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DEVELOPMENT OF A MINIMAL-PBPK MODEL FOR SIMULATING MONOCLONAL ANTIBODY PHARMACOKINETICS IN HUMAN

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ABSTRACT

Purpose

Development of monoclonal antibodies (mAb) represents a growing segment of the pharmaceutical industry. Physiologically based pharmacokinetic(PBPK) modelling has been applied extensively to describe the PK/PD properties of mAbs. A number of different approaches to the PBPK modelling have been applied and important differences exist between the models used. The purpose of this work was to develop a simplified PBPK model to predict the disposition of mAbs in human. The model accounts for endogenous IgG levels, FcRn recycling (Garg and Balthasar, 2007) and uses physiologically relevant values for lymph flow in humans.

Methods

The structure of the model is illustrated in Figure 1. Physiological parameters were obtained from literature. The predicted PK parameters of mAbs (adalimumab, daclizumab) and an Fc-fusion protein (etanercept) that exhibit linear elimination behaviour were compared with previously published clinical data. Modelling and simulations were performed in Matlab version 7.11.0 (R2010b).

Results

The doses used and predicted half-life and clearance of adalimumab, daclizumab and etanercept are shown in Table 1 together with reported clinical values for these parameters.

Conclusion

The predicted data show that the simplified PBPK model accurately described the disposition of adalimumab, daclizumab and etanercept in humans.

References

Dirks NL, Meibohm B. Clin Pharmacokinet, 2010, 49(10): 633-659

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Pescovitz MD et al. Clin Transplant, 2003, 17: 511-517

Zhou H. Clin Pharmacol, 2004, 45(5): 490-497

Figure 1 PBPK Model Structure

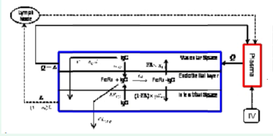


Table 1 Predicted and Observed CL and Half-life

Parameter		adalimumab					daclizumab	etanercept
Dose (mg/kg)		0.3	1.0	3.0	10.0	1.0	2[a]	
Half-life (day)	predicted	17.3	17.3	17.3	17.3	17.3	20.0	6.3
	observed	20 (11-50)[c]	20 (11-50)[c]	20 (11-50)[c]	20 (11-50)[c]	18.3[d]	14.3[e]	4.5[e],[f]
Clearance (L/ day)	predicted	0.27	0.27	0.27	0.27	0.27	0.24	0.73
	observed	0.20[c]	0.20[c]	0.20[c]	0.20[c]	0.284 (0.14)[d]	0.336 (0.14)[e]	1.70[f]

[a] mg; [b]Dirks and Meibohm, 2010; [c]Pescovitz et al, 2003; [d]Zhou 2004;

OBJECTIVE

Develop a physiologically-based pharmacokinetic (PBPK) model for simulating pharmacokinetics (PKs) of therapeutic mAbs in humans with the following features:

- simultaneous modelling of endogenous IgG and mAbs
- incorporation of physiologically realistic system parameters
- a model to account for the effect of FcRn recycling on IgG kinetics
- incorporate a model to allow the effect of target mediated disposition to be accounted for in either interstitial space or plasma
- initial efforts focussed on a minimal PBPK model to allow rapid simulation speeds to be achieved

METHODS

- The model has a minimal physiological structure with all the organs lumped into one tissue compartment, which is further divided into three sub-compartments consistent with previously published PBPK model structure for mAbs [1].
- The competitive binding of endogenous IgG and administered mAb to FcRn is modelled allowing for different binding affinities for the two species.
- Catabolic clearances of endogenous and exogenous species can be modelled independently.
- Models describing target-mediated disposition are coupled with the minimal PBPK model in either the plasma or the interstitial compartment.
- The majority of model parameters were taken from literature; recycling rate and catabolic rate were set by calibration to obtain the known synthesis rate and half-life of endogenous IgG [8] .

MINIMAL-PBPK MODEL

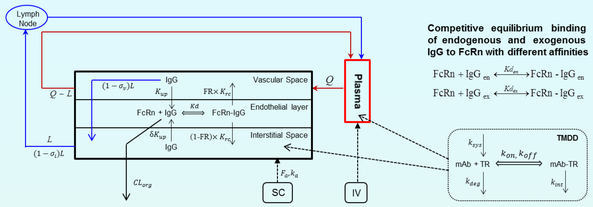


Figure 1. The minimal PBPK model structure and coupling with TMDD models.

Table 1. Model parameters.

Parameters	Values
Lymph flow rate	120 mL. h^{-1}
FcRn abundance	40 μM
K_D for endogenous IgG	728 nM
δ	1

Parameters	Values
K_{up}	0.715 day^{-1}
K_{rc}	14.08 day^{-1}
FR	0.715
Cl_{org}	0.420 L. day^{-1}

K_D, dissociation constant; K_{up}, the rate of uptake into endothelial space; δ, adjustment factor for K_{up} from interstitial space; K_{rc}, recycling rate from endothelial space; FR, recycling fraction of FcRn bound mAb; Cl_{org}, endothelial clearance.

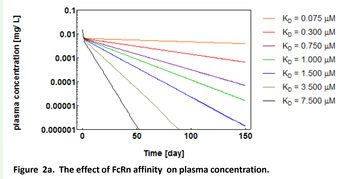


Figure 2a. The effect of FcRn affinity on plasma concentration.

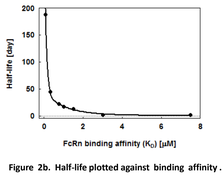


Figure 2b. Half-life plotted against binding affinity .

The minimal PBPK model is very sensitive to the IgG-FcRn K_D used (Figures 2a and 2b). The reported values for wild type IgG Fc-FcRn binding vary widely in the literature (Table 2). To cope with this variability we adopted a strategy where the K_D for IgG-FcRn binding for a given mAb was calibrated against the binding of WT IgG to FcRn measured under the same experimental conditions.

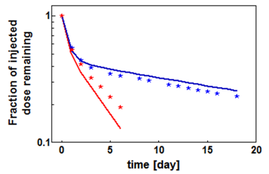
Table 2. K_D values of binding between WT IgG Fc-domain-containing therapeutic proteins and human FcRn.

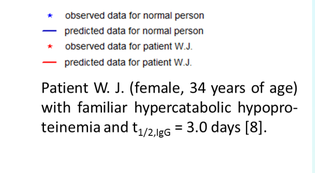
FcRn	IgG	K_D (nM) @ pH 6.0	IgG subtype on chip	Reference
hFcRn	hIgG1	K_{D1} = 370; K_{D2} = 2100	IgG on chip	[2]
hFcRn	hIgG1	K_D = 31	FcRn on chip	[3]
hFcRn	hIgG1	K_{D1} = 10; K_{D2} = 1923	FcRn on chip	[4]
hFcRn	hIgG1	K_{D1} = 12; K_{D2} = 530	FcRn on chip	[5]
hFcRn	hIgG1	K_{D1} = 1670; K_{D2} = 1370	FcRn on chip	[6]
hFcRn	wt IgG	K_D = 728	FcRn on chip	[7]

hFcRn, human FcRn; hIgG, human IgG; K_D, dissociation constant.

RESULTS

The fractions of the injected IgG remaining In the serum.





Patient W. J. (female, 34 years of age) with familiar hypercatabolic hypoproteinemia and $t_{1/2,IgG}$ = 3.0 days [8].

Figure 3. The minimal PBPK with TMDD [8].

adalimumab (Humira (R))

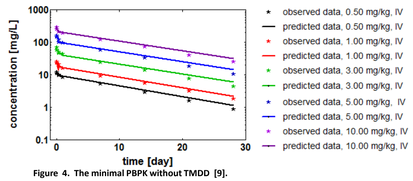


Figure 4. The minimal PBPK without TMDD [9].

bevacizumab (Avastin (R))

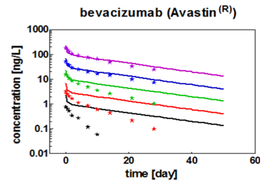


Figure 5a. The minimal PBPK without TMDD [10].

bevacizumab (Avastin (R))

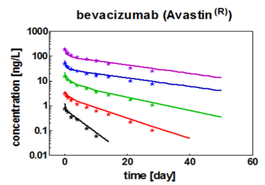


Figure 5b. The minimal PBPK with TMDD [10].

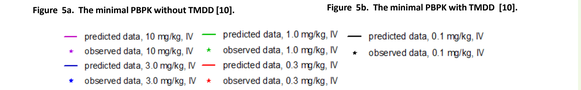


Table 3. The minimal PBPK model predictions of half-lives and clearances of mAbs and fusion protein etanercept.

Compound	K_D (nM)	Half-life (days)		Clearance (L/day)	
	observed	Observed	Predicted	Observed	Predicted
Adalimumab	872 [7]	10 – 20 [11]	**17**	0.21 [11]	**0.27**
Bevacizumab	994 [7]	20 [12]	**17**	0.21 [12]	**0.23**
Daclizumab	846 [7]	17 [13]	**18**	0.38 (SD: 0.14) [13]	**0.24**
Etanercept	3612 [7]	4.5 [14]	**6.3**	1.70 [14]	**0.73**

DISCUSSION

Current model: In the described PBPK model all of the critical features needed to describe IgG disposition were incorporated namely 1) IgG enters the tissue vascular sub-compartment driven by blood flow 2) IgG distributes to the interstitial sub-compartment and lymphatic system by convective transport 3) IgG distributes to the endothelial space via fluid phase endocytosis 4) it is assumed that the intact IgG in the endothelial sub-compartment binds to FcRn and bound IgG recycles to either the vascular or interstitial sub-compartments by exocytosis. 5) unbound IgG within the endothelial sub-compartment is cleared. Using a single value of Cl_{org} we could accurately describe the human PKs of 2 mAbs and a fusion protein using published K_D values for the binding of the compounds to FcRn at pH 6.0. Using the same value of Cl_{org}, a published K_D value and a model for TMDD we could also describe the non-linear PKs of bevacuzimab at several doses.

Some studies have suggested that improvement in PKs can be achieved by increasing the affinity of the interaction between the Fc region of IgG and FcRn (16). However, other studies have not shown PK improvement with increased FcRn affinity (7,20) and no improvement on PKs was seen in the only reported study in humans (21). Whilst the current model suggests a direct relationship between binding of IgG to FCRN at pH 6 and the half-life of the mAb in human, and accurately describes the PKs of the compounds investigated, we feel that a more complex model for IgG-FcRn binding will be needed for the model to be broadly applicable. These include incorporation of a 2:1 FcRn-IgG stoichiometry [5] and consideration of the influence of binding of IgG FC to FcRn at pH 7.4 [18-20]

CONCLUSION

The FcRn dependent minimal PBPK model described, using a single value for Cl_{org}, can accurately describe

- **the plasma levels and behaviour of endogenous IgG**
- **the PKs of 3 mAbs and a fusion protein in humans**

REFERENCES

[1] Garg A, Balthasar JP. J Phamacokinet Pharmacodyn, 2007 Oct; 34(5): 687-709. **[2]** Zhou et al, J Mol Biol, 2005, 345(5): 1071-81. **[3]** Mezo et al, Bioorg Med Chem, 2008, 16(12): 6394-405. **[4]** Bitionti et al, 2004, PNAS, 2004, 101(26): 9763-8. **[5]** West and Bjorkman, Biochemistry, 2000, 39(32): 9698-708. **[6]** Magistrelli et al, 2012, J Immunol Methods, 375(1-2): 20-9. **[7]** Suzuki et al, 2010, J Immunol, 184(4): 1968-76. **[8]** Waldmann and Terry, J Clin Invest, 1990, 86(6):2093-8. **[9]** De Boeder et al, J Rheumatol, 2002, 29(11): 2288-98. **[10]** Gordon et al, J Clin Oncol, 2001, 19(3):843-50. **[11]** Velagapurdi *et al*, Clin Pharmacol Ther, 2005, 77, P84. **[12]** Lu *et al*, Cancer Chemother 2008, 62(5): 779-861. **[13]** Pescovitz *et al*, Clin Transplant, 2003, 17(6): 511-7. **[14]** Zhou et al, J Clin Pharmacol, 2001, 864-75. **[15]** Hayashi et al, Br J Clin Pharmacol, 2007, 63(5): 548-61. **[16]** Datta-Mannan et al, J. Bio Chem,2007. 282(3): 1709-1717; **[17]** Yeung et al, J Immunol, 2009. 182:7663-7671. **[18]** Hinton et al, J Biol Chem, 2004, 279(8):6213-6; **[19]** Hinton et al, J Immunol. 2006, 176(1):346-56. **[20]** Wang et al., DMD, 39, 1469, 2011; **[21]** Zheng et al., 2011 Clin. Pharm. Ther., 89, 2, 283-290.

***Corrections in the abstract*: because of a mistake in the original abstract bevacizumab has been replaced by adalimumab**

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