Population pharmacokinetics of tacrolimus in pediatric heart transplant patients

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INTRODUCTION

Tacrolimus is an immunosuppressive agent prescribed for the prevention of rejection in solid organ transplant recipients. It is known to have large pharmacokinetic (PK) variability in patients with solid organ transplantation and the generic substitution for brand product may also contribute to the PK variability that may impact graft status.

This study aims to develop a population PK model of tacrolimus in pediatric heart transplant patients to facilitate the evaluation of its bioequivalence between a generic version and the brand name product.

METHODS

- ❑ A retrospective observational study with data extracted from Intermountain Healthcare Systems (01/2006 -12/2013)
- ❑ Inclusion criteria
  - pediatric heart transplant recipients aging 2- 18 years when admitted into hospital
  - received tacrolimus as in-label use (oral capsules, generic drug by Sandoz or Prograf by Astellas Pharma US, Inc.)
  - had ≥ 1 trough blood sample(s) taken for therapeutic drug monitoring as standard in-patient care per institutional guideline.
- ❑ Exclusion criteria
  - Patients had tacrolimus as off-label use (oral suspension, *etc*)
  - Patients on ECMO, hemodialysis, or peritoneal dialysis
- ❑ Tacrolimus concentrations were measured by LC/MS
- ❑ Nonlinear mixed effects modeling (NONMEM 7.3) was used to develop population PK models

Table 1. Demographics and clinical status of patients at admission

		Number (%) or median (interquartile range)	Range
Sex			
	Male	19 (48.7%)	
	Female	20 (51.3%)	
Race			
	Caucasian	35 (89.7%)	
	Asian	4 (10.3%)	
Ethnicity			
	Non-hispanic/latino	31 (79.5%)	
	Hispanic/latino	3 (7.7%)	
	Unavailable	5 (12.8%)	
Formulation			
	Brand (Prograf)	72 (71.3%)	
	Generic (Sandoz)	29 (28.7%)	
Age (yrs)		15.78 (13.06 – 17.95)	5.90 – 18.92
Weight (kg)		50.2 (39.1 -61.2)	15.4 – 111.0
Height (cm)		161 (149 – 168)	52 - 193
Body mass index (kg/m^2)		19.1 (15.7 – 21.9)	12.3 – 39.4
Post-transplant time (yrs)		2.479 (0.167 – 7.027)	0.003 – 18.252
Hematocrit (%)		36.2 (33.1 – 40.8)	25.3 – 49.7
Albumin (g/dL)		3.6 (3.3 – 4.0)	1.9 – 5.2
Blood urea nitrogen (mg/dL)		21 (15 – 25)	4 - 40
Aspartate aminotransferase (IU/L)		42 (33 – 60)	17 - 96
Alanine aminotransferase (IU/L)		43 (20 – 58)	7 - 156
Total bilirubin (mg/dL)		0.5 (0.3 – 0.8)	0.2 – 1.7
Serum creatinine concentration (mg/dL)		0.71 (0.60 – 0.94)	0.32 – 1.88
Creatinine clearance (mL/min/1.73m^2)		91.7 (66.8 – 108.0)	18.8 – 151.0

RESULTS

Table 2. Final model estimates and non-parametric bootstrap for tacrolimus (oral capsule) in pediatric heart recipients

PK parameters	Model estimate (%RSE)	Bootstrap median (95% CI) n=1000
CL = typical CL × (1 + 0.765 × Race)		
Typical CL for a Caucasian patient (L/hr)	11.1 (8.11)	11.1 (9.2 – 12.9)
Race on CL	0.765 (25.6)	0.797 (0.401 – 1.3)
V_d (L)	143 (17.8)	149 (88 – 209)
K_a (hr^{-1})	4.5 fixed[1]	4.5 fixed
Inter-individual variability (%)		
CL	36.2 (23.8)	39.2 (27.8 – 60.4)
V_d	39.9 (44.8)	40.3 (0.3 – 66.0)
Residual variability		
Additive error (ng/mL)	4.06 (15.8)	3.98 (3.27 – 4.64)

Bootstrap (n = 1000) success rate is 99.9%.
RSE, relative standard error; CI, confidence interval; Race, Caucasian = 0, Asian = 1.

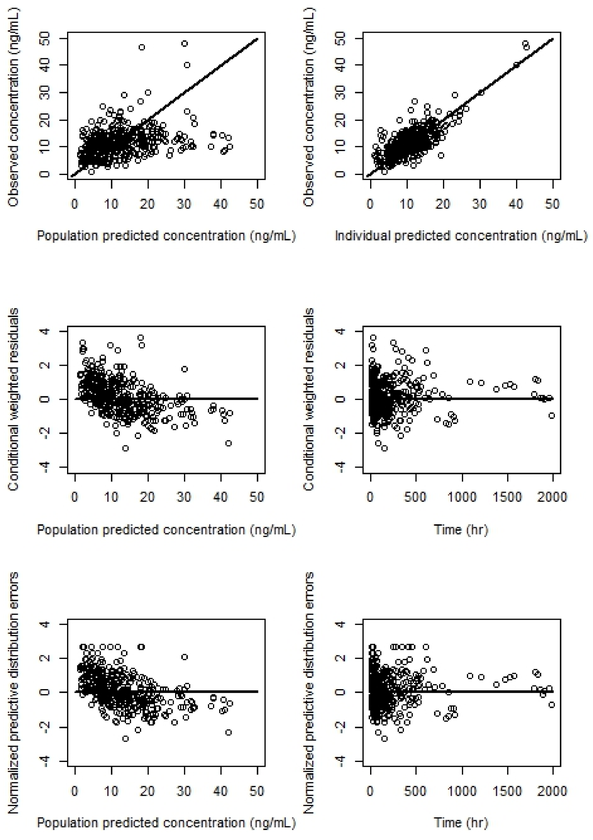

Figure 1. Diagnostic plots of final model of tacrolimus (oral capsules) in pediatric heart recipients. Final model showed good model fit to the data as predicted concentrations were close to observations around the line of identity; conditional weighted residuals or normalized predictive distribution errors showed no trends along population predicted concentrations or time.

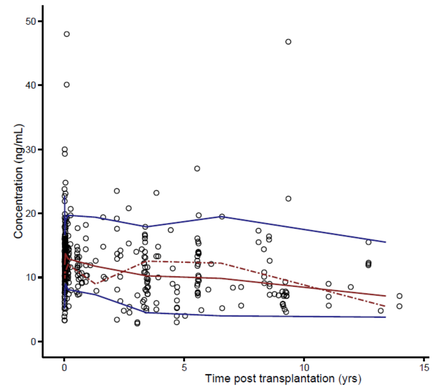

Figure 2. Visual predictive check of final model. Dots, observations; blue line, 5% and 95% percentiles of observations; red line, median of observations; red dashline, median of predictions. % observations outside 90% CI were 7%.

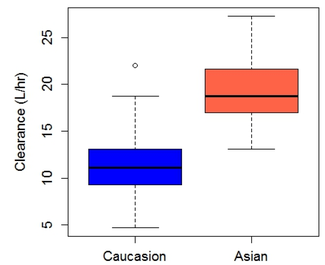

Figure 3. Sensitivity analysis of Individual clearances by race.

SUMMARY

- ❑ A total of 39 pediatric heart recipients (19 male and 20 female, 89.7% Caucasian) with 101 encounters were included in this study.
- ❑ The tacrolimus PK (oral capsules) was best described by a one-compartment model with first-order absorption.
- ❑ Sex, Race, and liver function biomarker total bilirubin were found to be significantly correlated with tacrolimus clearance in uni-covariate analysis. Race was remained in the final model as a significant covariate on clearance.
- ❑ Inclusion of co-medications of CYP3A inhibitors (ciprofloxacin, diltiazem, fluconazole, amiodarone, amlodipine, atorvastatin, fluoxetine) and inducers (hydrocortisone, prednisone (>25 mg), methylprednisolone, dexamethasone) did not significantly improve the model fit.

CONCLUSIONS

Tacrolimus PK was best described by a one-compartment model with first-order absorption in pediatric heart transplant recipients. Race was a significant covariate on its clearance in the final model, which implied the underlying CYP3A5*1 allele frequency difference between Caucasian and Asian[2] as CYP3A5 is the major hepatic enzyme responsible for the metabolism of tacrolimus.

A prospective trial is undergoing to collect tacrolimus samples at absorption/distribution/elimination phases as well as patient CYP3A genotype information to enable the evaluation of bioequivalence criteria of the generic tacrolimus comparative to its brand product.

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References: 1. Jusko, et al. 1995; 2. Thompson, et al. 2004, Wang, et al. 2006, Kuehl, et al. 2001 and Lamba, et al. 2002