Simulation of monoclonal antibody pharmacokinetics in humans using a minimal physiologically-based model – supplementary materials

Linzhong Li[a,*], Iain Gardner[a], Miroslav Dostalek[b], Masoud Jamei[a]

[a]Simcyp Limited, A Certara Company, Blades Enterprise Centre, John Street, Sheffield S2 4SU, U.K. [b]F. Hoffmann-La Roche AG, pRED, Pharma Research & Early Development, Non-Clinical Safety, Grenzacherstrasse, Basel, Switzerland

*Address for correspondence:
Linzhong Li, Simcyp Limited, A Certara Company, Blades Enterprise Centre, John Street, Sheffield S2 4SU, U.K. Tel: 01142 922341, Fax: 01142 922333; E-mail: l.li@simcyp.com

Keywords: PBPK, Monoclonal antibody, Pharmacokinetics, Simulation

Suggested Short Title: Minimal PBPK model for monoclonal antibodies

Appendix A: The competitive binding of endogenous and exogenous IgGs to FcRn

We consider two species, endogenous IgG and exogenous IgG, competing for the same binding site on FcRn. A binding stoichiometry of one to one is assumed. In reality IgG is known to bind to FcRn predominantly with a 1:2 stoichiometry (1), a 1:1 stoichiometry has been used in the current and other PBPK models for mAbs (2).

To simplify the notation *R* is used to represent FcRn and *G* to represent IgG, and brackets represent molar concentrations. Only equilibrium binding is considered, defined by equilibrium dissociation constants K_D^{en} and K_D^{ex} for endogenous and exogenous IgG binding to FcRn, respectively.

$$R + G^{en} \xleftrightarrow{K_D^{en}} RG^{en} \qquad R + G^{ex} \xleftrightarrow{K_D^{ex}} RG^{ex} \tag{A 1}$$

By definition

$$K_D^{en} = \frac{[R][G^{en}]}{[RG^{en}]} = \frac{[R]\left([G^{en}]_T - [RG^{en}]\right)}{[RG^{en}]} = [R]\frac{\left(1 - f_b^{en}\right)}{f_b^{en}}, \; f_b^{en} = \frac{[RG^{en}]}{[G^{en}]_T}, \tag{A 2}$$

$$K_D^{ex} = \frac{[R][G^{ex}]}{[RG^{ex}]} = \frac{[R]\left([G^{ex}]_T - [RG^{ex}]\right)}{[RG^{ex}]} = [R]\frac{\left(1 - f_b^{ex}\right)}{f_b^{ex}}, \; f_b^{ex} = \frac{[RG^{ex}]}{[G^{ex}]_T}, \tag{A 3}$$

where conservation relations (A 4) of endogenous IgG and exogenous IgG have been applied.

$$[G^{en}]_T = [G^{en}] + [RG^{en}], \; [G^{ex}]_T = [G^{ex}] + [RG^{ex}]. \tag{A 4}$$

From (A 2) and (A 3) the fractions of bound IgG can be represented by (A 5),

$$f_b^{en} = \frac{x}{x + \alpha_1}, \quad f_b^{ex} = \frac{x}{x + \alpha_2}, \tag{A 5}$$

with

$$x = \frac{[R]}{[R]_T}, \; \alpha_1 = \frac{K_D^{en}}{[R]_T}, \; \alpha_2 = \frac{K_D^{ex}}{[R]_T}. \tag{A 6}$$

The conservation of FcRn species gives

$$[R]_T = [R] + [RG^{en}] + [RG^{ex}] \tag{A 7}$$

from which the following can be derived

$$1 = x + \beta_1 f_b^{en} + \beta_2 f_b^{ex} \tag{A 8}$$

with

$$\beta_1 = \frac{[G^{en}]_T}{[R]_T}, \quad \beta_2 = \frac{[G^{ex}]_T}{[R]_T}. \tag{A 9}$$

Substituting (A 5) into (A 8), the equation for x (A 10) is derived.

$$1 = x + \beta - \frac{\beta_1\alpha_1}{x+\alpha_1} - \frac{\beta_2\alpha_2}{x+\alpha_2}, \quad \beta = \beta_1 + \beta_2 \tag{A 10}$$

The equation (A 10) can be converted into a cubic equation and it can be proved that the cubic equation has only one positive root, see (3). Here we prefer a numerical approach, i.e., employing Newton-Raphson method to find the root. Let

$$F(x) = x - 1 + \beta - \frac{\alpha_1\beta_1}{x+\alpha_1} - \frac{\alpha_2\beta_2}{x+\alpha_2} \tag{A 11}$$

then

$$F'(x) = 1 + \frac{\alpha_1\beta_1}{(x+\alpha_1)^2} + \frac{\alpha_2\beta_2}{(x+\alpha_2)^2} \tag{A 12}$$

Therefore Newton-Raphson method can be implemented as

$$x^{(k+1)} = x^{(k)} - \frac{F\left(x^{(k)}\right)}{F'\left(x^{(k)}\right)}, \quad k = 0,1,2,\ldots \tag{A 13}$$

Once x is obtained f_b^{en} and f_b^{ex} can be calculated by (A 5), and the fractions of unbound IgG in the endosome are thus given by

$$f_u^{en} = 1 - f_b^{en} \quad \textbf{and} \quad f_u^{ex} = 1 - f_b^{ex} \tag{A 14}$$

which, combined with (A 5), lead to (13) in the main text.

This formulation is a generalization of the binding of two partners without consideration of competition as being used widely in different context, such as IgG and FcRn binding in (4), TMDD in (5) and drug protein binding in (6), etc., just name a few of them. This can be seen by letting $K_D^{en} \to \infty$, meaning that the endogenous IgG has no affinity to FcRn and thus the endogenous and exogenous IgG are totally separated. Then $\alpha_1 \to \infty$, $f_b^{en} = 0, \quad f_u^{en} = 1,$ and equation (A 10) collapses to

$$1 = x\left(1 + \frac{\beta_2}{x+\alpha_2}\right) \tag{A 15}$$

which has only one positive root, i.e.,

$$x = \frac{1-\alpha_2-\beta_2+\sqrt{(1-\alpha_2-\beta_2)^2+4\alpha_2}}{2} \quad \textbf{(A 16)}$$

Using (A 5) and (A 14), the fraction of unbound IgG is simplified to

$$f_u^{ex} = \frac{\alpha_2}{x+\alpha_2} \quad \textbf{(A 17)}$$

Substituting (A 16) into (A 17), the well-known formula (A 18) can be eventually derived.

$$f_u^{ex} = \frac{1}{2[G^{ex}]_T}\left([G^{ex}]_T - [R]_T - K_D^{ex} + \sqrt{([R]_T - K_D^{ex} - [G^{ex}]_T)^2 + 4K_D^{ex}[R]_T}\right) \quad \textbf{(A 18)}$$

Appendix B: The steady-state solution of the endogenous IgG

For each subject in a population, a value for the serum concentration $C_{P,SS}^{en}$ can be assigned from the pre-defined distribution with a mean of 12.1 mg/ml and CV 12.6%. The objective here is to find the steady-state concentrations in vascular space $C_{V,SS}^{en}$, endothelial space $C_{TE,SS}^{en}$, interstitial space $C_{I,SS}^{en}$, and lymph node $C_{L,SS}^{en}$ so that the initial conditions in the differential equations for endogenous IgG can be determined. This can be done by solving the algebraic equations obtained by setting the LHS of differential equations 1-5 to zero, i.e.,

$$QC_{P,SS}^{en} + FR\cdot K_{rc}^{en}(1-f_u)C_{TE,SS}^{en}V_E - \left[K_{up}^{en}V_V + (1-\sigma_v)L + (Q-L)\right]C_{V,SS}^{en} = 0 \quad \textbf{(B 1)}$$

$$K_{up}^{en}C_{V,SS}^{en}V_V + \delta K_{up}^{en}C_{I,SS}^{en}V_I - \left[f_u Cl_{cat}^{en} + K_{rc}^{en}(1-f_u)V_E\right]C_{TE,SS}^{en} = 0 \quad \textbf{(B 2)}$$

$$(1-\sigma_v)LC_{V,SS}^{en} + (1-FR)K_{rc}^{en}(1-f_u)C_{TE,SS}^{en}V_E - \left[(1-\sigma_i)L + \delta K_{up}^{en}V_I\right]C_{I,SS}^{en} = 0 \quad \textbf{(B 3)}$$

$$(1-\sigma_i)LC_{I,SS}^{en} - LC_{L,SS}^{en} = 0 \quad \textbf{(B 4)}$$

Here f_u is the fraction of unbound IgG in the endosome (in the absence of exogenous IgG) and is a constant. This is in contrast to f_u^{en} and f_u^{ex}, which are the fractions of unbound endogenous and exogenous IgGs, respectively, used in the minimum PBPK model and change dynamically as the concentration of IgG and mAb vary.

In addition, the synthesis rate K_0 is also defined by

$$K_0 + (Q-L)C_{V,SS}^{en} + LC_{L,SS}^{en} - QC_{P,SS}^{en} = 0 \quad \textbf{(B 5)}$$

By adding equations (B 1-5) together we can derive the relation between the synthesis rate K_0 and the intrinsic catabolic clearance CL_{cat}^{en}

$$K_0 = Cl_{cat}^{en} C_{TE,SS}^{en} \quad \textbf{(B 6)}$$

that is, at the steady state, the amount of IgG being cleared in the endosome is equal to that being produced in the plasma.

From (B 1), we have

$$C_{V,SS}^{en} = a_0 + a_1\left(1 - f_u^{en}\right)C_{TE,SS}^{en} \quad \textbf{(B 7)}$$

$$a = K_{up}^{en}V_V + (1-\sigma_v)L + (Q-L), \quad a_0 = \frac{QC_P^{en}}{a}, \quad a_1 = \frac{FR \cdot K_{rc}^{en}V_E}{a}, \quad \textbf{(B 8)}$$

and substituting (B 7) into (B 2), we can derive

$$C_{I,SS}^{en} = -b_0 + (b_1 + b_2 f_u)C_{TE,SS}^{en} \quad \textbf{(B 9)}$$

$$b_0 = \frac{a_0 V_V}{\delta V_I}, \quad b_1 = \frac{K_{rc}^{en}V_E - a_1 K_{up}^{en}V_V}{\delta K_{up}^{en}V_I}, \quad b_2 = \frac{CL_{cat}^{en} + a_1 K_{up}^{en}V_V - K_{rc}^{en}V_E}{\delta K_{up}^{en}V_I}. \quad \textbf{(B 10)}$$

By substituting (B 7) and (B 9) into (B 3), we finally reach an equation defining the relationship between the total concentration in the endosome $C_{TE,SS}^{en}$ and its unbound fraction f_u,

$$d_0 + (d_1 - d_2 f_u)C_{TE,SS}^{en} = 0 \quad \textbf{(B 11)}$$

$$c_0 = (1-\sigma_i)L + \delta K_{up}^{en}V_I \quad c_1 = a_1(1-\sigma_v)L + (1-FR)K_{rc}^{en}V_E \quad \textbf{(B 12)}$$

$$d_0 = a_0(1-\sigma_v)L + c_0 b_0 \quad d_1 = c_1 - c_0 b_1 \quad d_2 = c_1 + c_0 b_2. \quad \textbf{(B 13)}$$

Because there is no exogenous IgG present, f_u is also governed by the binding of endogenous IgG to FcRn in the endosome. Here we assumed a one-to-one binding between these two species characterized by the equilibrium dissociation constant K_D^{en}, i.e.,

$$IgG + FcRn \xleftrightarrow{K_D^{en}} IgG - FcRn \quad \textbf{(B 14)}$$

By definition

$$K_D^{en} = \frac{[IgG][FcRn]}{[IgG - FcRn]} \quad \textbf{(B 15)}$$

from which we can derive

$$K_D^{en} = \frac{[IgG](1 - f_b)}{f_b}, \qquad f_b = \frac{[IgG - FcRn]}{[FcRn]_T} \tag{B 16}$$

Here, the conservation of receptor species, i.e., $[FcRn]_T = [FcRn] + [IgG - FcRn]$, has been applied. From (B 16), we can express f_b in terms of the total IgG in the endosome $[IgG]_T$, the fraction of unbound IgG in the endosome $f_u = [IgG]/[IgG]_T$, and K_D^{en},

$$f_b = \frac{[IgG]_T \, f_u}{[IgG]_T \, f_u + K_D^{en}} \tag{B 17}$$

Using the conservation relationship

$$[IgG]_T = [IgG] + [IgG - FcRn] \tag{B 18}$$

we finally derive another equation governing the relation between the total IgG in the endosome and its unbound fraction f_u

$$1 = f_u + \frac{[FcRn]_T}{[IgG]_T} \cdot \frac{[IgG]_T \, f_u}{[IgG]_T \, f_u + K_D^{en}} \tag{B 19}$$

Let $x_1 = C_{TE,SS}^{en} = [IgG]_T$ and $x_2 = f_u C_{TE,SS}^{en}$, then the equations (B 11) and (B 19) form the following set of nonlinear equations

$$\begin{aligned} F_1(x_1, x_2) &= x_1 - x_2 - R_T + \frac{R_T K_D^{en}}{x_2 + K_D^{en}} = 0 \\ F_2(x_1, x_2) &= d_0 + d_1 x_1 - d_2 x_2 = 0 \end{aligned} \tag{B 20}$$

where $R_T = [FcRn]_T$. Using the standard notation for nonlinear equations

$$Y = (x_1, x_2)^T, \quad F = (F_1, F_2)^T \tag{B 21}$$

(B 20) becomes

$$F(Y) = 0 \tag{B 22}$$

whose Jacobian matrix and the inverse of the Jacobian matrix are given by

$$\frac{\partial F}{\partial Y} = \begin{pmatrix} 1 & -1-\Delta \\ d_1 & -d_2 \end{pmatrix}, \; \Delta = \frac{R_T K_D^{en}}{\left(x_2 + K_D^{en}\right)^2}, \; \left(\frac{\partial F}{\partial Y}\right)^{-1} = \left[-d_2 + d_1(1+\Delta)\right] \begin{pmatrix} -d_2 & 1+\Delta \\ -d_1 & 1 \end{pmatrix} \tag{B 23}$$

Therefore, using the Newton-Raphson method

$$Y^{(i+1)} = Y^{(i)} - \left(\frac{\partial F}{\partial Y}\right)^{-1}_{Y=Y^{(i)}} F\left(Y^{(i)}\right), \quad i = 0,1,2,\cdots \tag{B 24}$$

with the initial value

$$Y^{(0)} = \left(C^{en}_{P,SS}, 0\right)^T \tag{B 25}$$

This initial condition provides a robust guess for the iteration and over the range of $C^{en}_{P,SS}$ values we are interested all the iterations performed achieved the convergences.

After $x_1 = C^{en}_{TE,SS}$ and $x_2 = f_u C^{en}_{TE,SS}$ are obtained by Newton-Raphson method, we can calculate $f_u\left(= x_2 / C^{en}_{TE,SS}\right)$ and thus using (B 7), (B 9), and (B 4), we can find $C^{en}_{V,SS}$, $C^{en}_{I,SS}$, and $C^{en}_{L,SS}$.

For a given set of parameters we may also calculate the fold reduction of plasma concentration level when FcRn is knocked out. Specifically, setting $f_u = 1$ in equations (B 1), (B 2), and (B 3), we can deduce the steady-state equations when FcRn is absent, i.e.

$$QC^{en}_P - \left[K^{en}_{up} V_V + (1-\sigma_v) L + (Q-L)\right] C^{en}_{V,SS} = 0 \tag{B 26}$$

$$K^{en}_{up} C^{en}_{V,SS} V_V + \delta K^{en}_{up} C^{en}_{I,SS} V_I - Cl^{en}_{cat} C^{en}_{TE,SS} = 0 \tag{B 27}$$

$$(1-\sigma_v) L C^{en}_{V,SS} - \left[(1-\sigma_i) L + \delta K^{en}_{up} V_I\right] C^{en}_{I,SS} = 0 \tag{B 28}$$

From (B 28), we have

$$C^{en}_{I,SS} = \frac{(1-\sigma_v) L C^{en}_{V,SS}}{(1-\sigma_i) L + \delta K^{en}_{up} V_I} \tag{B 29}$$

Substituting (B 29) into (B 27), we can derive

$$\left(K^{en}_{up} V_V + \delta K^{en}_{up} V_I \frac{(1-\sigma_v) L}{(1-\sigma_i) L + \delta K^{en}_{up} V_I}\right) C^{en}_{V,SS} = Cl^{en}_{cat} C^{en}_{TE,SS} \tag{B 30}$$

Here we can employ equation (B 6), i.e., $K_0 = Cl^{en}_{cat} C^{en}_{TE,SS}$, implying the assumption we made here that the synthesis rate of endogenous IgG is same for both healthy and deficient subject

in FcRn expression. Therefore, combining (B 30) and (B 26), gives a formula to calculate the steady-state endogenous IgG level when FcRn is absent,

$$C_{P,0}^{en}=\frac{K_0\left[K_{up}^{en}V_V+\left(1-\sigma_v\right)L+\left(Q-L\right)\right]}{QK_{up}^{en}\left(V_V+\frac{\delta V_I\left(1-\sigma_v\right)L}{\left(1-\sigma_i\right)L+\delta K_{up}^{en}V_I}\right)} \quad \textbf{(B 31)}$$

Therefore, for any given plasma IgG level C_P^{en} after solving for steady-state solution and thus K_0 is available, the fold reduction compared with a subject with FcRn knock-out can be calculated as

$$F_{RD}=\frac{C_P^{en}}{C_{P,0}^{en}} \quad \textbf{(B 32)}$$

When $K_D^{en}\to\infty$, from (B 19), we have $f_u\to 1$, thus C_P^{en} tends to $C_{P,0}^{en}$ and F_{RD} tends to 1. This is another way to study FcRn knock-out effect in the simulation, in addition to letting $[FcRn]_T\to 0$ in the algorithm.

Reference

1. Ghetie V, Ward ES. Multiple roles for the major histocompatibility complex class I-related receptor FcRn. Annu Rev Immunol. 2000;18:739-66.
2. Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. Nat Rev Immunol. 2007 Sep;7(9):715-25.
3. Wang ZX. An exact mathematical expression for describing competitive binding of two different ligands to a protein molecule. FEBS Lett. 1995 Feb 27;360(2):111-4.
4. Garg A, Balthasar JP. Physiologically-based pharmacokinetic (PBPK) model to predict IgG tissue kinetics in wild-type and FcRn-knockout mice. J Pharmacokinet Pharmacodyn. 2007 Oct;34(5):687-709.
5. Mager DE, Krzyzanski W. Quasi-equilibrium pharmacokinetic model for drugs exhibiting target-mediated drug disposition. Pharm Res. 2005 Oct;22(10):1589-96.
6. Berezhkovskiy LM. Some features of the kinetics and equilibrium of drug binding to plasma proteins. Expert Opin Drug Metab Toxicol. 2008 Dec;4(12):1479-98.