

Title: Immediate and Long-Term Effects of Tocilizumab on Neutrophil Counts in Pediatric Patients with Systemic Juvenile Idiopathic Arthritis.

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Purpose: Tocilizumab (TCZ) is a recombinant humanized IL-6 receptor monoclonal antibody that inhibits binding of IL-6 to its receptors. The aim of the analysis was to describe the time course of peripheral neutrophil counts (NTC) after TCZ administration in patients with active systemic juvenile idiopathic arthritis (sJIA).

Methods: Serum TVZ concentrations and NTC were available from 75 patients who received 12 mg/kg (patients < 30 kg) or 8 mg/kg (patients ≥ 30 kg) infusions of TCZ or placebo every 2 weeks (total of 6 doses). Neutrophil counts were assessed at screening, 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. Different direct and indirect response models were tested to characterize the TCZ-NTC relationship.

Results: The TCZ-NTC relationship was described by a model that included an immediate TCZ effect on NTC decline (possibly, neutrophil margination) and a longer term TCZ effect on NTC decline (toward normal levels) due to the improvement of patients' condition (e.g. decrease of inflammation). The immediate effect was described by a direct sigmoid E_{\max} model ($E_{\max} = 0.724$, $EC_{50} = 6.38 \mu\text{g/mL}$). These parameters were very similar to the respective values obtained earlier for adult patients ($E_{\max} = 0.788$, $EC_{50} = 7.49 \mu\text{g/mL}$). The maximum rate of decline of the long term effect was 0.166 day^{-1} and the TCZ concentration corresponding to half of this rate was $151 \mu\text{g/mL}$. The corresponding NTC decline for a typical patient was estimated to go from $8.12 \times 10^9/\text{L}$ to $5.72 \times 10^9/\text{L}$. The magnitude of the decline increased with the baseline concentrations of the C-reactive protein. Diagnostic plots and predictive check simulations indicated a good agreement of model predictions with the observed data.

Conclusions: The NTC time course following Q2W administration of 12 mg/kg (for patients < 30 kg) or 8 mg/kg (for patients ≥ 30 kg) of TCZ in pediatric patients with sJIA was characterized by a combination of an immediate response described by the sigmoid E_{\max} function of tocilizumab concentrations, and a slow decline possibly related to the improvement of the patients' condition.