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Application of PBPK Modeling to Predict Monoclonal Antibody Disposition after Intravenous and Subcutaneous Administration in Rats and Humans

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PURPOSE

Therapeutic monoclonal antibodies (mAbs) represent a growing segment of the development pipeline in the pharmaceutical industry. Physiologically based pharmacokinetic (PBPK) modeling has been extensively applied in small molecule drug development and has a great potential of helping in the development of mAbs and functional derivatives. In this study, a comprehensive PBPK model for mAbs was developed to simulate plasma as well as individual tissue concentrations after intravenous (IV) or subcutaneous (SC) administration in preclinical animals and humans.

METHODS

The whole-body PBPK model previously developed in GastroPlus™ (Simulations Plus, Inc.) was expanded to include mechanisms related to the absorption and disposition of mAbs. Each organ in the PBPK model is divided into three major compartments representing the vascular, endosomal, and interstitial spaces, as shown in Figure 1.

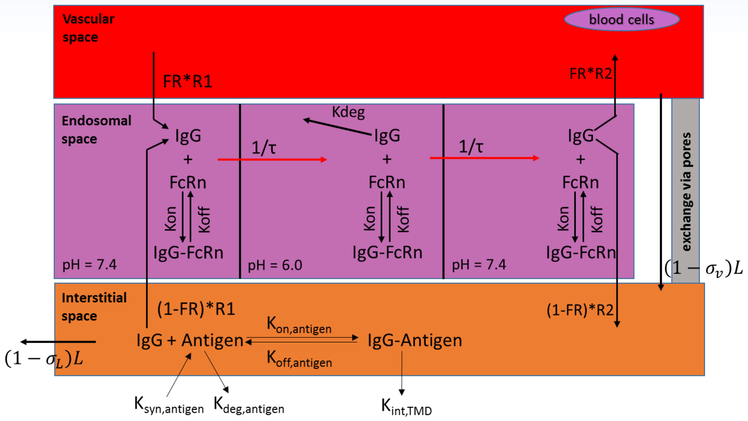


Figure 1: Schematic representation of individual tissue compartments

The following mechanisms are included in the PBPK model:

- Transport of mAb into the tissue interstitial space via convective flow through the paracellular pores in the vascular endothelium
- Uptake of mAb from the vascular and interstitial spaces into the endosomal space via fluid-phase endocytosis
- pH-dependent binding of mAb to FcRn in the endosomal space
- FcRn binding competition between therapeutic mAb and endogenous IgG
- Recycling of mAb to the vascular and interstitial spaces
- Endosomal degradation of the unbound mAb
- Return of mAb from the tissue to the bloodstream through convective transport with lymph flow
- Specific mAb binding to antigen (TMDD)

After SC injection, the mAb was initially distributed in the interstitial space of the local subcutaneous tissue. The local tissue was also divided into three compartments as shown in Figure 1. The same endosomal nonspecific clearance processes were applied to both the systemic clearance and local first-pass clearance after SC administration.

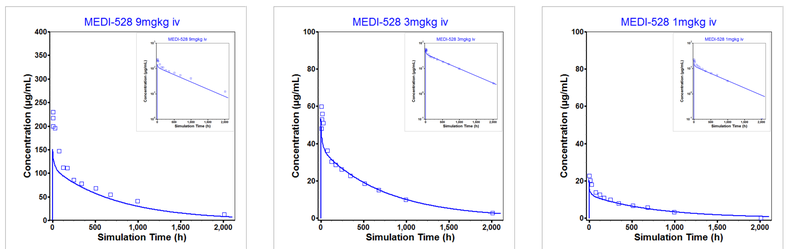
Convective transport through the lymphatic endothelium and fluid-phase endocytosis are the main mechanisms of absorption into the systemic circulation following SC administration of mAb.

The vascular (σ_V) and lymph (σ_L) reflection coefficients, and the fraction of mAb recycled (FR) were obtained from literature (Garg & Balthasar, J Pharmacokinet Pharmacodyn, 34 (2007), 687-709). Other model parameters (pH-dependent mAb-FcRn binding constants, mAb degradation in endosomal space, endosomal uptake, and recycle rates) were fitted using datasets from studies of 14 different antibodies and the reported synthesis rate of endogenous IgG (Junghans, Blood, 90 (1997), 3815-3818; Cure & Cremer, J Immunol, 102 (1969), 1345-1353) for different species. The fitted mAb-FcRn binding constants were within the range of reported *in vitro* values (Datta-Mannan et al., J Biol Chem, 282 (2007), 1709-1717; Andersen et al., J Biol Chem, 285 (2010) 4826-4836).

RESULTS

The PBPK model for mAbs was used to simulate plasma concentration-time profiles of MEDI-528 in human and Rituximab in rats across different dose levels after IV and SC administration. The simulated profiles were in close agreement with published clinical results (White et al., Clin Ther, 31 (2009), 728-740; Kagan et al., Pharm Res, 29 (2012), 490-499).

(a)



(b)

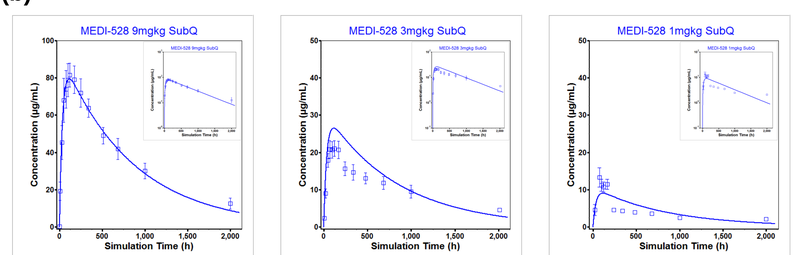
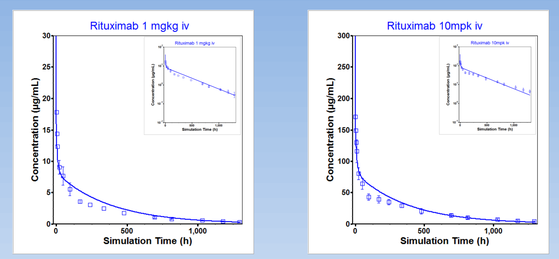


Figure 2: Comparison of simulated (lines) and measured (points) MEDI-528 for 9, 3, and 1 mg/kg doses in healthy subjects after IV **(a)** and SC **(b)** doses.

Default model parameters for human were used for MEDI-528 simulations.

(a)



(b)

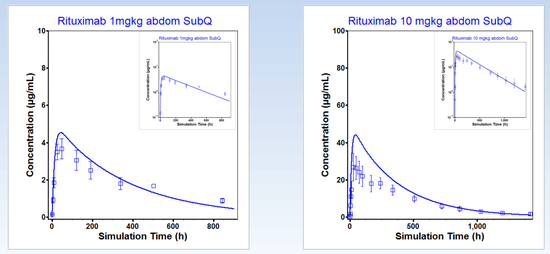
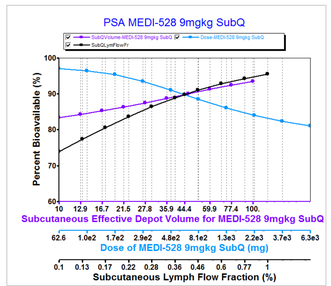


Figure 3: Comparison of simulated (lines) and measured (points) Rituximab for 1 and 10 mg/kg doses in Wistar rats after IV **(a)** and SC **(b)** doses

The association coefficient between Rituximab and rat FcRn was estimated using the data from the 1 mg/kg IV dose. For the simulation of Rituximab in rats after SC administration, an additional linear clearance was included in the local first-pass clearance in addition to the endosomal nonspecific clearance processes and was estimated using the data from the 1 mg/kg SC dose. Other parameters used the default GastroPlus values for rat.



SC bioavailability is sensitive to dose, subcutaneous lymph flow, and effective depot volume:

- Bioavailability decreases as dose increases
- Bioavailability increases as the lymph flow or effective depot volume increases

Figure 4: Parameter sensitivity of bioavailability

CONCLUSIONS

- PBPK modeling of mAbs in GastroPlus accurately simulates PK profiles after IV and SC administration.
- This model can help to investigate the factors responsible for the systemic disposition of mAbs in preclinical animals and human.
- This model could also be applied to assess dose-dependent nonlinear clearance related to TMDD

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