Supplementary material

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Title:

Identifying Safety Thresholds for Immunosuppressive Drugs: Applying Insights from Primary Antibody Deficiencies to Mitigate Adverse Events in Secondary Antibody Deficiencies Using Mathematical Modeling of Preclinical and Early Clinical Data

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Supplementary materials

Change in total atacicept concentration was described using a two-compartment model with first-order absorption, adequately capturing the central tendency and variability in the data obtained for total atacicept concentrations in three clinical trials: Phase I, single-dose study in Caucasian and Japanese HV (EMR700461-022); Phase II study in SLE (NCT00624338, APRIL-SLE) where 75 or 150 mg subcutaneous (sc) doses were administered once weekly for 52 weeks (bi-weekly for the first 4 weeks of treatment); and Phase II study in SLE (NCT01972568, ADDRESS II) with once-weekly sc dosing of 75 or 150 mg for 24 weeks.

A diagram of the model adapted from (1) is shown in Figure A1; the impact of the drug on the biomarker is shown in Figure A2.

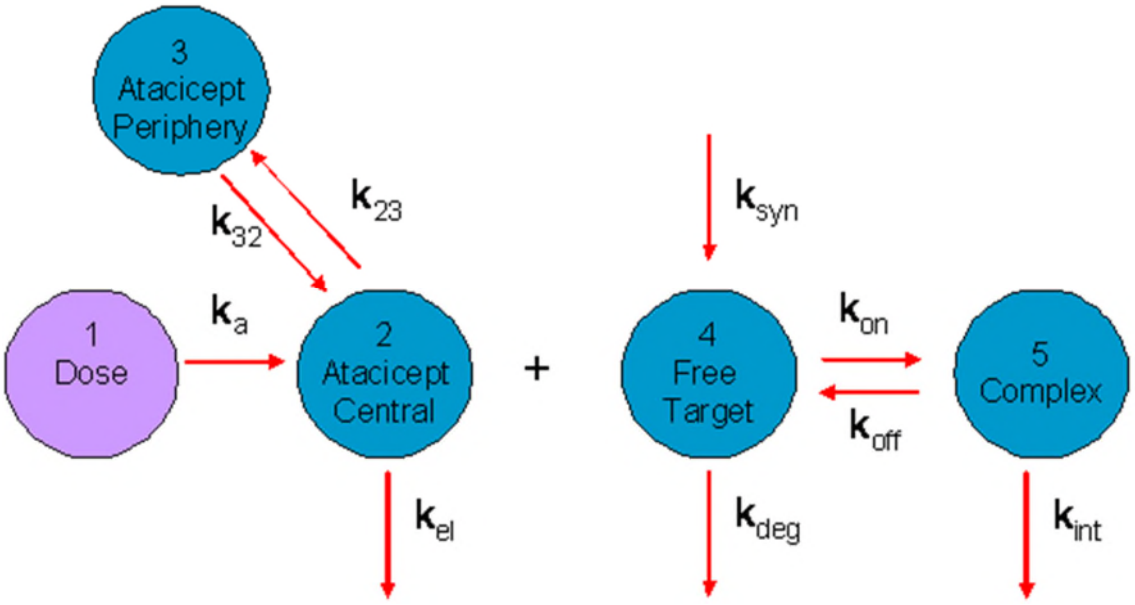

Figure A1. Schematic Representation and Differential Equations of the Two-Compartment Quasi Steady-State Target Mediated Drug Disposition Binding (QSS TMDD) Model for Atacicept. Figure is adapted from (2).

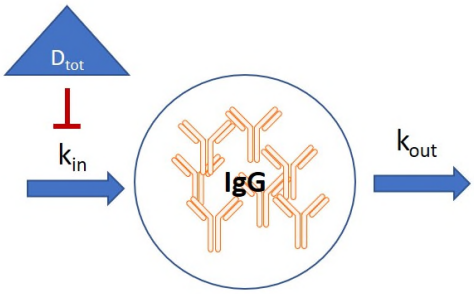

Figure A2. Schematic representation of IgG indirect response model used on modeling the effect of atacicept on IgG production.

The interactions between atacicept and its ligands is described by the following system of equations:

$$\begin{aligned}
\frac{dA_1(t)}{dt} &= -k_a A_1(t) \\
\frac{dC_{tot}(t)}{dt} &= k_a \frac{A_1(t)}{V_c} - \left(k_{el} + k_{23}\right) C(t) - \frac{k_{\text{int}} C R_{tot}(t)}{K_{ss} + C} + k_{32} \frac{A_3(t)}{V_c} \\
\frac{dA_3(t)}{dt} &= K_{23} C(t) V_c - K_{32} A_3(t) \\
\frac{dR_{tot}(t)}{dt} &= k_{syn} - k_{\text{deg}} R_{tot}(t) - \left(k_{\text{int}} - k_{\text{deg}}\right) \frac{C(t) R_{tot}(t)}{K_{ss} + C(t)}
\end{aligned} \tag{A1}$$

where $A_n(t)$ is the amount of atacicept in nth compartment; C(t) is the total concentration of free atacicept calculated as $C = \frac{1}{2}\left[\left(C_{tot} - R_{tot} - K_{ss}\right) + \sqrt{\left(C_{tot} - R_{tot} - K_{ss}\right)^2 + 4K_{ss}C_{tot}}\right]$, with steady state constant $K_{ss} = \frac{k_{off}}{k_{on}} + \frac{k_{\text{int}}}{k_{on}}$. $C_{tot}(t)$ is the total atacicept concentration (bound and unbound drug) and $R_{tot}(t)$ is the total target concentration. Notably, the target in this model refers to an abstract quantity that characterizes an overall interaction of atacicept with its ligands. Full description of parameters and corresponding estimates can be found in Table A1 and in (2).

Table A1. Parameters used in System (A1).

Parameter	Description	Unit	Value
k_{23}	Transfer rate from central to peripheral compartments	1/h	0.004105
k_{32}	Transfer rate from peripheral to central compartment	1/h	0.003870
k_a	Drug absorption rate constant	1/h	0.0705
k_{deg}	Target elimination rate constant	1/h	0.00362
k_{el}	Drug elimination rate constant	1/h	0.008926
k_{int}	Drug-target complex elimination constant	1/h	0.00618
k_{off}	Dissociation rate constant	h/ng/mL	Cannot be estimated from data
k_{on}	Binding rate constant	1/h	Cannot be estimated from data
k_{syn}	Target synthesis rate	ng/mL/h	2.5883
V_c	Volume of central compartment	L	36.3

Simulations vs results of Address II clinical trial

For the main part of ADDRESS II trial (not the long-term extension), 103 subjects in the 150 mg QW dose group provided 829 IgG observations in the data set modeled. None of these observations were below the threshold of 3g/L. This result is very consistent with the simulated profile of Figure A3 below, according to which less than 1% of the simulated subjects (profiles) are expected to have IgG below 3 g/L at any time during a treatment period of 24 weeks.

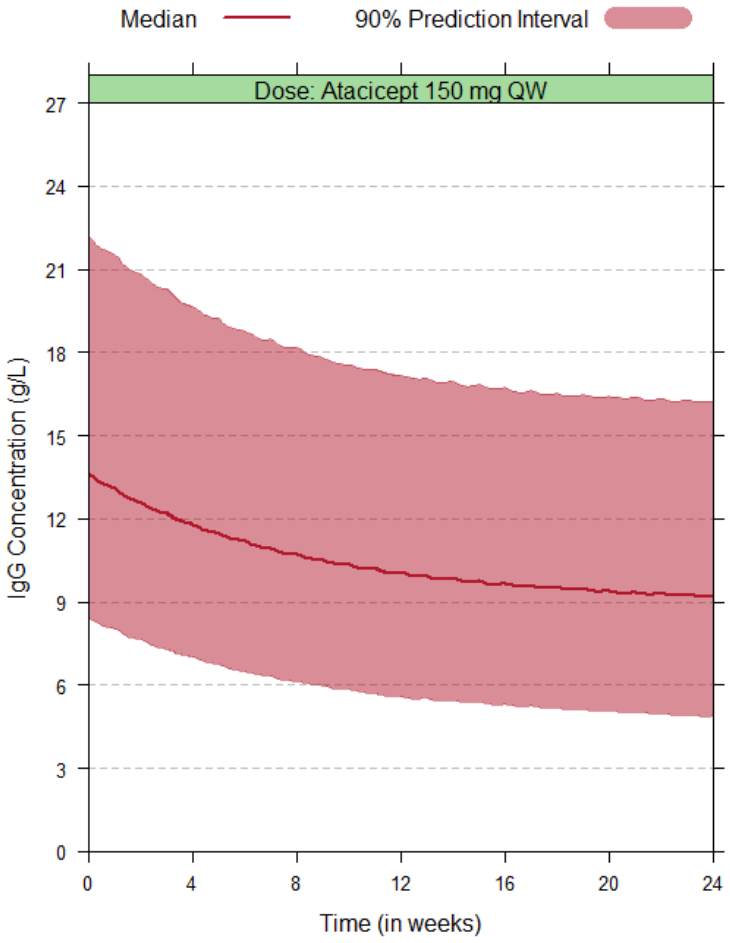

Figure A3. Simulated IgG profiles following 150 mg QW administration of atacicept in SLE subjects for 24 weeks.

References:

1. Pitsui M, Papasouliotis O, Farrell C, Girard P, Yalkinoglu O, Vazquez-Mateo C. Population Pharmacokinetics of Atacicept in Systemic Lupus Erythematosus (SLE)-an Analysis of Three Clinical Trials. ARTHRITIS & RHEUMATOLOGY. WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA; 2019.

2. Papasouliotis O, Yalkinoglu Ö, Golob M, Willen D, Girard P. AB0529 Population Pharmacokinetics of Atacicept in Systemic Lupus Erythematosus (SLE). Annals of the Rheumatic Diseases. BMJ Publishing Group Ltd; 2015;74:1077.