Population PKPD Modeling of the Relationship Between TACI-Ig Exposure and Biomarker Response in Patients with Rheumatoid Arthritis (RA)

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Objective

To establish and characterize quantitatively the relationship between the *IgG, IgM and IgA antibody levels* and the *systemic exposure* with TACI-Ig after single and repeated subcutaneous (SC) doses in patients with RA.

TACI-Ig, a recombinant fusion protein containing the extracellular, ligand-binding portion of the receptor TACI, acts as an inhibitor of BLyS and APRIL, two potent stimulators of normal and autoimmune B-cell maturation, proliferation and survival. The molecule is currently in development for several indications, including treatment of patients with RA.

Methods

Data

Data were obtained from a phase Ib, multi-centre, double-blind, placebo-controlled, dose-escalating study to assess the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of TACI-Ig when administered subcutaneously to 73 patients with RA (Table 1). Sample collections for PK, PD and biomarker assessment and assessment of safety and disease activity were conducted at pre-defined intervals up to 14 weeks for single-dose cohorts, 18 weeks for Cohorts 2 and 4 and 26 weeks for Cohort 6.

Cohort	Dose (mg)	Administration	# of Subjects
1	1x70	Single dose	6 active, 2 placebo
2	3x70	3 doses, 2 weeks apart (EOW)	9 active, 3 placebo
3	1x210	Single dose	6 active, 2 placebo
4	3x210	3 doses, 2 weeks apart (EOW)	9 active, 3 placebo
5	1x630	Single dose	6 active, 2 placebo
6	7x420	7 doses, 2 weeks apart (EOW)	19 active, 6 placebo

Table 1. RA study design.

PK and PD Variables

Pharmacokinetic variables analyzed were concentrations of Free TACI-Ig and Total TACI-Ig (comprising free TACI-Ig and TACI/BLyS Complex). Both were measured using ELISA assays.

IgM, IgG, and IgA antibody levels in blood were the primary markers of TACI-Ig biological activity, following the cascading PK/PD concept of biomarkers, recently introduced by M. Danhof *et al.* (2005).

Population PK/PD Analyses

Total TACI-Ig was selected as exposure variable as it contained information for both the free and bound drug. First, a population PK model was developed which was subsequently used to construct separate population PK/PD models for IgM, IgA and IgG. Biomarker responses (defined as percent of measured baseline values) were characterized by indirect PD models with TACI-Ig dependent inhibition of immunoglobulin production. The covariation between the three biomarkers was explored. To account for this covariation within an individual, a PKPD model with all three responses (as a multivariate observation) was developed.

All population models were developed using First Order Conditional Estimation with Interaction (FOCEI) method implemented with NONMEM version 5 software.

Results

The common structure of the population PK/PD model, consisting of a two compartment PK model and an indirect response model is presented schematically in Figure 1.

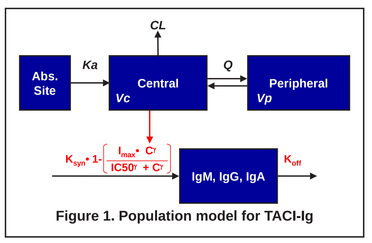

Figure 1. Population model for TACI-Ig

Population PK Model

The population PK parameter estimates are given in Table 2. The model-generated percentiles (5%, 25%, 50%, 75% and 95%) and the clinical data for Cohort 6 are given in Figure 2.

Separate Population PK/PD Models

The population parameter estimates of the indirect PK/PD models for IgM, IgG and IgA are given in Table 3. The model-generated percentiles (5%, 25%, 50%, 75% and 95%) and the clinical data for IgM depletion in Cohort 6 are given in Figure 3.

PK Parameter	Covariate Model	Symbol	Estimate
Clearance/F (L/h)	$TVCL= \theta_1 * DPW\ \theta_6$ $CL=TVCL* exp\ \{\eta_1\}$	θ_1	0.193
		θ_6	0.324
		IIV (%)	29.5
Central VC/F (L)	$TVVC= \theta_2$ *(if female)*	θ_2	15.0
	$TVVC= \theta_2 * \theta_7$ *(if male)*	θ_7	0.211
	$VC=TVVC* \{\eta_2\}$	*IIV (%)*	55.6
Peripheral (Vp/F (L)	$TVVP= \theta_3 * DPW\ \theta_8$ $CL=TVVP* exp\ \{\eta_3\}$	θ_3	148
		θ_8	0.214
		IIV (%)	37.8
Intercompartmental Clearance/F (L/h)	$TVQ= \theta_4 * DPW\ \theta_9$ $CL=TVQ* exp\ \{\eta_4\}$	θ_4	1.04
		θ_9	-0.282
		IIV (%)	57.1
Absorption Rate (1/h)	θ_5	θ_5	0.0211
Residual Error (%)	Proportional	*CV (%)*	17.7

Table 2. Parameter estimates of the final Total TACI population model used for Pk/PD model building. DPW stands for Dose per Weight.

Parameter	IgM	IgG	IgA
I_{max} (% change from baseline)	88.1 (10.3)	28 (3.66)	62.3 (9.07)
IC50 (ng/ml)	1730 (354)	1390 (330)	2000 (552)
CV of Residual Error (%)	7.25	6.25	8.13

Table 3. Population parameter estimates of the PK/PD models.

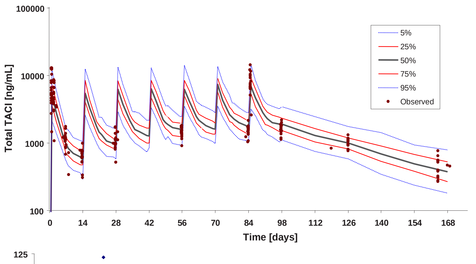

Figure 2. Total TACI-Ig concentration - time profiles for Cohort 6: Observed (dots) and model simulated (percentile curves).

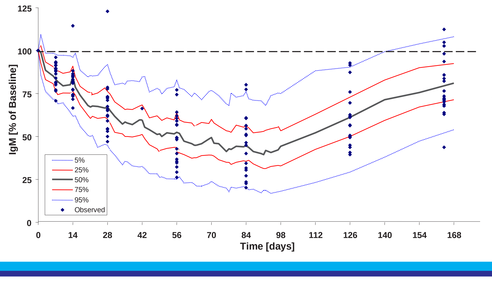

Figure 3. IgM (% of baseline) - time profiles for the active dose patients in Cohort 6: Observed (dots) and model simulated (percentile curves).

Simultaneous population PK/PD model

The correlations between the three biomarkers (based on the percent of baseline profiles) are high, with correlation coefficients calculated from all patients data in excess of 0.7 (Figure 4). The population parameter estimates of the combined PK/PD model for IgM, IgG and IgA are given in Table 4. The diagnostic plots for the model are given in Figure 5.

The existing correlation is reflected in the PK/PD model by high correlation coefficients both between the Imax random effects for IgM, IgG and IgA, and between the residual errors. Serious NONMEM convergence difficulties were encountered while estimating block OMEGA and SIGMA matrices simultaneously. The probable reason for this is the inadequate sample size (N=73). With the accumulation of data from Phase 2 and phase 3, this obstacle will be overcome.

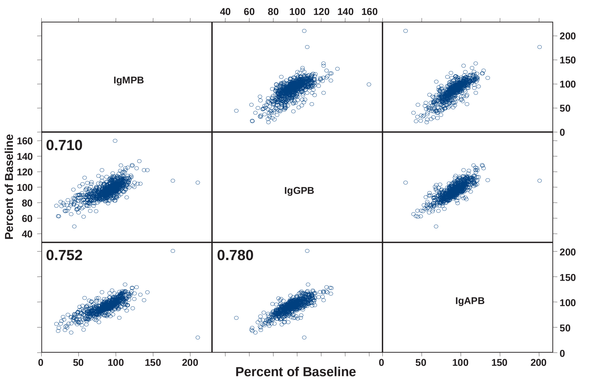

Figure 4. Correlations between IgA, IgG and IgM (percent of baseline) profiles. Correlation coefficients are inserted in the respective panels.

Parameter	IgM	IgG	IgA
I_{max} (% change from baseline)	93.6	21.6	63.1
IC50 (ng/ml)	1700	1010	2060
CV of Residual Error (%)	8.19	6.28	8.41
Correlation Matrices	On I_{max} (OMEGA) 1 0.335 1 0.648 0.933 1	Residual (SIGMA) 1 0.653 1 0.754 0.703 1	

Table 4. Population parameter estimates of the combined PK/PD indirect response models for IgM, IgG and IgA.

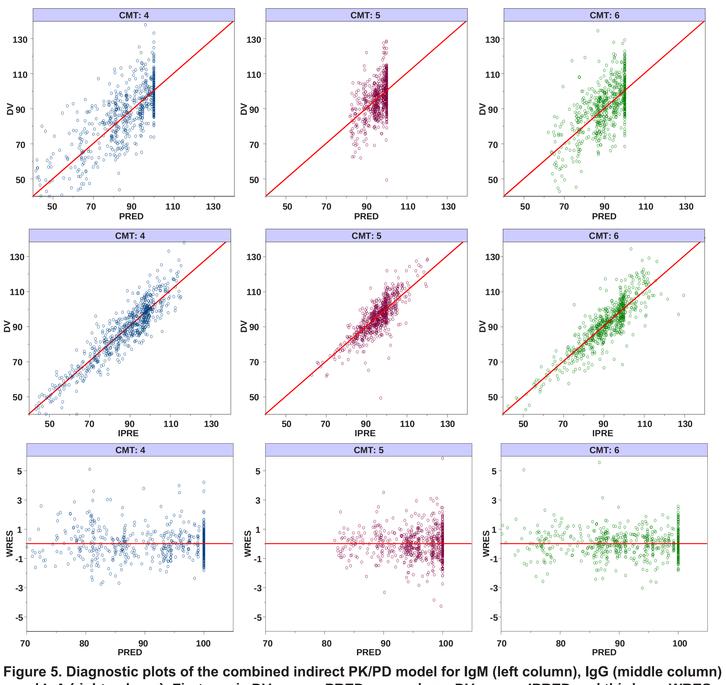

Figure 5. Diagnostic plots of the combined indirect PK/PD model for IgM (left column), IgG (middle column) and IgA (right column). First row is DV versus PRED, second row DV versus IPRED and third row WRES versus PRED.

Conclusions

- **The biological activity of TACI-Ig in RA patients was demonstrated by the IgM, IgG and IgA data. The relationship between TACI-Ig exposure and IgM, IgA and IgG antibody response was characterized quantitatively. IgM antibody levels were the most responsive to TACI-Ig exposure, followed by IgA and IgG.**
- **Population PK/PD models on each of the three biomarkers were developed successfully. Those capture both the central tendencies and the variability in the data.**
- **The existing high correlations between the three biomarkers (as "percentage of baseline" profiles) are captured by the simultaneous PK/PD model, which treats IgM, IgA, and IgG as multivariate observations.**
- **The population PK/PD models on the biomarkers can be used in exploring various scenarii for the design of dosing regimens in future studies.**

References

1. M. Danhof, G. Alvan, S.G. Dahl, J. Kuhlmann, G. Paintaud. Mechanism –based pharmacokinetic-pharmacodynamic modeling – a new classification of biomarkers. Pharm. Res. 22:1432-1437 (2005).
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