Calibration of an IgG turnover model using data from administration of monoclonal antibodies targeting FcRn receptor

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BACKGROUND

FcRn recycling plays an important role in non-specific clearance of endogenous and therapeutic antibodies [1]. The following compartmental model of IgG turnover was proposed to describe the process [2-5]:

$$dA_1/dt = I_0 - (k_{10} - V_{max}/(K_M+A_1/V_1))\cdot A_1 - k_{12}\cdot A_1 + k_{21}\cdot A_2; \quad A_1(0) = IgG_0\cdot V_1;$$
$$dA_2/dt = k_{12}\cdot A_1 - k_{21}\cdot A_2; \quad A_2(0) = IgG_0\cdot V_2; \quad (1)$$
$$I_0 = (k_{10}-V_{max}/(K_M+IgG_0))\cdot IgG_0\cdot V_1,$$

where A_1 and A_2 are the IgG amounts in the central and peripheral compartments, I_0 is zero-order IgG production rate, $k_{12}=Q/V_1$, $k_{21}=Q/V_1$ are the inter-compartment rate constants; Q, V_1, and V_2 are inter-compartment clearance, central volume, and peripheral volume, respectively; $k_{10}=CL/V_1$ and CL are IgG non-specific elimination rate and clearance in absence of FcRn recycling, and V_{max} and K_M are the Michaelis-Menten parameters. The Michaelis-Menten term in the model represents FcRn-mediated IgG recycling from the intra-cellular space to the central compartment. Several different sets of model parameters were suggested depending on data and techniques used for model calibration [5]. Recent studies of therapeutic monoclonal antibodies (mAb) targeting the FcRn receptor provide the longitudinal data of IgG suppression resulting from blocking FcRn recycling [6, 7] and thus allow to re-evaluate and update the model.

PURPOSE

We aim to use these data to evaluate the IgG turnover model, to modify the model, and to obtain the parameter estimates consistent with the observed data.

METHODS

Pharmacodynamic data of an anti-FcRn mAb illustrated in Figure 1-2 were obtained by digitizing from [7]. The mAb binds with high affinity to the FcRn receptor and prevents endogenous IgG from binding FcRn, thus increasing IgG clearance and decreasing its concentrations. The data of FcRn receptor occupancy by mAb and IgG concentrations following administration of various single and multiple doses of this mAb [7] were used to evaluate IgG turnover model predictions for all previously identified sets of parameters. Assuming that FcRn recycling is proportional to the fraction of FcRn receptors not bound by mAb, the time course of IgG suppression was predicted and compared with the observed data. Based on the evaluation results and mechanistic considerations, the model was modified. A new set of parameters was obtained, by estimating some of the parameters and fixing others at typical values for mAbs.

RESULTS

Simulations from the model with previously suggested sets of parameters did not fit the observed IgG profiles. Attempts to estimate the parameters showed that the model was over-parameterized and Q was estimated to be 0, thus collapsing the model to a one-compartment model. A one-compartment model for IgG contradicts the notion that IgG is distributed throughout the body. Thus, the model was modified to include IgG synthesis, elimination, and FcRn recycling in the peripheral compartment:

$$dA_1/dt = I_{01} - (k_{10} - F_{free}\cdot V_{max}/(K_M+A_1/V_1))\cdot A_1 - k_{12}\cdot A_1 + k_{21}\cdot A_2; \; A_1(0) = IgG_0\cdot V_1;$$
$$dA_2/dt = I_{02} - (k_{10} - F_{free}\cdot V_{max}/(K_M+A_2/V_2))\cdot A_2 + k_{12}\cdot A_1 - k_{21}\cdot A_2; \; A_2(0) = IgG_0\cdot V_2; \quad (2)$$
$$I_{01} = (k_{10} - V_{max}/(K_M + IgG_0))\cdot IgG_0\cdot V_1; \quad I_{02} = (k_{10} - V_{max}/(K_M + IgG_0))\cdot IgG_0\cdot V_2.$$

For simplicity, equal IgG concentrations in central and peripheral compartments were assumed. Here F_{free} is the fraction of receptors unoccupied by the FcRn-targeting mAb. The model (2) fit the data but was still over-parameterized. Fixing V_1, V_2, and Q to the typical values for IgG ($V_1=V_2=3$ L, Q=0.38 L/day) provided the same fit as when these parameters were estimated. The ratio $R=V_{max}/K_M$ and IgG clearance from each compartment in absence of FcRn binding were estimated as R=0.176 1/day and CL=0.575 L/day with high precision (RSE<7%), while K_M constant was estimated as K_M=1220 µmol/L with high uncertainty (RSE=65%). The estimated value of R is consistent with the values obtained in [3-5], while the K_M value is higher than was obtained in [3-5] and higher than the expected value of dissociation constant of IgG-FcRn binding [8]. At typical IgG concentration of IgG_0=80 µmol/L, non-specific IgG clearance that accounts for recycling can be computed as

$$CL_{NS}=2\cdot(CL-R\cdot V_1/(1+ IgG_0/K_M)=0.160 \text{ L/day}.$$

The value is consistent with the expected clearance of endogenous IgGs. Fit of the model, illustrated in Figure 2, shows that model predictions closely follow the observed data except for some deviation at the lowest dose (lowest receptor suppression). Coefficient of variation of the proportional residual error was 12.3%.

Figure 1: Digitized data of [7]

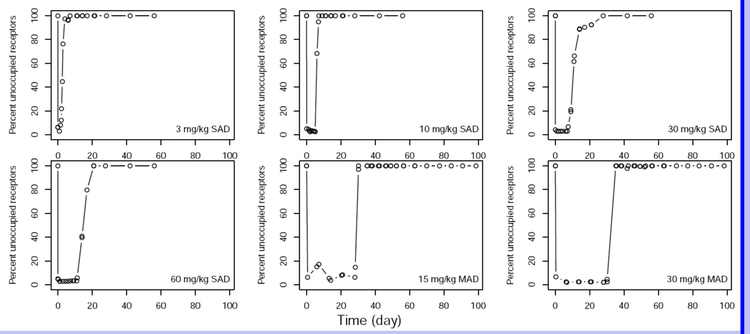
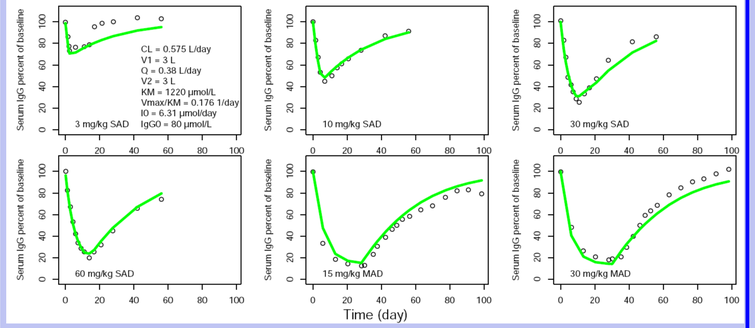


Figure 2: Digitized Data of [7] and Fit of Final Model



DISCUSSION / CONCLUSIONS

The presented work illustrates how data observed following administration of therapeutic antibodies targeting the FcRn receptor can be used to calibrate the IgG turnover model. Further development of the model could be performed by inclusion of additional experimental data, e.g., following treatments with IVIG.

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