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 returning 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 wellnoticeable. 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.