Development of a physiologically based pharmacokinetic model of tacrolimus in adult organ transplant patients

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INTRODUCTION

Tacrolimus is an immunosuppressive agent prescribed for the prevention of rejection in solid organ transplant recipients. Switching tacrolimus use from brand to generic product may potentially introduce different pharmacokinetic (PK) characteristics and result in altered clinical outcomes. In this study, we developed a preliminary physiologically based PK (PBPK) model to describe tacrolimus PK by incorporating hepatic and intestine clearance in the simulated healthy subject population. More detailed model about the absorption process is under development to better understand the impact of formulation differences between the brand and generic tacrolimus products on the PK.

The long term purpose of the study is to develop PBPK models to explore the difference in formulation characteristics between brand and generic tacrolimus products to facilitate the bioequivalence evaluation in adult stable kidney recipients.

METHODS

- ❑ A PBPK model of tacrolimus was developed in Simcyp® Simulator version 14 (Certara USA, Inc.) based on its physiological and PK properties.
- ❑ Simulated population contained 100 patients (10 trials with 10 patients each).
- ❑ The model was refined and validated against a published bioequivalence trial in adult stable kidney transplant patients[1,2].
- ❑ Absorption phase PK parameters were systematically varied for generic tacrolimus in comparison to brand product.
- ❑ The models were further validated against the therapeutic drug monitoring records extracted from Intermountain Healthcare Systems (01/2006 -12/2013) where patients met the following inclusion criteria similar to that of the published trial[1,2]:

- Adult kidney recipients in stable condition without multiple organ transplants;
- Switched tacrolimus as in-label use (oral capsules) between brand (Astellas Pharma) and generic (Sandoz) products;
- had ≥ 1 trough blood sample(s) taken for therapeutic drug monitoring for each product type.

- ❑ Tacrolimus concentrations were measured by LC-MS/MS.

Table 1. Summary of tacrolimus physiological properties and PK parameters*

Parameter	Input
Molecular weight (g/mol)	804
Compound type	Neutral
LogP	3.26
Blood/plasma concentration ratio	35
Fraction unbound in the plasma	0.013
Absorption model	First order
Fraction absorbed in intestine	0.1 (CV 32.0%)
K_a (hour^{-1})#	0.35 (CV 36.5%)
Effective permeability (10^{-4} cm/s)	5.95
Distribution model	Full PBPK model
Prediction model	Rodgers and Rowland (method 2)
Renal clearance (L/hour)	0.00084
Elimination	Whole organ metabolic clearance
Hepatic intrinsic clearance (µL/min/10^6)	9.753 (CV 30%)
Unbound intrinsic clearance in intestine (µL/min/mg protein)	658 (CV 67%)

#K_a, absorption rate constant; the PBPK model for generic tacrolimus has the value of 0.38 hour^{-1}.

RESULTS

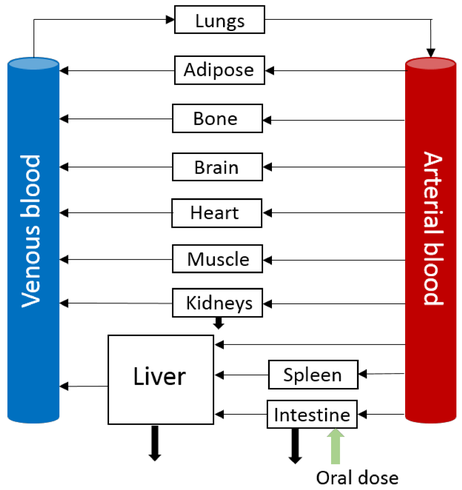

Figure 1. PBPK model structure of tacrolimus given as oral capsules.

Table 2. Population demographics of the patients in the bioequivalence trial[1,2] and the patients under therapeutic drug monitoring

	Bioequivalence trial (n=68)	Therapeutic drug monitoring (n=4)
Sex	58.8% male	50.0% male
Race	64.7% non-African American	100% White patients
Age (years)	51.8 ± 12.5	53.3 ± 18.9
Body mass index (kg/m^2)	28.6 ± 4.5	30.1 ± 8.1
Time post transplantation (years)	4.2 ± 3.3	7.8 ± 2.8
Tacrolimus dose at baseline (mg/day)	5.8 ± 4.3	4.8 ± 3.2

Data = mean ± standard deviation.

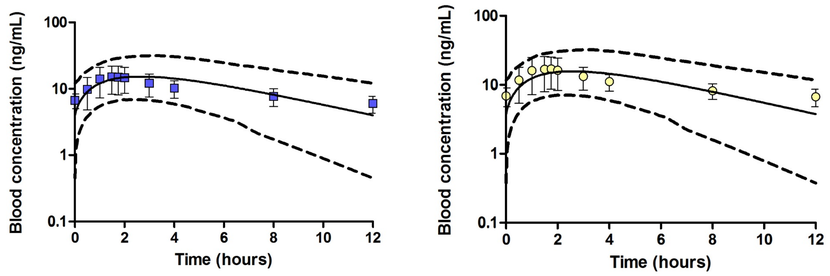

Figure 2. Concentration time profiles for brand (left) and generic (right) tacrolimus at steady state in adult kidney recipients receiving 5.8 mg/day, twice daily dose regimen. Blue squares represent the trial observations from brand dose (mean ± standard deviation); yellow circles represent the trial observations from generic dose. The observations were from 44 non-African American patients. The solid lines represent the simulated mean and the dashed lines stand for the simulated 90% confidence interval.

Table 3. Summary of tacrolimus PK parameters for brand and generic product following oral administration at steady state

	AUC			C_{max}		
	Observed (ng·hour/mL)	Simulation (ng·hour/mL)	Error (%)	Observed (ng/mL)	Simulation (ng/mL)	Error (%)
Brand	112.7	121.1	7.5	15.2	15.6	2.6
Generic	123.5	121.1	1.9	17.0	16.0	5.9

Data = mean. AUC, area under tacrolimus blood concentration time curve during the dosing interval at steady state. C_{max}, maximum blood concentration at steady state.

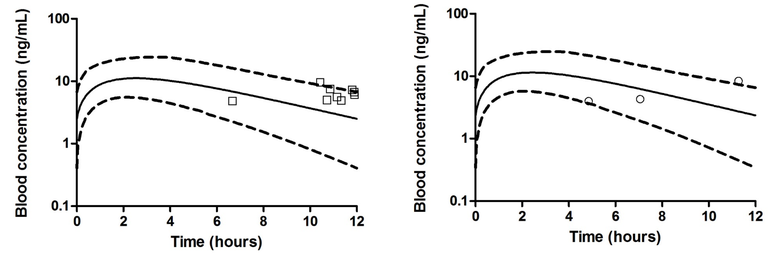

Figure 3. Concentration time profiles for brand (left) and generic (right) tacrolimus at 4.8 mg/day, twice daily dose regimen. Open squares, dose normalized concentrations from brand dose; open circle, dose normalized concentrations from generic dose. The solid lines represent the simulated mean and the dashed lines stand for the simulated 90% confidence interval.

SUMMARY AND CONCLUSION

The PBPK model incorporating hepatic and intestine clearance information (Table 1, Figure 1) predicted the observed PK profiles in patients from bioequivalence trial (Table 2, Figure 2) as well as the trough concentrations from therapeutic drug monitoring (Figure 3).

The PK difference between brand and generic products may be due to absorption phase, partially attributed to the increased K_a (0.38 hour^{-1}) for generic tacrolimus. However, this difference was small and the results on drug exposure were small (Figure 2, Table 3).

The PBPK modeling provides advantages over population based PK analysis by allowing for exploration of underlying mechanisms, potentially the variation in formulation characteristics between brand and generic products, that lead to changes in PK during the absorption phase. This altered PK during absorption phase may result in different partial AUC that could impact the pharmacodynamic endpoints and subsequent clinical outcomes. Further study is underway to refine the model by utilizing ADAM absorption model, enzyme kinetics elimination, and model validation by PK data from intravenous dosing.

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References: 1. Alloway, *et al.* 2012; 2. Bloom, *et al.* 2013.
*Gertz, *et al.* 2011; Ohtani, *et al.* 2011; Gerard, *et al.* 2014; Moller, *et al.* 1999.