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Predictive Performance of Existing Population Pharmacokinetic Models of Tacrolimus in Pediatric Kidney Transplant Recipients

Alenka Chapron
Children's Mercy Hospital, Kansas City, MO

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Submitting/Presenting Author (must be a trainee): Alenka Chapron
Primary Email Address: achapron@cmh.edu

☐ **Resident/Psychology Intern**
☐ **Fellow**

Primary Mentor (one name only): Susan Abdel-Rahman
Other authors/contributors involved in project: /

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Describe role of Submitting/Presenting Trainee in this project (limit 150 words):
Trainee was responsible for review of the literature, extraction of relevant data from publications, analysis and interpretation of the results.

Background
Tacrolimus (TAC) has been a mainstay of immunosuppressive therapy following pediatric renal transplantation. TAC has a narrow therapeutic index, thus, frequent therapeutic drug monitoring is employed to maximize efficacy and avoid toxicity. Dose adjustments based on measured TAC trough levels are challenging, since the drug displays complex pharmacokinetic behavior that is affected by a multitude of genetic, physiologic and environmental factors.

Objectives/Goal
With the goal of developing a clinician-driven TAC pharmacokinetic dosing tool, our initial objectives were 1) to examine whether published TAC population pharmacokinetic (popPK) models could serve as a foundation to the dosing tool, and 2) evaluate their performance predicting TAC concentrations in an independent cohort of 58 kidney transplant recipients (age 1-20 years) at Children's Mercy (CM).

Methods/Design
We searched the Pubmed database for TAC popPK modelling reports in pediatric renal transplantation. From the publications, we extracted estimated model parameters (i.e., thetas) and covariates that were identified to significantly affect TAC levels. Population clearances, volumes of distribution and absorption rate constants were then modelled for the CM cohort. For each observed post-transplant drug level, population predicted trough concentration was estimated. The predictive performance of each model was evaluated visually by plotting predicted vs. measured TAC trough levels for the entire CM cohort, and numerically via bias (estimated as mean residual error, MRE) and imprecision (estimated as root mean squared error, RMSE). Models were finally assessed according to their strength of predictive performance, with the best model having MRE closest to a value of 0 and lowest RMSE estimate. Summary statistics and analyses were performed in Excel and R.

Results

Six pediatric popPK models were identified. All models reported TAC pharmacokinetics best described by a 2-compartment structural model with first-order absorption preceded by a lag time, and elimination from the central compartment. The following covariates were shown to significantly affect TAC trough levels: CYP3A5 genotype, total body weight, hematocrit, donor status (living vs. deceased), eGFR and gamma-glutamyl transferase levels. Four models consistently underpredicted measured TAC levels, and two consistently overpredicted measured TAC levels (MRE range: -27.3% to 65.2%). A high degree of variability between predicted and measured TAC levels was noted for all models (RMSE range: 48.2% to 120%). The model with the best predictive performance had the following estimates: MRE: -9.8%, RMSE: 54%.

Conclusions

Four popPK models predicted TAC trough levels sufficiently well on average, however none of the evaluated models predicted individual TAC levels with high precision. This suggests that variability in measured TAC levels cannot entirely be explained by the covariates nested in established models. Development of a reliable and accurate dosing tool will require significant refinement of existing models or the creation of a de novo model.