Genotype-guided tacrolimus dosing equation for African American kidney transplant recipients

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INTRODUCTION

Tacrolimus is used after kidney transplant for maintenance immunosuppression. It has a narrow therapeutic index and large inter-individual variability in the dose required to achieve target trough concentrations.[1-4] African Americans do poorer after transplantation with significantly higher rates of acute rejection, return to dialysis and mortality. [5-7] Tacrolimus dose requirements in African American patients are significantly higher than Caucasians to achieve the same target trough blood concentrations.[8-9] Not all African Americans will require higher doses since many will carry one or more of the *CYP3A5* nonfunctional variants that occur only in African Americans. These variants result in reduced metabolic capacity.

Tacrolimus is metabolized in the gut and liver by cytochrome P450 enzymes, 3A5 and 3A4. CYP3A5 is the predominate enzyme. Genetic variation affects tacrolimus clearance. The *CYP3A5*3* is a non-functional intronic variant that has been extensively studied and is associated with significantly lower tacrolimus clearance.[4,10] This variant is common in Caucasians but occurs in only about 15% of African American. [11] However, there are two other low or non-functional alleles, *CYP3A5*6* and *CYP3A5*7*, that are common in African Americans and have a minor allele frequency of 16-18% and 10-12%, respectively. These variants are absent in Caucasians. The impact of these variants on tacrolimus clearance is large and have been underappreciated in importance.[11]

The objective of this study was for the first time to develop an African American specific genotype-guided dosing model which comprehensively includes the common African American specific *CYP3A5* variants and clinical factors.

METHODS

This was a multicenter, observational study conducted at 7 transplant centers in US and Canada (www.clinicatrials.gov , NCT00270712).

Subjects: African American kidney transplant recipients (n=354) who received maintenance tacrolimus immunosuppression were selected for the analysis. Trough tacrolimus blood concentrations were obtained at the treating center as a part of routine clinical care. Medical records were used to obtain recipient and donor clinical and demographic characteristics. Trough concentrations were obtained from each subject for the first 6 months (twice each week for first 2 months, and then twice each month up to 6 months) . In general, concentrations of 8-12 ng/mL were targeted for the first 3 months and 6-10 ng/mL for 3-6 months posttransplant.

Randomization: The dataset was divided in a ratio of 60:40 into a development (n=212 subjects, 3704 trough concentrations) and validation cohort (n=142 subjects, 2333 trough concentrations) to develop and validate a tacrolimus apparent oral clearance (Cl/F) model, respectively.

Model development and covariate selection: Population pharmacokinetics using NONMEM was used to estimate the typical value of oral clearance (TVCl/F). The following genotypes and clinical factors were then examined for their effect on TVCl/F.

- Clinical: Recipient and donor age, gender, days posttransplant, steroid use, calcium channel blocker use, ACE-inhibitor use, CMV sero-status at time of transplant, diabetes at time of transplant, body mass index , actual body weight at baseline, and glomerular filtration rate and actual body weight at time of trough as time varying covariates.
- Genotypes: *CYP3A5*3*(rs776746), *CYP3A5*6* (rs10264272), *CYP3A5*7* (rs41303343), *POR*28* (rs1057868), *CYP3A4*22* (rs35599367) (See poster #259 on May 03 for genotyping details)

Model evaluation: A non-parametric bootstrap was conducted to evaluate model adequacy using a development cohort. Population predicted trough concentrations (PRED) were obtained for each observed concentration (the dependent variable, DV) in the validation cohort. Median prediction error (MPE) and median percentage prediction error (MPPE) was then used to calculate the bias and median absolute prediction error (MAPE) was used to calculate the imprecision.

MPE = Median (PRED –DV)
MPPE = Median [(PRED-DV)/DV X 100]
MAPE = Median [|(PRED-DV)|]

RESULTS

Table 1 shows patient characteristics in the development and validation cohorts.

Structural Model: Tacrolimus trough concentrations were assumed to be average steady state concentrations (Css) and were related to the Cl/F as follows:

Css = Total Daily Dose/[(Cl/F)*24]

Error Model: An exponential error model was used to describe between subject variability (BSV) and an additive error model was used to describe the residual unexplained variability (RUV).

The following were identified as significant covariates towards TVCl/F.
-Days post transplant, steroid and/or anti-viral drug co-administration, recipient age
-CYP3A5*3, CYP3A5*6* and *CYP3A5*7

Table 2 shows the parameter estimates with relative standard error obtained from the original dataset and the median of bootstrap estimates with 95% confidence intervals. Parameter estimates were comparable indicating that the model is robust and reproducible.

Table 3 shows the prediction performance of the developed model using the validation cohort.

Table 1: Patient Characteristics

	Development cohort	Validation cohort
No. of subjects	212	142
No. of male subjects (%)	140(62.7)	87(61.2)
Daily dose (mg)[a]	8(0.5-36)	8(1-30)
Tacrolimus trough (ng/mL)[a]	6.5 (0.10-65.60)	6.40(0.70-50.00)
Weight at baseline (kg)[a]	85.29(42.27 -140)	83.80(47-137)
No. of recipients in age category (%)		
18-34 years	36 (16.98)	30 (21.12)
35-64 years	163(76.89)	105 (73.94)
>64 years	13 (6.13)	7 (4.92)
No. of troughs with antiviral drug (%)	2128(57.45)	1313(56.28)
No. of troughs with steroid (%)	1941(52.45)	1342(57.52)
No. of individuals with genotype (%)		
*CYP3A5*1/*3*	65 (30.67)	31 (21.83)
*CYP3A5*3/*3*	20 (9.43)	14 (9.8)
*CYP3A5*1/*7*	14 (6.6)	22 (15.49)
*CYP3A5*7/*7*	0	0
*CYP3A5*1/*6*	30 (14.15)	17 (11.97)
*CYP3A5*6/*6*	1 (0.47)	3 (2.11)
*CYP3A5*3/*6*	15 (7.07)	6 (4.2)
*CYP3A5*3/*7*	8 (3.77)	7 (4.92)
*CYP3A5*6/*7*	5 (2.38)	6 (4.22)
*CYP3A5*1*1*	49 (23.11)	31 (21.83)
CYP Not determined[b]	5	5
*POR*1/*1*	91 (42.92)	60 (42.25)
*POR*1/*28*	55 (25.94)	31 (21.83)
*POR*28/*28*	15 (7.07)	10 (7.04)
*CYP3A4*1/*1*	140 (66.03)	89 (62.67)
*CYP3A4*1/*22*	12 (5.66)	5 (3.5)
*CYP3A4*22/*22*	0	0

[a]data are median (range) [b]These individuals did not have one or more of the CYP3A5 genotypes available and were excluded from the all analyses

EXAMPLE OF THE UTILITY OF THE MODEL

The tacrolimus dosing model can be used clinically to personalize dosing to achieve the desired target drug concentrations in two steps.

1. Determine tacrolimus TVCL/F.
TVCl/F (L/hr) = 54.6 L/hr x (1.33, if days less than 9 posttransplant) x [(0.53, if *CYP3A5*3/*3* or *CYP3A5*3/*7* or *CYP3A5*3/*6* or *CYP3A5*6/*7 or CYP3A5*6/*6*)] x (0.85, if *CYP3A5*1/*3* or *CYP3A5*1/*6* or *CYP3A5*1/*7*) x (1.23, if receiving a steroid) x (0.92 if receiving an antiviral drug) x (1.24 if recipient age 18-25 years)

2. Determine dose (mg/day).
Daily dose = [TVCl/F X target tacrolimus trough concentration (ng/ml) X 24hrs] /1000

CONCLUSION

We developed a genotype-guided tacrolimus dosing model using *CYP3A5*3, *6* and *7* variants and clinical factors specific for African American kidney transplant recipients. This model can be used to estimate a tacrolimus dose for any desired trough concentration. Knowledge gained from this study will assist in individualizing tacrolimus regimens posttransplant thereby improving immunosuppressive therapy.

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Table 2 : The effect of genotypes and clinical covariates on tacrolimus clearance (Cl/F) and final parameters estimates

Parameter/Covariate	Model development cohort. Estimate (%RSE[a]) of the effect on TVCl/F	Bootstrap analysis. Median (95% confidence interval)
Typical Value of Cl/F (TVCl/F) in L/hr	54.60 (10.0%)	54.48 (44.51-66.63)
Two loss of function alleles (*CYP3A5*3/*3* or *3/*7* or *3/*6* or *6/*7* or *6/*6*)	0.53 (10.9%)	0.53 (0.43-0.66)
One loss of function alleles (*CYP3A5*1/*3 or CYP3A5*1/*6 or CYP3A5*1/*7*)	0.85 (9.7%)	0.85 (0.70-1.04)
Less than day 9 posttransplant	1.33 (4.2%)	1.33 (1.23-1.45)
Steroid coadministration	1.23 (6.9%)	1.24 (1.07-1.42)
Antiviral coadministration	0.92 (2.9%)	0.91 (0.87-0.97)
Recipient age (18-25 yrs)	1.24 (7.8%)	1.24 (1.07-1.47)
Between subject variability[b]	0.21 (18.1%) [CV%=48.6]	0.21 (0.14- 0.28) [CV%= 46.7(38.8-56.8]
Residual unexplained variability in trough (ng/mL)	2.76 (7.5%)	2.75 (2.55-2.96) ng/mL

[a]RSE is relative standard error [b]0.21 represents the estimate of the variance of individual $\eta_{(1)}$. CV% is the coefficient of variance and represents between subject variability in the population

Goodness of fit diagnostic plots were assessed during the model development steps (Figure 1) and shows that the model adequately explained the observed data

Figure 1: Diagnostic Plots
A) Observed concentration (DV) vs population predicted concentration (PRED)
B) Observed Concentration (DV) vs individual predicted concentration
C) Conditional weighted residuals (CWRES) vs PRED D) CWRES vs TIME

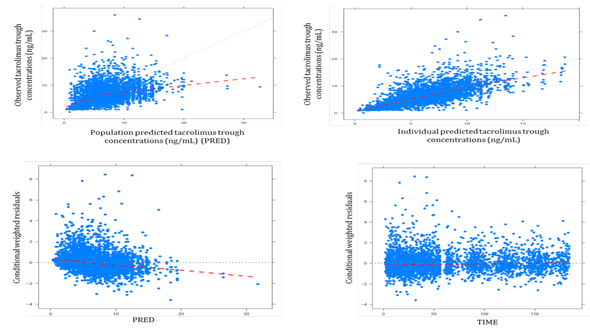

Table 3: Predictive performance of the tacrolimus Cl/F model

Predictive performance measure	Estimate
Median prediction error (MPE, 95% CI)	0.48(0.31-0.65)
Median percentage prediction error (MPPE, 95% CI)	9.45(6.44-12.45)
Median absolute prediction error (MAPE, 95% CI)	2.32(2.21-2.44)

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