W-035

Effects of Tocilizumab on Neutrophil Counts in Patients With Rheumatoid Arthritis (RA)

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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 intravenous (IV) and subcutaneous (SC) formulations, was shown to be effective in the treatment of patients with RA. The population pharmacokinetic (PK)-neutrophil count models that described the time course of neutrophil counts after TCZ IV doses were developed earlier.[1] The current analysis builds on those models to incorporate both IV and SC administration of TCZ using data from studies WA22762 (SUMMACTA)[2] and NA25220 (BREVACTA).[3] The population PK model (poster W-026) was used to predict individual TCZ concentrations over time for the exposure-safety analysis

OBJECTIVES

- The objectives of the present analysis were
  - To establish a predictive population PK-pharmacodynamic (PD) model that describes the neutrophil count time course after TCZ IV and SC administration
  - To identify covariate factors that may influence the PK-neutrophil count relationship
  - To perform model-based simulations of neutrophil counts after clinically important dosing regimens

METHODS

- Circulating neutrophil count (NTT) data from two phase 3 studies, WA22762 (**Figure 1**) and NA25220 (**Figure 2**), were analyzed using NONMEM 7.2.0. The population PK model (poster W-026) was used to predict individual TCZ concentrations over time for the exposure-NTT analysis

Figure 1. WA22762 study design.

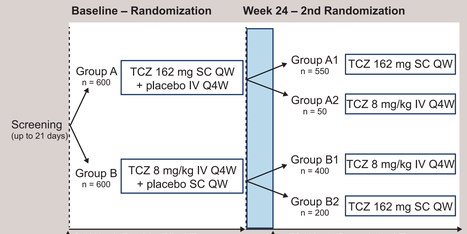
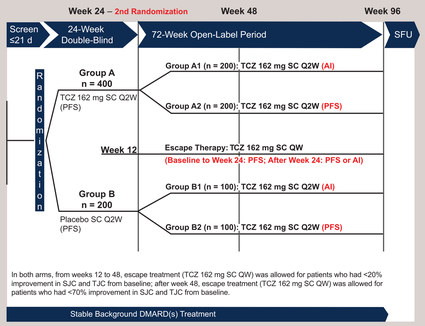


Figure 2. NA25220 study design.



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

- Following the previously performed population PK-PD modeling of neutrophil counts after TCZ IV administration,[1] the time course of neutrophil counts was described by an indirect response model with stimulation of elimination

$$\frac{d(\mathrm{NTT})}{dt} = k_{in} - k_{out} \times (1 + \mathrm{H(C)}) \times \mathrm{NTT}$$

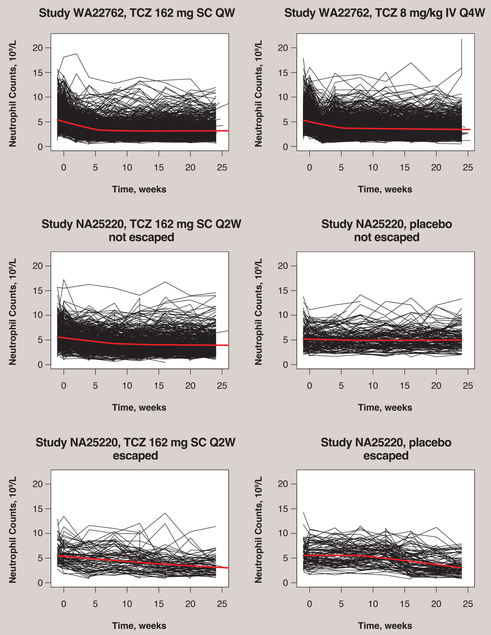
$$\mathrm{H(C)} = \frac{E_{max} \times C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}}$$

- Here NTT represents circulating neutrophil counts, k_{in} = BASE × k_{out} and k_{out} are the zero-order production rate and the first-order elimination rate of neutrophils, BASE is the baseline value of neutrophil counts, E_{max} is the maximal effect of the drug, EC_{50} is the TCZ concentration at which 50% of the E_{max} is reached, and γ is the sigmoidicity parameter
- A full-model approach was implemented for the covariate model development. Selection of the covariates for the investigation was based on previous knowledge of the typical covariate relationships for monoclonal antibodies and on the previously developed TCZ population PK-NTT model for the IV data. 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 the 95% confidence intervals [CIs] that included the null value) were also excluded if they were not statistically significant at the $\alpha = 0.001$ level. Extensive model evaluation using diagnostic plots and various visual predictive check (VPC) procedures were performed

RESULTS

- The data set included 15,870 neutrophil values from 1887 patients. Among those, 10,873 NTT samples were from 1250 patients in study WA22762, and 4997 samples were from 637 patients in study NA25220. Of 1887 subjects, 629, 621, 350, and 126 subjects, respectively, received TCZ 8 mg/kg IV Q4W, TCZ 162 mg SC QW, TCZ 162 mg SC Q2W, or placebo TCZ doses. In addition, 90 and 71 subjects, respectively, were administered placebo or TCZ 162 mg SC Q2W doses for 12 weeks, but starting at week 12 they escaped by switching to the TCZ 162 mg SC QW dosing regimen (**Figure 3**)

Figure 3. Individual neutrophil count-time profiles.



Observed neutrophil counts versus nominal time (weeks). Subjects who escaped starting at week 12 were moved to the 162 mg TCZ SC QW dosing regimen.

- Parameters of the final model are presented in **Table 1**

Table 1. Parameter Estimates for the Final PK-NTT Model

Parameter	Estimate	%RSE	Parameter	Estimate	%RSE
BASE (10^9/L)	4.70	1.22	$EC_{50,SEX}$	0.78	11.3
k_{out} (1/day)	0.206	7.69	$E_{max,CRP}$	0.0635	25.4
EC_{50} (μg/mL)	6.67	4.76	$E_{max,IL\text{-}6}$	0.665	9.3
E_{max}	0.832	2.21	ω^2_{BASE}	CV = 28.4%	3.66[a]
γ	1.85	4.98	ω^2_{kout}	CV = 152%	12.1[a]
$BASE_{CRP}$	0.102	5.84	ω^2_{EC50}	CV = 88.8%	12.1[a]
$BASE_{PCOR}$	1.23	1.47	ω^2_{EMAX}	CV = 52.8%	6.47[a]
$BASE_{SMK}$	1.18	1.87	σ^2	CV = 23.0%	1.01[a]
$k_{out,AGE}$	0.676	16.4			

BASE, baseline NTC; CRP, C-reactive protein; E_{max}, maximal stimulation of k_{out}; EC_{50}, TCZ concentration at half the effect; γ, sigmoidicity parameter; k_{out}, rate constant of NTC elimination; PCOR, previous corticosteroid therapy; RSE, relative standard error of estimate; SMK, smoker.
[a]%RSE for the estimate of variance.

- The following covariates were included in the final model: baseline CRP, previous corticosteroid treatment, and smoking on BASE; age on k_{out}; sex on EC_{50}; and baseline CRP and IL-6 concentrations on E_{max}. The magnitude of the covariate effects on model parameters is illustrated in **Table 2**

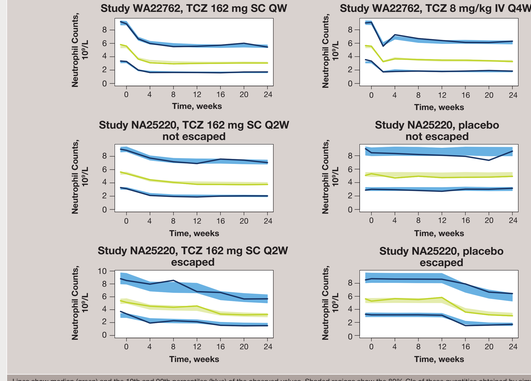
Table 2. Covariate Effects as Predicted by the Final Model

Parameter	Covariate: Name	Median (range) or Level	Reference	Value	Effect, % (95% CI)
BASE	CRP, mg/L	13.5 (0.2–205)	10	1	–20.9 (–23, –18.8)
				100	26.5 (23.1, 29.9)
	PCOR	PCOR: Yes/No	No	Yes	22.9 (19.3, 26.4)
	Smoker	Nonsmoker/Smoker	Nonsmoker	Smoker	17.5 (13.2, 21.9)
k_{out}	Age, years	54 (18–86)	50	20	–46.2 (–55.9, –34.3)
				80	37.4 (24.1, 52.1)
EC_{50}	Sex	Females/Males	Females	Males	–22 (–39.2, –4.7)
E_{max}	CRP, mg/L	13.5 (0.2–205)	10	1	–13.6 (–19.7, –7.1)
				100	15.7 (7.6, 24.5)
	Log(10 × IL-6, pg/mL)	5.14 (1.39–10.7)	Log(10 × 20)	Log(10 × 1)	–42.5 (–48.1, –36.4)
				Log(10 × 10^3)	44.4 (35.1, 54.5)

PCOR, previous corticosteroid therapy.

- For all covariates (except CRP on the 162 mg SC Q2W regimen) the differences were small, and none of the covariates had a clinically meaningful influence on the time course of neutrophil counts
- Results of the VPC evaluations (**Figure 4**) indicated that the model correctly captured both the central tendency and the interindividual variability of neutrophil counts as well as the dependence of the TCZ PK-PD parameters on covariates

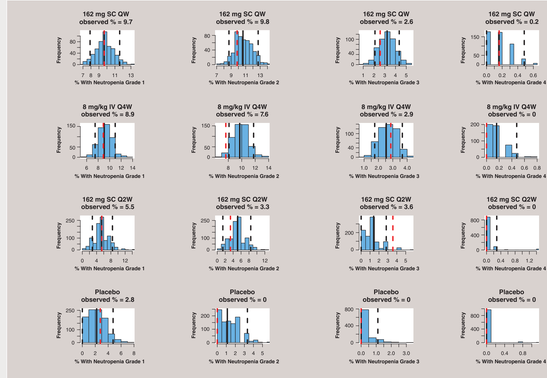
Figure 4. VPC for the final model 246: neutrophil counts versus time, by study, route of administration, and escape status.



Lines show median (green) and the 10th and 90th percentiles (blue) of the observed values. Shaded regions show the 80% CIs of these quantities obtained by simulations. Simulated values were computed from 500 trials simulated using dosing, sampling, PK parameters, and covariate values of the analysis data set.

- Distributions of the incidence rates of neutropenia over 12 weeks superimposed with the observed rates (**Figure 5**) show very good agreement for most treatments and neutropenia grades

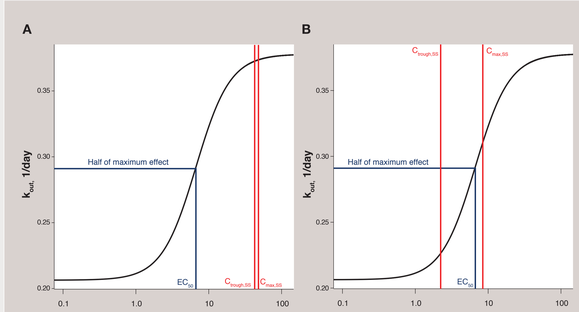
Figure 5. Predictive check plots for the final model 246: neutropenia incidence rate, by treatment (12 weeks).



Red dashed lines show the observed values. Vertical black solid and dashed lines show, respectively, median and 95% prediction intervals over 500 simulated studies. In some plots, the red and black vertical lines coincide.

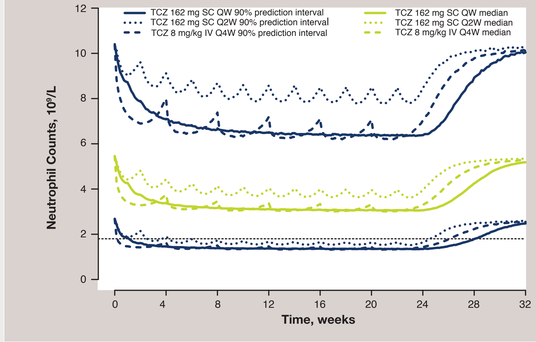
- For only grade 2 neutropenia in the 8 mg/kg IV Q4W group and grade 3 neutropenia in the 162 mg SC Q2W group, the observed rates were outside the 5th and 95th percentiles of the simulated distributions; this is in line with the expected variability
- The relationship between neutrophil elimination rate (k_{out}) and TCZ concentrations, including the mean concentration range at steady state ($C_{min,ss}$ – $C_{max,ss}$) for the 162 mg SC QW and Q2W dose regimens, is shown in **Figure 6**

Figure 6. Relationship between neutrophil elimination rate (k_{out}) and TCZ concentration, and typical TCZ steady state concentration range for (A) 162 mg SC QW and (B) 162 mg SC Q2W dosing.



- A more pronounced effect was achieved for the QW regimen compared with the Q2W regimen because of the exposure difference: the TCZ effect ranged from 96.9% to 97.5% of the maximum effect compared with 11.7% to 60.7% for concentrations achieved with the QW and Q2W regimens, respectively
- Median and 90% prediction intervals of the simulated neutrophil counts for all patients in each dosing regimen are presented in **Figure 7**

Figure 7. Simulated neutrophil counts over time.



Horizontal thin black dashed line shows the lower limit of normal neutrophil counts (1.8 × 10^9/L). Simulations were performed 100 times for each subject in the analysis data set using the subject's covariates, PK parameters, and nominal dosing. Residual variability was included.

SUMMARY/CONCLUSIONS

- The indirect-response model with stimulation of elimination driven by TCZ serum concentrations adequately described the time course of circulating neutrophil counts
- TCZ stimulated the loss of circulating neutrophils by way of a sigmoid E_{max} function. The population mean of the maximum effect of TCZ would translate to a 45% decrease of neutrophil counts from baseline
- The relationship between neutrophil counts and TCZ concentration is independent of the route of administration
- As with the PK-efficacy relationship (poster W-026), the PK-safety relationship of TCZ was similar for the 8 mg/kg IV Q4W and the 162 mg SC QW regimens
- The effect of TCZ on neutrophil counts was smaller and fluctuations were higher for the 162 mg SC Q2W regimen than for the 162 mg SC QW and 8 mg/kg IV Q4W regimens
- The effects of TCZ on neutrophil counts were similar for the 162 mg SC QW and 8 mg/kg IV Q4W regimens
- No covariate, including the presence of neutralizing anti-TCZ antibodies, was found to have a clinical impact on the effect of TCZ on circulating neutrophil counts

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