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 (possible increase of neutrophil margination)3 and a longer-term TCZ effect on PNC (Figure 1). Observed PNC data are consistent with the TCZ mechanism of action and can be fully explained by model predictions with observed data

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
2. Roche Internal Documents.

Table 1. Parameter Estimates for the Final Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (95% CI)</th>
<th>%RSE</th>
<th>Bootstrap Median (95% CI)</th>
<th>Variability</th>
<th>Shrinkage</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNCi (10%)</td>
<td>0.15 (0.14, 0.16)</td>
<td>10.3</td>
<td>0.14 (0.13, 0.15)</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>BPNCl (10%)</td>
<td>0.20 (0.18, 0.22)</td>
<td>10.0</td>
<td>0.19 (0.18, 0.21)</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>Kmax (10%)</td>
<td>0.50 (0.45, 0.55)</td>
<td>10.0</td>
<td>0.49 (0.45, 0.54)</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>Emax (10%)</td>
<td>0.70 (0.65, 0.75)</td>
<td>10.0</td>
<td>0.68 (0.65, 0.73)</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>Kout (10%)</td>
<td>0.05 (0.04, 0.06)</td>
<td>10.0</td>
<td>0.04 (0.03, 0.05)</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>Kout × BPNC2 Kout</td>
<td>0.01 (0.00, 0.02)</td>
<td>10.0</td>
<td>0.01 (0.00, 0.02)</td>
<td>10%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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