

Effects of Tocilizumab on DAS28 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 DAS28 time-course following administration of 8 mg/kg IV Q4W (IV1), 162mg SC QW (SC1) and Q2W (SC2) tocilizumab, or placebo, including identification of covariate factors influencing PK-DAS28 relationships.

Methods: DAS28 observations (13,998) of 1890 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 an inhibitory E_{max} effect on DAS28 ‘production’ rate by tocilizumab concentrations adequately described the time-course of DAS28. Model parameters were estimated precisely (Table 1). The population mean of the maximum effect of tocilizumab corresponded to 56.5% reduction of DAS28 from baseline (Δ DAS28). The relationship between tocilizumab concentrations and DAS28 was independent of route of administration. The efficacy of tocilizumab was similar for IV1 and SC1 regimens (50% Δ DAS28), and was higher compared to SC2 (41% Δ DAS28). Following 24 weeks of treatment, Δ DAS28 was predicted to be 50% for IV1 and SC1 regimens, and 41% for SC2 regimen. No covariates, including presence of neutralizing anti-tocilizumab antibodies had a clinical impact on the effect of tocilizumab on DAS28.

Conclusions: The indirect-response model with an inhibitory effect on DAS28 ‘production’ rate by tocilizumab serum concentrations adequately described the magnitude and the time-course of DAS28 score reduction following both IV and SC administrations. There were no differences in the exposure-response relationships between the IV and SC administrations. Similar to the PK-safety relationship (shown on another poster at this conference), the PK-efficacy relationship of tocilizumab are similar for 8 mg/kg IV Q4W and 162 mg SC QW dosing regimens, and the efficacy for the 162 mg SC QW was higher than that of the 162 mg Q2W SC regimen.

Table 1. Parameter Estimates for the Final Model

Parameter	Estimate	%RSE	Parameter	Estimate	%RSE
EC_{50} (μ g/mL)	1.86	12.8	$L_{Emax,IL6}$	-0.457	19.9
LE_{max}	0.77	3.46	ω^2_{EC50}	CV=135%	12.1 ^a
k_{out} (1/day)	0.0402	2.33	$R\omega_{EC50}\omega_{BASE}$	R=0.317	25.6 ^a
BASE (DAS28)	6.67	0.289	ω^2_{BASE}	CV=44.7%	9.18 ^a
C_{DMARD}	0.581	16.7	$R\omega_{EC50}\omega_{kout}$	R=0.455	19.3 ^a
$BASE_{CRP}$	0.02	11.3	$R\omega_{kout}\omega_{BASE}$	R=-0.622	9.37 ^a
$BASE_{HAQ}$	0.0962	8.18	ω^2_{kout}	CV=62.9%	7.56 ^a
$BASE_{PAIN}$	0.103	7.95	$R\omega_{LEmax}\omega_{BASE}$	R=0.176	34.5 ^a
$BASE_{VASP}$	0.134	7.45	$R\omega_{LEmax}\omega_{kout}$	R=0.144	34.7 ^a
$LE_{max,SEX}$	0.641	6.08	ω^2_{LEmax}	CV=81.4%	5.58 ^a
$LE_{max,AGE}$	0.594	15.2	σ^2	SD=0.676	1.09 ^a
Derived Parameter: $E_{max} = 1/(1+LE_{max})$			^a %RSE for the estimate of (co)variance		
$E_{max, females}$	0.565		HAQ = baseline health assessment questionnaire, VASP = physicians global score of disease activity at baseline, PAIN = patient’s assessment of pain at baseline, CRP = C-reactive protein concentration at baseline; IL6: IL6 concentration at baseline.		
$E_{max, males}$	0.670				
“System-related” parameters: BASE = DAS28 score, k_{out} = rate constant of elimination of DAS28.					
“Drug-related” parameters: E_{max} = maximal inhibition of K_{in} , EC_{50} =tocilizumab serum concentration at half of the effect, C_{DMARD} =parameter describing the effect of DMARD medications.					