Population Pharmacokinetics of Tacrolimus in Pediatric Patients with Kidney Transplant

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INTRODUCTION

Every year, immunosuppressant drugs are required by nearly 29,000 children and adults who receive solid organ or bone marrow transplants. Tacrolimus is one of the most widely used immunosuppressant agents for this purpose.

In this preliminary study, we aim to develop a population pharmacokinetic (popPK) model of tacrolimus in pediatric patients with kidney transplant. Using the popPK model, we aim to evaluate the bioequivalence of a generic tacrolimus (by Sandoz) to the brand name one (Prograf by Astellas Pharma, Inc.).

METHODS

- A retrospective observational study was conducted in pediatric kidney transplant recipients receiving tacrolimus oral capsules between 01/2006 and 12/2013.
- Patients of age more than 28 days and less than 18 years were included.
- Data were extracted from Intermountain electronic data warehouse.
- The popPK model was developed using NONMEM 7.3 and PsN 4.4.0.
- Data formatting and post-model analysis was done using R packages.

Table 1. Demographics of pediatric patients receiving tacrolimus (n=74)

Characteristics	Category	N	% of Total
Sex	Male	42	56.8%
	Female	32	43.2%
Race	White	67	90.5%
	Native Hawaiian or other pacific islander	3	4.1%
	Other/declined	4	5.4%
Ethnicity	Non-Hispanic/non-Latino	52	72.8%
	Hispanic/Latino	18	10.9%
	Unavailable	4	16.3%
Age Group	2 to 11 years	51	32.7%
	12 to 18 years	105	67.3%
Formulation	Brand (Prograf)	70	44.9%
	Generic (Sandoz)	86	55.1%
	Mean	**Range**	
Weight (kg)	49.4	13 – 115	
Post-Transplant Time (day)	1054	1 – 4963	
Hematocrit (%)	31.4%	10% – 49.1%	

DATA

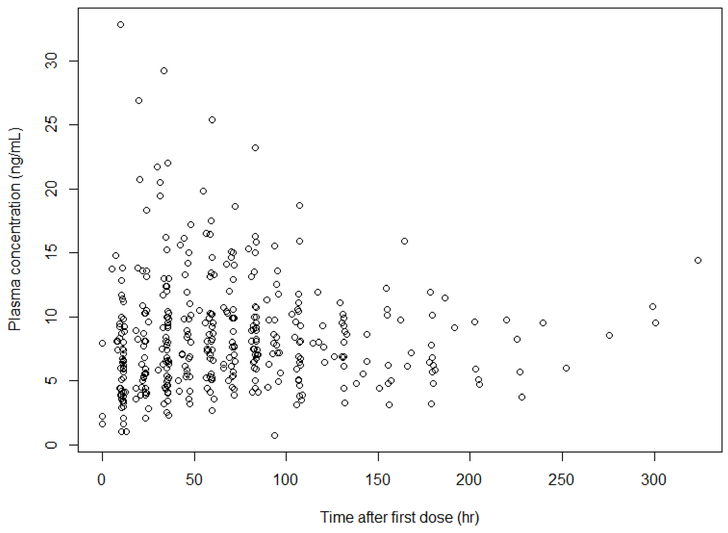

Figure 1. Plasma concentrations of tacrolimus vs. time after first dose.

RESULTS

Table 2. Parameter estimates

Parameter	Estimate	95% CI	Bootstrap Estimate	Bootstrap 95% CI
Clearance (θ1, L/hr)	12.4	10.9 – 13.9	12.4	11 – 14.1
Volume of distribution (V/F, L)	122	92.0– 152.0	123	92.4 – 155
Absorption rate (KA, hr^{-1})	0.462 (fixed)	–	0.462 (fixed)	–
θ2 (PTT ~ CL)	-0.080	-0.112 – -0.049	-0.081	-0.112 – -0.050
θ3 (WT ~ CL)	0.518	0.340 – 0.684	0.523	0.322 – 0.682
Between Subject Variability (BSV)				
$\omega_{CL/F}^2$ (CV%)	0.205 (45.3%)	0.148 – 0.262	0.203	0.143 – 0.264
Residual Error				
Proportional error (CV%)	0.111 (33.3%)	0.078 – 0.144	0.110	0.078 – 0.145

$$CL/F = \theta 1 \times \left(\frac{PTT}{595.9}\right)^{\theta 2} \times \left(\frac{WT}{44.6}\right)^{\theta 3} \times \exp(\eta)$$

Note: CI, confidence interval; PTT, post-transplant time; WT, weight; F, fraction absorbed; CV, coefficient of variation; η, random effect; θ, fixed effect; Bootstrap n=500.

Acknowledgement

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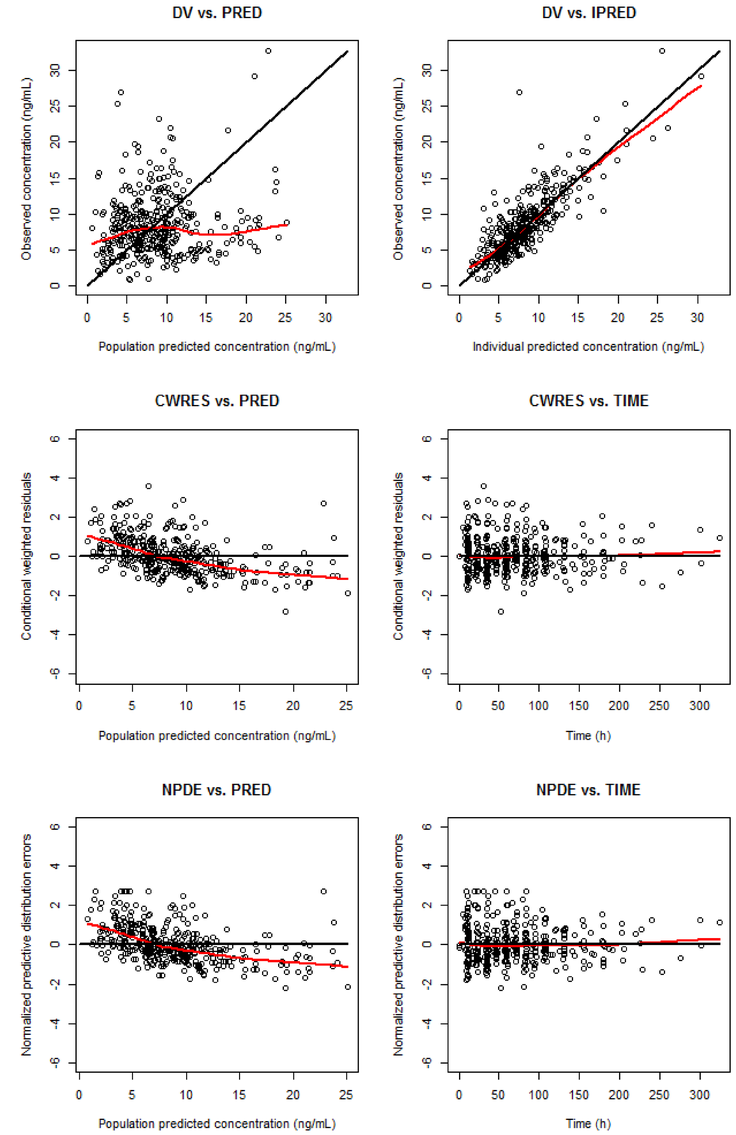

Figure 2. Goodness-of-fit plots. A loess smoothing curve (red line) was fitted for each plot (degree=1, span=0.5).

CONCLUSION

In pediatric patients with kidney transplant, tacrolimus PK (via oral capsule administration) was best described by a one-compartment, first order absorption without lag time, linear elimination model. Future studies will investigate the bioequivalence of the generic drug in comparison to the brand product.