Adaptation of a population pharmacokinetic model to inform tacrolimus therapy in heart transplant recipients

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ABSTRACT

Introduction: Existing tacrolimus population pharmacokinetic models are unsuitable for guiding tacrolimus dosing in heart transplant recipients. This study aimed to develop and evaluate a population pharmacokinetic model for tacrolimus in heart transplant recipients that considers the tacrolimus-azole antifungal interaction. **Methods:** Data from heart transplant recipients (n=87) administered the oral immediate-release formulation of tacrolimus (Prograf®) were collected. Routine drug monitoring data, principally trough concentrations, were used for model building (n=1099). A published tacrolimus model was used to inform the estimation of Ka, V2/F, Q/F, and V3/F. The effect of concomitant azole antifungal use on tacrolimus CL/F was quantified. Fat-free mass was implemented as a covariate on CL/F, V2/F, V3/F and Q/F on an allometry scale. Subsequently, stepwise covariate modelling was performed. Significant covariates influencing tacrolimus CL/F were included in the final model. Robustness of the final model was confirmed using prediction-corrected visual predictive check (pcVPC). The final model was externally evaluated for prediction of tacrolimus concentrations of the fourth dosing occasion (n=87) from 1–3 prior dosing occasions. **Results:** Concomitant azole antifungal therapy reduced tacrolimus CL/F by 80%. Haematocrit (ΔOFV = -44, $p<0.001$) was included in the final model. The pcVPC of the final model displayed good model adequacy. One recent drug concentration is sufficient for the model to guide tacrolimus dosing. **Conclusion:** A population pharmacokinetic model that adequately describes tacrolimus pharmacokinetics in heart transplant recipients, considering the tacrolimus-azole antifungal interaction was developed. Prospective evaluation is required to assess its clinical utility to improve patient outcomes.