Minimal Physiological Model of Trastuzumab and Rituximab Subcutaneous Absorption Across Species

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Objectives: To investigate the relative contribution of kinetic processes at the subcutaneous (SC) site on the overall absorption kinetics of trastuzumab, develop a general pharmacokinetic model for simultaneously describing SC absorption of trastuzumab across species, and to examine the capabilities of predicting human SC PK from preclinical data.

Methods: Trastuzumab serum concentrations were measured following intravenous (1, 10, and 40 mg/kg) and subcutaneous (1 and 40 mg/kg) injection at the back and abdomen of rats. The effect of co-administration with human nonspecific IgG was also examined. A minimal physiologically-based pharmacokinetic (mPBPK) model was constructed in ADAPT5 (BMSR, USC, LA) and used to characterize the absorption and disposition of trastuzumab in rats. The model was then scaled across species (rat, minipig, and man) using allometric methods to predict the concentration-time course in man. Rituximab and belimumab PK in humans were used as external validation of the mPBPK model.

Results: Trastuzumab bioavailability in rats was inversely related to dose level (with greater bioavailability at low doses) and varied among injection sites. Decreases in the area under the concentration-time curve were obtained after co-administration with IgG in rats, showing greater reductions following back injection (2.4-fold decrease). The final mPBPK model characterized trastuzumab pharmacokinetics across all species and includes allometric relationships for linear non-specific clearance and the apparent capacity of carrier-mediated uptake. Human rituximab and belimumab pharmacokinetic profiles following SC injection were predicted well after scaling the final model.

Conclusions: A pharmacokinetic model was successfully developed that describes the absorption and disposition of several subcutaneously dosed monoclonal antibodies. The model and approach may prove useful in predicting the concentration time-course of monoclonal antibodies in humans from preclinical species.