Mechanistic Modeling of the Link between Interleukin-6 Receptor Blockade with Tocilizumab and Its Hematological Effects

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BACKGROUND

Tocilizumab (TZ) is a recombinant humanized IL-6 receptor monoclonal antibody that inhibits binding of IL-6 to its soluble (sIL-6R) and membrane-expressed (mIL-6R) receptors. Elevated serum IL-6 levels have been reported in rheumatoid arthritis (RA) patients and have been shown to be associated with disease activity.

OBJECTIVES

The aim of this study was to investigate whether the decline in peripheral neutrophil and platelet counts after TZ administration can be directly explained by IL-6R blockade, thus demonstrating its mechanism of action. Specific goals were to develop:

- Population PK model of observed tocilizumab concentrations;
- Population PK-PD (TZ- sIL-6R) model of observed sIL-6R concentrations
- Population sIL-6R–neutrophil counts model of observed changes in neutrophil counts (ANC)
- Population sIL-6R– platelet counts model of the observed changes in platelet counts (PLC)

No covariate investigation was conducted.

METHODS

Serum concentrations of TZ, total sIL-6R (bound and unbound to TZ), and neutrophil and platelet counts from 4 phase 3 studies in patients with moderate to severe active RA who received 4 or 8 mg/kg TZ infusions every 4 weeks (total of 6 doses) were used. Mechanistic population PK/PD models were developed to describe the relationship between TZ and sIL-6R concentrations and subsequent changes in neutrophil and platelet counts.

RESULTS

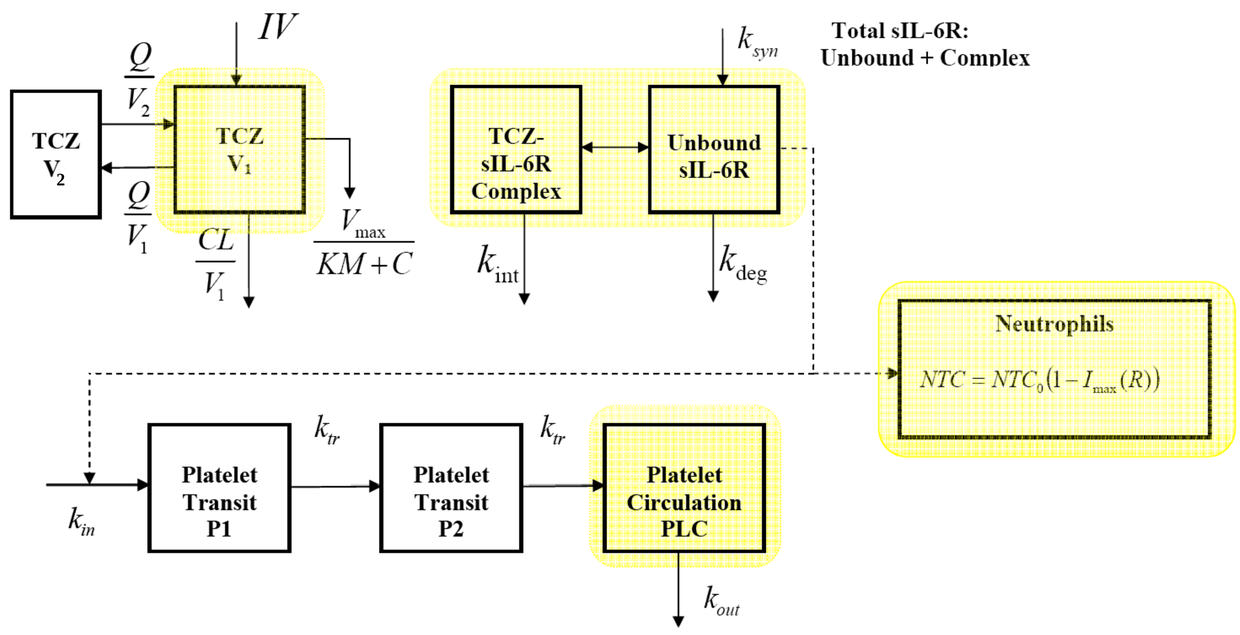
- Following TZ administration, concentrations of total sIL-6R increased, while neutrophil and platelet counts declined. These changes were transient, with counts starting to return to baseline levels after TZ infusion. The nadir of cell counts was similar for 4 and 8 mg/kg dose groups. However, the rate of rebound was dose-dependent, with cell counts returning to baseline approximately 4 weeks later for 8 mg/kg compared to the 4 mg/kg dose.
- A 2-compartment model with parallel linear and Michaelis-Menten (MM) elimination described the TZ time course.
- Quasi-steady-state (QSS) approximation of the target-mediated drug disposition model described the relationship between TZ and total sIL-6R, allowing computation of unbound sIL-6R concentrations. Interestingly, MM and QSS constants were found to be similar to the in-vitro values for TZ binding to mIL-6R and sIL-6R, respectively.
- The observed neutrophil changes were described as a direct function of the unbound sIL-6R concentrations. Fast onset and offset of the tocilizumab effect on neutrophils is consistent with the fast turnover of neutrophils in the body (with neutrophil life-span in circulation of just a few hours) and with IL-6 effect on neutrophil margination (that is even quicker).
- The observed platelet counts were described by the transit-compartment lifespan model with inhibition of production that depended on the unbound sIL-6R concentrations. The delay between tocilizumab concentration, estimated unbound sIL-6R concentrations and platelet counts is well-noticeable. Slow onset and offset of the tocilizumab effect on platelet counts is consistent with long life span of platelets.
- Diagnostic plots and predictive check simulations indicated excellent agreement of model predictions with the observed data.

CONCLUSIONS

The observed changes in sIL-6R, neutrophil and platelet data are consistent with the TZ mechanism of action and can be fully explained by TZ binding to both soluble and membrane-expressed IL-6R.

Figure 1 Schematic Representation of the Tocilizumab Hypothesized Mechanism of Action

Yellow shaded regions show observed quantities. The models are described in the text.



TZ Concentration - sIL-6R Model:

$$\frac{dR_{tot}}{dt} = k_{syn} - k_{\deg} R_{tot}\left(1 - E_{\max}\frac{C}{K_{SS}+C}\right);$$

$$E_{\max} = 1 - \frac{k_{\text{int}}}{k_{\deg}}; \quad R_{tot}(0) = R_{base} = \frac{k_{syn}}{k_{\deg}} .$$

$$R_{\text{unbound}} = \frac{R_{tot}K_{SS}}{K_{SS}+C}; \quad R_{\text{bound}} = \frac{R_{tot}C}{K_{SS}+C}.$$

Tocilizumab-sIL-6R Population Model

Parameter		Estimate	RSE %	CV (%)	Shrinkage
k_{syn} (ng/mL/d)	θ_7	47.8	2.19		
k_{deg} (1/d)	θ_8	1.26	2.13		
E_{max}	θ_9	0.939	0.0801		
K_{SS} (ng/mL)	θ_{10}	0.182	3.31		
ω^2_{kdeg}		0.0558	7.41	CV=23.6%	16.6%
$R\omega_{kdeg}\,\omega_{KSS}$		-0.128	12.4	R = -0.575	
ω^2_{KSS}		0.895	7.34	CV=94.6%	32.8%
σ^2_{prop}		0.0447	5.46	CV=21.1%	
$k_{deg} = \theta_8 \exp(\eta_1)$;		$K_{SS} = \theta_{10}\exp(\eta_2)$;		$R_{base} = k_{syn} / k_{deg}$	
$Y = R_{tot}\exp(\varepsilon)$					

The individual PK parameters were fixed at values estimated by the tocilizumab population model.

sIL-6R – Neutrophil Counts Model:

$$ANC = ANC_{base} \quad \text{if} \quad R_{\text{unbound}} \geq R_{\text{base}};$$

$$ANC = ANC_{base}\left(1 - I_{\max}\left[1 - \frac{R_{\text{unbound}}}{R_{\text{base}}}\right]^{\gamma}\right)$$

$$\text{if} \quad R_{\text{unbound}} < R_{\text{base}}$$

sIL-6R-Neutophil Counts Population Model

Parameter		Estimate	RSE%	CV (%)	Shrinkage
ANC_{base} (10^9/L)	θ_1	5.12	1.21		
L_{max}	θ_2	-0.376	7.06		
γ	θ_3	0.6	7.27		
ω^2_{ANC0}		0.0998	5.81	CV=31.6%	8.8%
ω^2_{Lmax}		0.27	9.49	CV=52.0%	31.4%
ω^2_{γ}		1.51	11.8	CV=123%	40.4%
σ^2_{prop}		0.0663	1.08	CV=25.7%	
I_{max}		0.407		95%PI: 0.198-0.657	
$ANC_{base} = \theta_1\exp(\eta_1)$;		$I_{max} = 1/(1+\exp(-\theta_2 - \eta_2))$;		$\gamma = \theta_3\exp(\eta_3)$	
$Y = ANC\exp(\varepsilon)$					

The individual PK and sIL-6R parameters were fixed at values estimated by tocilizumab and tocilizumab-sIL-6R population models. The 95% prediction interval (PI) for the derived parameter I_{max} was computed by simulations.

sIL-6R – Platelet Counts Model:

$$Eff = 1 \quad \text{if} \quad R_{\text{unbound}} \geq R_{\text{base}};$$

$$Eff = 1 - I_{\max}\left[1 - \frac{R_{\text{unbound}}}{R_{\text{base}}}\right]^{\gamma} \quad \text{if} \quad R_{\text{unbound}} < R_{\text{base}};$$

$$\frac{dP_1}{dt} = k_{in}\text{Eff} - k_{tr}P_1;$$

$$\frac{dP_2}{dt} = k_{tr}(P_1 - P_2); \qquad P_1(0) = P_2(0) = \frac{k_{\text{in}}}{k_{\text{tr}}};$$

$$\frac{dPLC}{dt} = k_{tr}P_2 - k_{out}PLC; \qquad PLC(0) = \frac{k_{\text{in}}}{k_{\text{out}}}.$$

sIL-6R – Platelet Counts Population Model

Parameter		Estimate	RSE (%)	CV (%)	Shrinkage
PLC_{base}(10^9/L)	θ_1	316	0.88		
L_{max}	θ_2	-0.839	2.91		
γ	θ_3	0.268	22.4		
k_{in}(10^9/L/d)	θ_4	109	11.7		
$k_{transit}$ (1/d)	θ_5	0.298	6.23		
ω^2_{PLC0}		0.0544	5.99	CV=23.3%	5.4%
ω^2_{Lmax}		0.196	10.4	CV=44.2%	24.8%
$\omega^2_{kin}=\omega^2_{ktr}$		0.123	18.6	CV=35.1%	43.8%
σ^2_{prop}		0.0142	3.96	CV=11.9%	
I_{max}		0.301		95%PI: 0.152-0.509	
$PLC_{base} = \theta_1\exp(\eta_1)$; $I_{max} = 1/(1+\exp(-\theta_2 - \eta_2))$; $\gamma = \theta_3$; $k_{in} = \theta_4\exp(\eta_3)$; $k_{transit} = \theta_5\exp(\eta_3)$; $k_{out} = k_{in} / PLC_{base}$;					
$Y = PLC\exp(\varepsilon)$					

The individual PK and sIL-6R parameters were fixed at values estimated by tocilizumab and tocilizumab-sIL-6R population models. The 95% prediction interval (PI) for the derived parameter I_{max} was computed by simulations.

Model-Based Simulation of Typical Tocilizumab Concentration, Total sIL-6R Concentration, Neutrophil Counts, and Platelet Counts.

Green and black lines show 4 mg/kg and 8 mg/kg dosing regimens, respectively

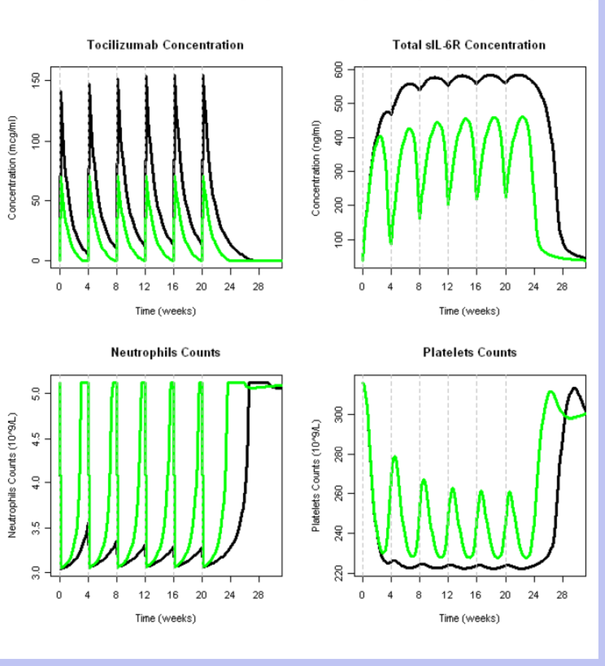


Figure 10 Visual Predictive Check of the Total sIL-6R Concentration, Neutrophil Counts, and Platelet Counts.

Bold lines show 10th, 50th and 90th percentiles of the observed data. Shaded regions show 80% confidence intervals for the corresponding quantities.