Tacrolimus PBPK modeling using realistic physiological factors in renal transplant patients

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BACKGROUND: Large variability in tacrolimus pharmacokinetics (PK) has been contributed to multiple physiological factors. We developed a PBPK model using patient population-specific physiological factors to systematically characterize the mechanisms behind the large PK variability observed in renal transplant patients.

METHODS: A base tacrolimus PBPK model was developed for healthy Caucasians with the Simcyp platform (ver. 16) using physicochemical parameters, *in vitro* kinetic data for CYP3A4 and 3A5, and realistic *in vivo* renal clearance values reported in the literature. After model validation, realistic distributions of body-weight, hematocrit, serum albumin and creatinine levels, as observed in renal transplant patients participating in a large intensively sampled PK study (NCT01889758), were implemented into the model. Simulated PK profiles were compared with full-PK data observed in the clinical study. Sensitivity analysis was also conducted to evaluate the influence of CYP3A4 abundance, hematocrit, serum albumin and creatinine levels.

RESULTS: The PBPK model generated results in CYP3A5-genotyped patients which were comparable to their observed clinical PK profiles. The ratios of predicted to observed dose-normalized C_{max}, $AUC_{0\text{-}12hr}$, and C_{trough}, ranged from 0.89- to 1.14-fold in CYP3A5 expressers and non-expressers. Sensitivity analysis demonstrated that predictions of PK were sensitive to changes in CYP3A4 abundance, hematocrit and serum albumin levels, while the impact of serum creatinine level was negligible.

CONCLUSION: The inclusion of realistic data of the target population improved the predictive performance of the PBPK model. This study highlights the importance of demographics and pathophysiology data specific to the targeted patient population.