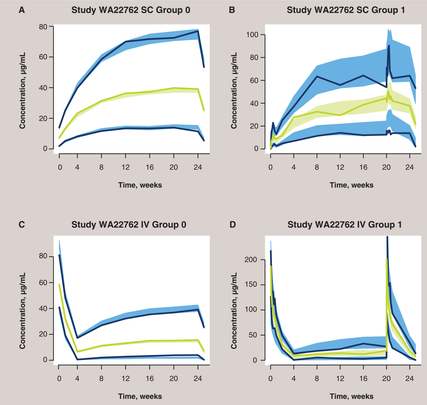
- Covariate effects are illustrated in **Table 2**. Weight was the most important predictor of clearance and volume parameters. Absorption rate constant was lower for study NA25220

Table 2. Covariate Effects as Predicted by the Final Model

Parameter	Covariate				Effect (95%, CI), %
	Name	Range	Reference	Value	
CL	Weight, kg	34.4–149	70	40	–24.9 (–26.8, –22.9)
				140	42.6 (38, 47.2)
	HDL, mmol/L	0.31–4.46	1.5	0.75	19.4 (15, 24.1)
				3.5	–19.5 (–23.2, –15.7)
V_2, V_3	Weight, kg	34.4–149	70	40	–31.8 (–33.7, –29.8)
				140	60.6 (54.9, 66.4)
	Albumin, g/L	22–49	35	25	25.4 (20.3, 30.7)
				50	–21.3 (–24.7, –17.8)
	Protein, g/L	59–96	75	60	–15.0 (–18.2, –11.6)
				90	14.2 (10.6, 17.9)
V_M	Normalized creatinine clearance, mL/min/1.73 m^2	28.4–251 (restricted by 150 in the model)	100	50	–14.7 (–16.6, –12.7)
				150	9.7 (8.3, 11.2)
k_a	Age, years	18–86	50	30	25.4 (16.1, 35.3)
				80	–18.8 (–24.3, –12.9)
	Study	WA27262/NA22520	WA27262	NA22520	–39.0 (–43.3, –34.7)
F_{SC}	Injection site	Arm/abdomen/thigh/unknown	Arm/abdomen/thigh/unknown	Thigh	10.9 (9.3, 12.4)

- VPC plots (**Figures 4** and **5**) indicated that the model correctly captured both the central tendency and the intersubject variability of TCZ PK
- Small underprediction of median concentrations and overprediction of variability at weeks >12 for study NA25220 (**Figure 4**) were likely due to the nonrandom escape therapy allowed after 12 weeks in that study based on response (dosing every week [QW] instead of every 2 weeks [Q2W] was allowed for patients who experienced <20% improvement from baseline in swollen joint count and tender joint count)

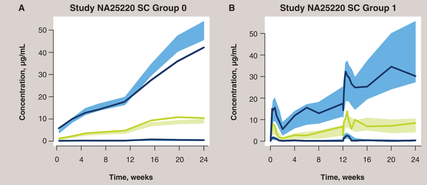
Figure 4. VPC for model 317: study WA22762 concentration versus time by route of administration and sampling density. (A) SC group 0. (B) SC group 1. (C) IV group 0. (D) IV group 1.



PD, pharmacodynamics.
Lines show the median (green) and the 10th and 90th percentiles (blue) of the observed concentrations. Shaded regions show the 80% CIs on these quantities obtained by simulations. Simulated values were computed from 500 trials simulated using dosing, sampling, and the covariate values of the analysis data set. Group: 0 = sparse sampling, 1 = PK-PD subgroup.

- Subjects with high exposure (lower clearance) were less likely to escape. VPC did not account for that, resulting in higher median and upper 90th percentile values compared with the observed concentrations after week 12

Figure 5. VPC for model 317: study NA25220 concentration versus time by route of administration and sampling density. (A) SC group 0. (B) SC group 1.

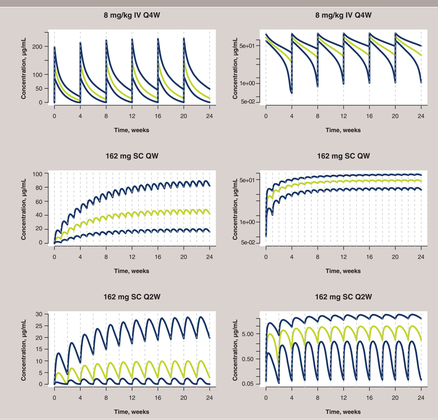


Lines show the median (green) and the 10th and 90th percentiles (blue) of the observed concentrations. Shaded regions show the 80% CIs of these quantities obtained by simulations. Simulated values were computed from 500 trials simulated using dosing, sampling, and the covariate values of the analysis data set. Group: 0 = sparse sampling, 1 = PK-PD subgroup.

Model-Based Simulations

- Population concentration-time profiles (median values and 90% prediction intervals) based on simulation from the final model of 5000 patients for each dosing regimen are shown in **Figure 6**

Figure 6. Simulated time course of TCZ serum concentrations over 4 months of treatment.



Median (green) and 90% prediction intervals (blue) of the simulated concentration-time profiles. For each dosing regimen, concentrations were simulated every 12 hours and at 1 hour after each dose for 5000 patients, with the covariate values sampled with replacement from the analysis population.

- Simulations show a large difference in concentrations between QW and Q2W SC dosing: trough concentrations are much higher—more than dose proportionally higher—after QW SC dosing
- Faster clearance at low concentrations (because of the dominance of the nonlinear elimination pathway) during the second week in the Q2W dosing regimen led to lower accumulation than in the QW dosing regimen
- Compared with Q4W IV dosing, trough concentrations at steady state after QW SC dosing were significantly higher whereas peak concentrations were much lower. The steady state profiles after QW SC dosing were almost flat, with very little fluctuation between trough and peak values

SUMMARY/CONCLUSIONS

- The serum concentration-time course for TCZ after multiple IV and SC administration in RA patients was accurately described by a 2-compartment PK model with first-order absorption (after SC administration) and parallel linear and Michaelis-Menten elimination
- Steady state exposure was similar for the 162 mg QW SC and 8 mg/kg IV regimens (C_{mean} of 49.1 and 58.7 µg/mL, respectively), whereas trough concentrations were 2.4 times higher (45.3 vs 18.8 µg/mL) and peak concentrations were 3 times lower (51.3 vs 152.7 µg/mL) after QW SC dosing
- Nonlinear clearance led to a more than dose-proportional increase in exposure for the 162 mg QW and Q2W SC dosing regimens, leading to an average steady state concentration (C_{mean}) of 49.1 and 10.3 µg/mL, respectively. Trough concentrations were 45.3 and 5.9 µg/mL, respectively
- Nearly complete target saturation was achieved at steady state during the entire dosing interval for the 162 mg QW SC and 8 mg/kg Q4W IV regimens. For the 162 mg Q2W SC regimen, the target-mediated elimination pathway was not saturated, which led to high total clearance and high fluctuation of clearance over the dosing interval
- TCZ clearance increased with body weight. As a result, for weight-based dosing of 8 mg/kg IV Q4W, steady state C_{mean} was 19% lower for patients weighing ≤60 kg and was 38% higher for patients weighing ≥100 kg compared with the mean C_{mean} for patients weighing 60 to 100 kg. Weight dependence was higher and in reverse direction for weight-independent (flat) SC dosing. For the 162 mg SC QW regimen, steady state C_{mean} was 46% higher for patients weighing ≤60 kg and 45% lower for patients weighing ≥100 kg compared with the mean C_{mean} for patients weighing 60 to 100 kg. For the 162 mg SC Q2W regimen, steady state C_{mean} was 80% higher for patients weighing ≤60 kg and 60% lower for patients weighing ≥100 kg compared with the mean C_{mean} for patients weighing 60 to 100 kg. The stronger weight dependence of exposure for the Q2W flat SC regimen compared with QW dosing was attributed to the nonlinear TCZ clearance prevalent at low concentrations. Given that steady state concentrations after the Q2W regimen were much lower than after the QW regimen, the difference in clearance for subjects with low and high values of weight was greater for the Q2W regimen
- Apart from the effect of body size on linear clearance and volume parameters of TCZ, no other covariate influence had a clinically relevant effect on TCZ PK

REFERENCES

1. Frey N et al. *J Clin Pharmacol*. 2010;50:754-776.
2. Burmester GR et al. *Ann Rheum Dis*. 2014;73:69-74.
3. Kivitz A et al. *Arthritis Care Res*. 2014:DOI 10.1002/acr.22384.

To receive a PDF of this poster on your mobile phone:
• Go to getscanlife.com from your mobile browser to download the free barcode reader application
• Scan the code and get access to content

http://bit.ly/1sBCoSJ

Presented at the American Conference on Pharmacometrics; October 12–15, 2014; Las Vegas, Nevada

This study was funded by Roche.

Support for third-party editorial assistance for this poster was provided by F. Hoffmann-La Roche Ltd.