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

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Introduction

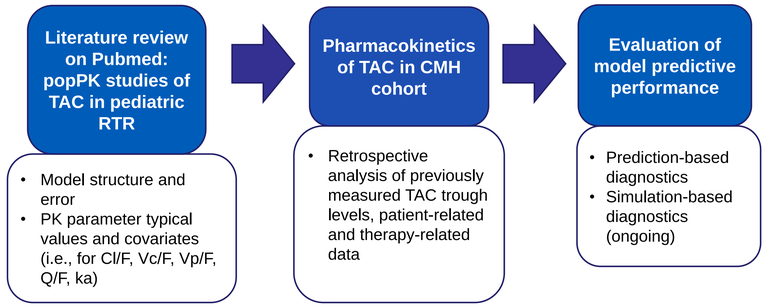
Tacrolimus (TAC) has been a mainstay of immunosuppressive therapy following pediatric renal transplantation. TAC has a narrow therapeutic index, thus, frequent therapeutic drug monitoring is employed to maximize efficacy and avoid toxicity. Dose adjustments based on TAC trough levels are challenging,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

Objective

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 for the dosing tool, and 2) evaluate their performance predicting TAC concentrations in an independent cohort of Children's Mercy (CM) patients.

Methods

Figure 1. Analysis workflow.



Pharmacokinetic data analysis. From the collected 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 TAC concentration (C_{obs}), population predicted concentration (C_{pred}) was estimated.

Estimation of bias via mean residual error (MRE):

$$\mathrm{MRE}\ (\%) = \frac{1}{n}\sum_{i=1}^{n}\left(\frac{C_{pred}-C_{obs}}{C_{obs}}\right)$$

Estimation of precision via root mean squared error (RMSE):

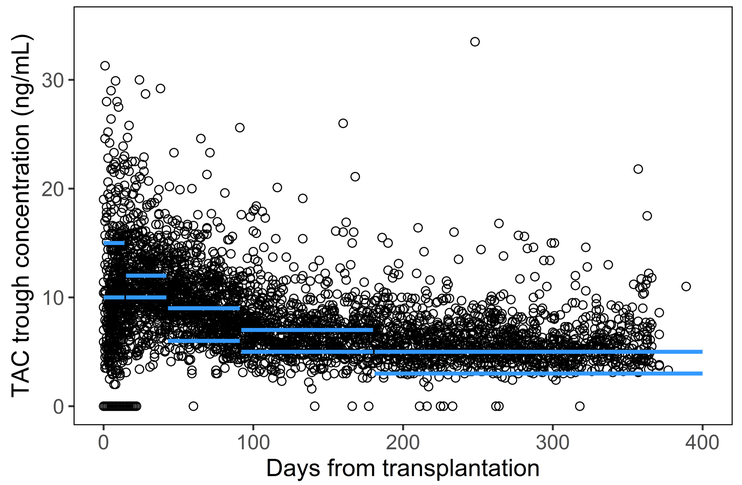
$$\mathrm{RMSE}\ (\%) = \sqrt{\frac{1}{n}\sum_{i=1}^{n}\left(\frac{C_{pred}-C_{obs}}{C_{obs}}\right)^2}$$

Results

Table 1. Published model covariates shown to significantly affect TAC exposure (and oral clearance, Cl/F) in pediatric renal transplant recipients. Six pediatric popPK models from 4 studies were identified. All models reported that TAC pharmacokinetics was best described by a 2-compartment structural model with first-order absorption preceded by a lag time, and elimination from the central compartment. The most commonly identified covariates were allometrically scaled body weight and CYP3A5 genotype. "X" denotes that covariate was included in the popPK model; Gamma GT, gamma glutamyltransferase enzyme.

Study	Model	Covariates included			Notes
		Body weight (kg)	CYP3A5 genotype	Other	
Andrews 2018	M1	X	X	Donor, status eGFR, hematocrit	Final model
	M2	X	X	Donor status	Simulation model
Prytula 2016	M3	X	X	Gamma GT, hematocrit	/
Zhao 2009	M4	X	X	Hematocrit	/
Jacobo-Cabral 2015	M5		X		All TAC formulations
	M6		X		Prograf only

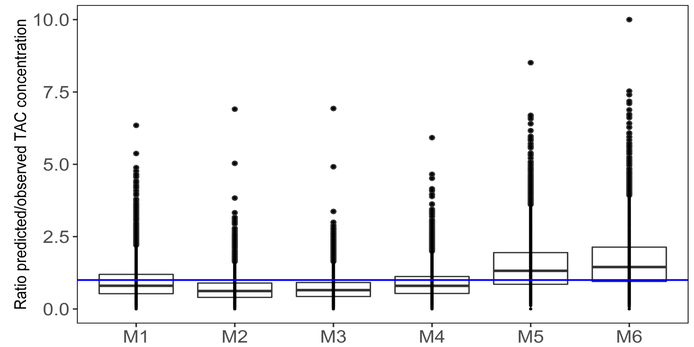
Figure 2. Variability in tacrolimus (TAC) trough blood concentrations in the first year following kidney transplantation. Fifty-eight children (age 1-20 years) who were enrolled in TAC pharmacokinetics study at CM had their TAC trough levels measured as a part of routine clinical care. A total of 3809 samples (average 66 per subject) were collected. Blue lines represent the upper and lower limit of targeted therapeutic interval at a given period post-transplantation.



Results

Figure 3. Bias and precision of each popPK model. Four models underpredicted measured TAC levels (negative MRE), and two overpredicted measured TAC levels (positive MRE). A high degree of variability between population predicted and measured TAC levels was noted for all models. Boxplots represent ratios of each predicted-to-observed concentration pair, with blue horizontal line indicating a ratio of 1. M4 is considered having the best predictive performance.

	M1	M2	M3	M4	M5	M6
MRE (%)	-4.8	-29.8	-27.3	-9.8	50.2	65.2
RMSE (%)	64.4	53.5	51.5	54.1	103.9	120



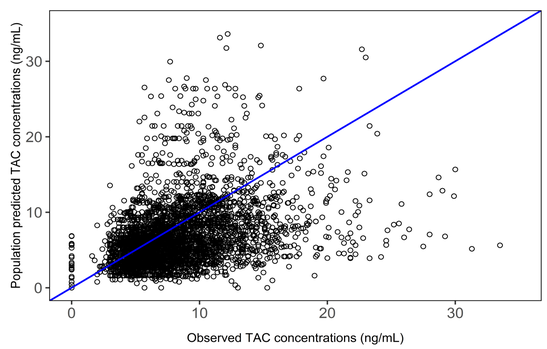


Figure 4. M4-predicted versus observed TAC concentrations. Data scatter is present on both sides of the blue line of identity, although it appears non-symmetrical. One outlier (C_{pred} = 62.8 ng/mL, C_{obs} = 10.6 ng/mL) was omitted for better visualization of the rest of the data.

Conclusions

Four popPK models predicted TAC trough levels sufficiently well on average, however none of the evaluated models predicted 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.

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