Effects of Tocilizumab on Neutrophil Counts in Patients with Rheumatoid Arthritis (RA)

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Objectives: Tocilizumab is a recombinant humanized anti-IL-6R monoclonal antibody. The analysis aimed to establish a predictive population PK-PD model that describes the time-course of peripheral neutrophil counts (NTC) following tocilizumab administration of 8 mg/kg IV Q4W (IV1), 162mg SC QW (SC1) and Q2W (SC2) regimens, or placebo, including identification of covariate factors influencing PK-NTC relationships.

Methods: NTC observations (15,870) of 1887 RA patients from two Phase III studies were analyzed. Tocilizumab concentrations were predicted using the population PK model developed earlier. Impact of identified covariates was investigated by simulations.

Results: The indirect-response model with stimulatory Hill effect on NTC elimination by tocilizumab provided an excellent fit of the observed NTC data. The relationship between neutrophil counts and tocilizumab concentration is independent of the route of administration. The parameter estimates (Table 1) translate into 3.36 days half-life of the effect, 45% maximal decrease of NTC from baseline, and the lowest possible NTC level of 2.56 10^9/L. The effect of tocilizumab on NTC was smaller and fluctuations were larger for SC2 compared to SC1 and IV1 regimens. The effects were similar for SC1 and IV1 regimens.

Six covariates remained in the final PK/PD model: C-reactive protein (CRP) and IL-6 levels at baseline, previous administration of corticosteroids, smoking, age, and gender. No covariate, including presence of neutralizing anti-tocilizumab antibodies, was found to have a clinical impact on the effect of tocilizumab on circulating neutrophil counts.

Conclusions: The NTC time-course following IV and SC administration of tocilizumab was well described by the indirect-response model with stimulation of elimination. Analyses results have confirmed that there were no differences in exposure-response relationships between the IV and SC administrations. Similar to the PK-efficacy relationship (shown on another poster at this conference), the PK-safety relationship of tocilizumab are similar for 8mg/kg IV Q4W and 162 mg SC QW regimens.

Table 1. Parameter Estimates for the Final Model

Parameter	Estimate	%RSE	Parameter	Estimate	%RSE
BASE (10^9/L)	4.70	1.22	$EC_{50,SEX}$	0.78	11.3
k_{out} (1/day)	0.206	7.69	$E_{max,CRP}$	0.0635	25.4
EC_{50} (µg/mL)	6.67	4.76	$E_{max,IL6}$	0.665	9.3
E_{max}	0.832	2.21	ω^2_{BASE}	CV=28.4%	3.66 [a]
γ	1.85	4.98	ω^2_{kout}	CV=152%	12.1 [a]
$BASE_{CRP}$	0.102	5.84	ω^2_{EC50}	CV=88.8%	12.1 [a]
$BASE_{PCOR}$	1.23	1.47	ω^2_{EMAX}	CV=52.8%	6.47 [a]
$BASE_{SMK}$	1.18	1.87	σ^2	CV=23.0%	1.01 [a]
$k_{out,AGE}$	0.676	16.4	[a] %RSE for the estimate of variance		

BASE: baseline NTC; k_{out}: rate constant of NTC elimination; E_{max}: maximal stimulation of k_{out}; EC_{50}: tocilizumab concentration at half of the effect; γ: sigmoidicity parameter; PCOR: previous treatment with corticosteroids.