IV_04

Short- and Long-Term Effects of Tocilizumab on Neutrophil Counts in Paediatric Patients with Systemic Juvenile Idiopathic Arthritis

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BACKGROUND

- Tocilizumab (TCZ) is a recombinant humanised interleukin-6 (IL-6) receptor monoclonal antibody that inhibits binding of IL-6 to its receptors

OBJECTIVE

- The aim of the analysis was to describe the time course of peripheral neutrophil counts (PNCs) after TCZ administration in the paediatric population

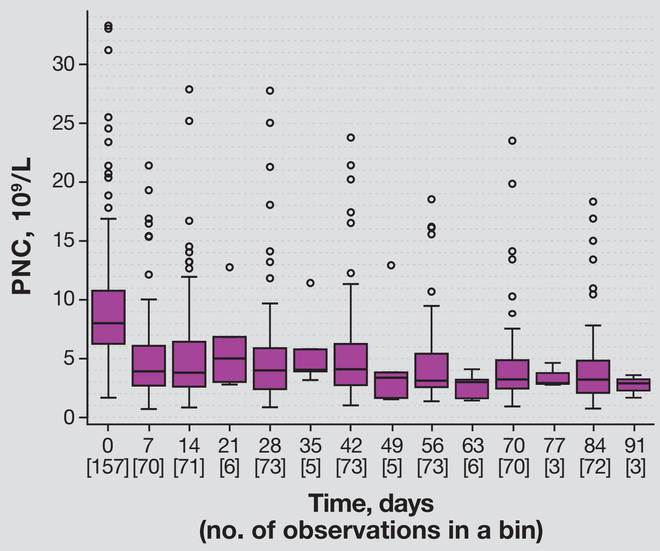
METHODS

- Serum TCZ concentrations and PNCs were available in 75 paediatric patients with active systemic juvenile idiopathic arthritis (sJIA) who received 12 mg/kg (for patients <30 kg) or 8 mg/kg (for patients ≥30 kg) infusions of TCZ every 2 weeks (total of 6 doses). Neutrophil counts were assessed at screening, at baseline (week 0) and at 1, 2, 3, 6, 8, 10 and 12 weeks. A previously developed two-compartment model with parallel linear and Michaelis-Menten elimination described TCZ concentrations.[1,2] Different pharmacokinetic (PK)/pharmacodynamic (PD) models with direct and indirect response were tested to characterise the TCZ-PNC relationship

RESULTS

- The TCZ-PNC relationship was described by a model that included an immediate TCZ effect on PNC decline (possible increase of neutrophil margination)[3] and a longer-term TCZ effect on PNC decline (towards normal levels) due to improvement in patients' conditions (e.g. decrease in inflammation). The immediate effect was described by a direct sigmoid E_{max} model (E_{max} = 0.724 [% relative standard error (RSE) 14.8%] and half-maximal effective concentration [EC_{50}] = 6.38 µg/ml [%RSE 15.8%]). The PK/PD parameters were very similar to the respective values obtained earlier for adult patients[2] (E_{max} = 0.788 and EC_{50} = 7.49 µg/ml). The maximum rate of decline of the long-term effect was 0.166 day^{-1}, and the TCZ concentration inducing half this rate was 151 µg/ml. The corresponding PNC decline for a typical patient was estimated to go from 8.12 × 10^9/L to 5.72 × 10^9/L. The magnitude of the decline increased with the baseline concentration of C-reactive protein (CRP). Diagnostic plots and predictive check simulations indicated good agreement of model predictions with observed data

Figure 1. Observed PNC data versus nominal time.



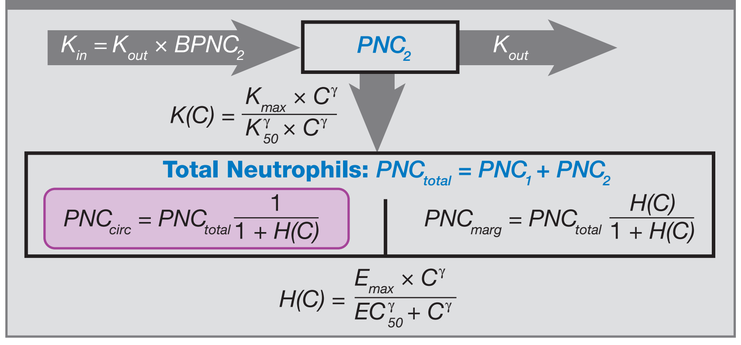
TCZ Concentration—PNC Model

$$PNC_{total} = PNC_1 + PNC_2$$

$$\frac{dPNC_2}{dt} = K_{out}\,(BPNC_2 - PNC_2) - K(C) \times PNC_2 \qquad K(C) = \frac{K_{max} \times C^{\gamma 1}}{K_{50}^{\gamma} + C^{\gamma 1}}$$

$$PNC_{circ} = \frac{PNC_{total}}{1 + H(C)} \qquad H(C) = \frac{E_{max} \times C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}} \qquad BPNC_2 = \theta_2 \left(\frac{BCRP}{100}\right)^{BPNC_2,\,CRP}$$

Figure 2. Schematic representation of the final TCZ-PNC model. The pink shaded region shows the observed quantity. The model is described in the text. K_{out} was small and poorly estimated; it was fixed to zero in the final model.



- PNC_{total} is the sum of observed circulating neutrophils (PNC_{circ}) and unobserved marginalised neutrophils (PNC_{marg}). PNC_{total} slowly decreases with time on TCZ due to decrease of PNC_2 from its baseline level $BPNC_2$. $BPNC_2$ was higher in patients with high CRP (high inflammation)
- K_{out} was estimated to be small and was fixed to zero

Table 1. Parameter Estimates for the Final Model

Parameter		Estimate (95% CI)	%RSE	Bootstrap Median (95% CI)	Variability	Shrinkage
PNC_1 (10^9/L)	θ_1	5.72	13.4	4.22, 7.21		
$BPNC_2$ (10^9/L)	θ_2	2.40	30.2	0.981, 3.82		
K_{50} (µg/ml)	θ_3	151	66.1	0, 347		
K_{max}	θ_4	0.166	244	–0.627, 0.959		
EC_{50} (µg/ml)	θ_5	6.38	15.8	4.4, 8.36		
E_{max}	θ_6	0.724	14.8	0.514, 0.935		
γ (≤5)	θ_7	5		At upper bound		
$RATIO_{ETA}$	θ_8	0.579	35.1	0.18, 0.977		
$BPNC_{2,CRP}$	θ_9	0.523	59.8	–0.09, 1.14		
ω^2_{PNC1}	$\Omega(1,1)$	0.315	31.0	0.124, 0.506	CV = 56.1%	9.8%
R ω_{PNC1} ω_{PNC2}	$\Omega(2,1)$	–0.391	59.5	–0.846, 0.0646	R = –0.638	
ω^2_{PNC2}	$\Omega(2,2)$	1.19	45.5	0.129, 2.25	CV = 109%	28.0%
ω^2_{Emax}	$\Omega(3,3)$	2.10	70.5	0, 5	CV = 145%	17.7%
σ^2_{prop}	$\Sigma(1,1)$	0.0961	5.22	0.0863, 0.106	CV = 31.0%	9.1%

95% CI, 95% confidence intervals; CV, coefficient of variation (CV = 100 × SD%); PE, parameter estimate; RSE, relative standard error (RSE = 100 × SE/PE); SD, standard deviation; SE, standard error.

Model Validation (VPC) and Model-Based Simulations

Figure 3. Visual predictive check for model 310: PNC versus time, all patients and by nominal TCZ dose.

The lines show median (purple) and the 10th and 90th percentiles (blue) of the observed PNC counts. The shaded regions show the 80% CIs on these quantities obtained by simulations. The simulated values were computed from 500 trials simulated using dosing, sampling and the covariate values of the analysis data set.

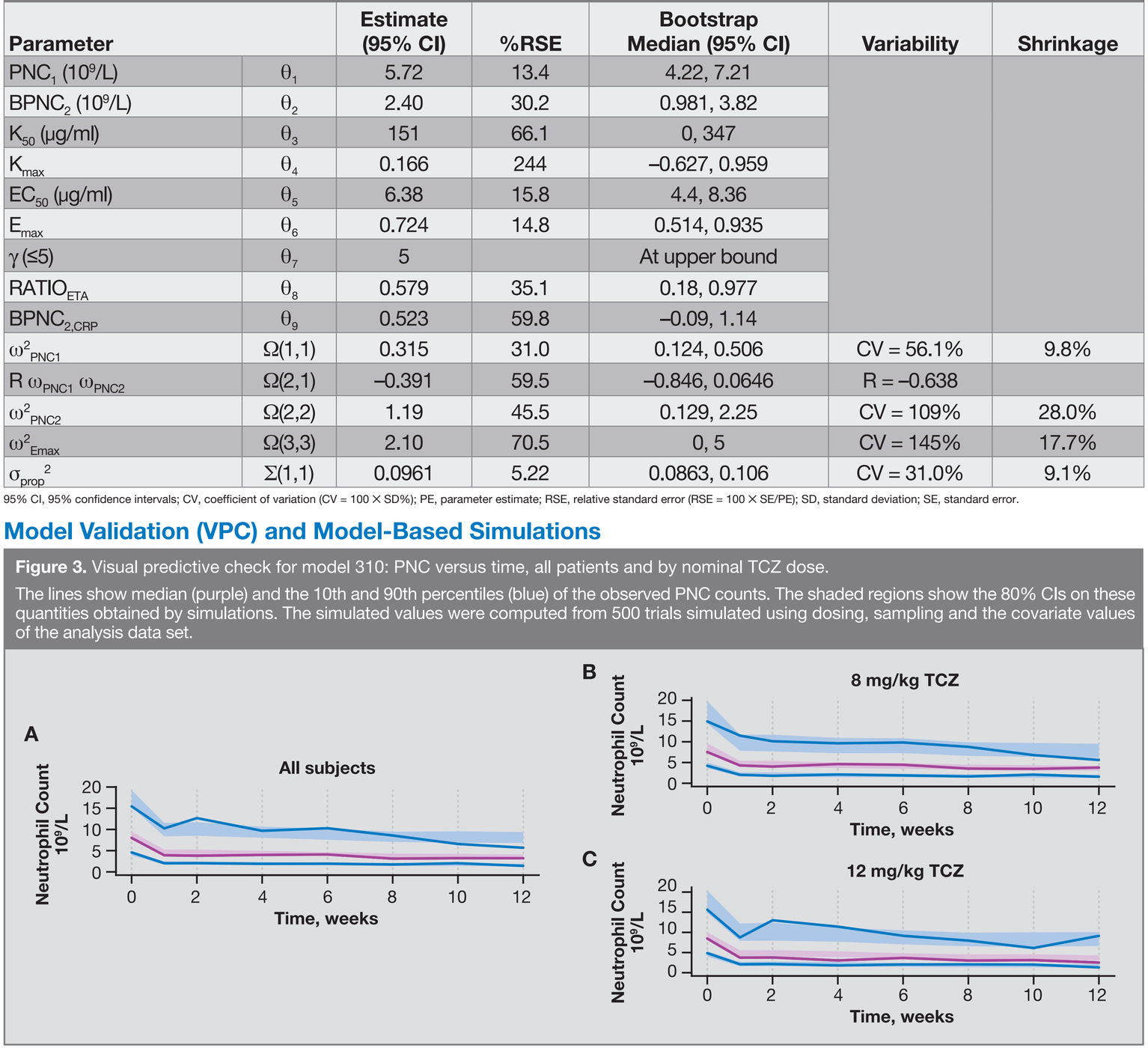


Figure 4. Model-based simulation results, by TCZ dose (weight [WT]) group.

Top row: Blue lines correspond to 90% coverage intervals of the simulated neutrophil counts. Purple lines show medians of the simulated values. Grey lines show the normal range for neutrophil counts (1.5 to 8 × 10^9/L). Bottom row: Blue lines correspond to 90% coverage intervals of the individual predictions of the TCZ concentration in the analysis population. Purple lines show medians of these values.

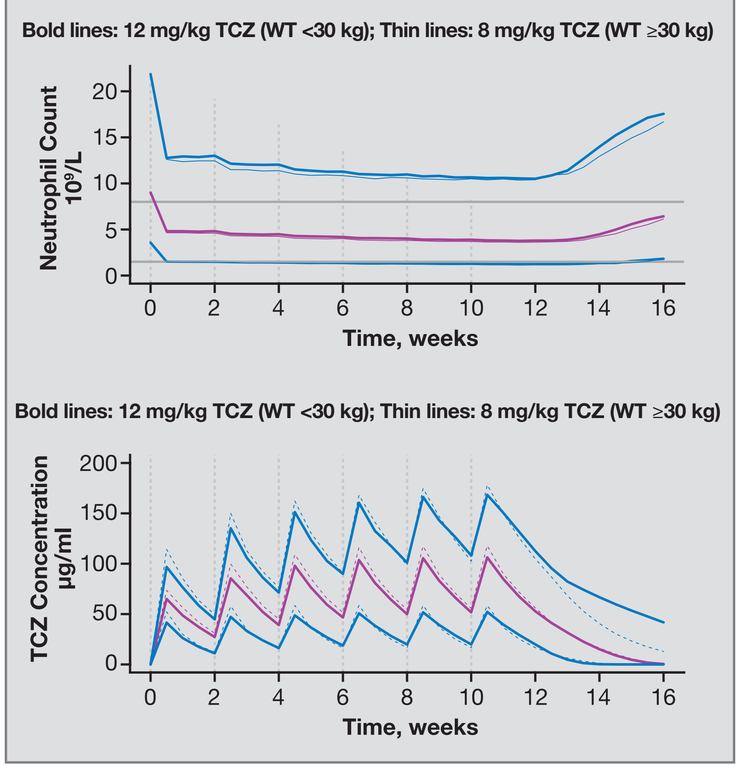


Figure 5. Basic goodness-of-fit plots for the final model.

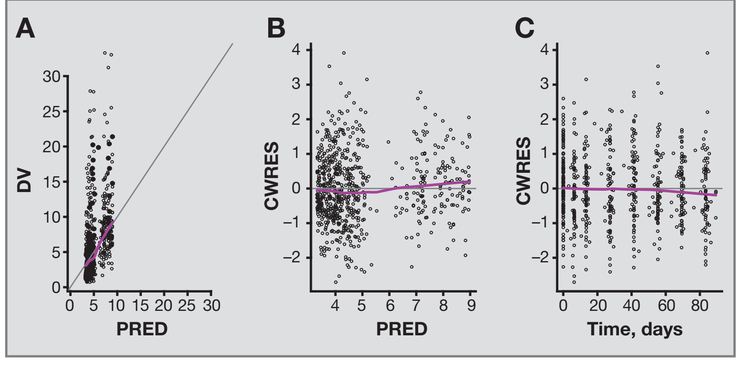
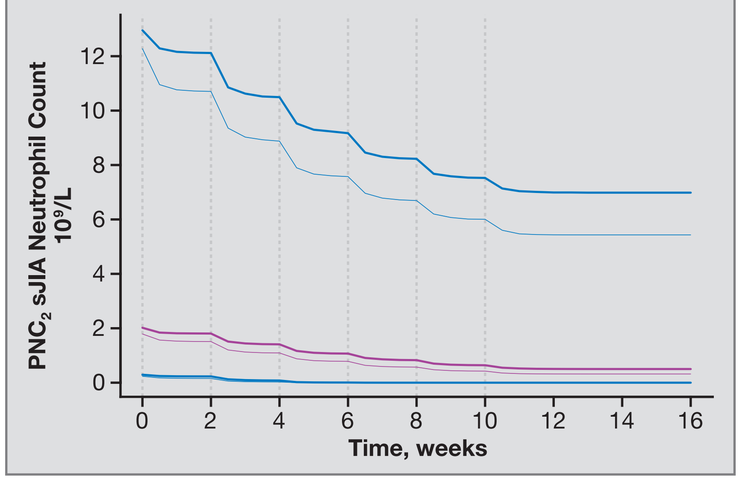


Figure 6. Model-based simulation results: PNC_2 time course.



CONCLUSION

- The observed changes in neutrophil data are consistent with the TCZ mechanism of action and can be fully explained by a short-term effect assuming neutrophil margination and a long-term effect assuming improvement in patient condition (e.g. decrease in inflammation)

REFERENCES

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