Tacrolimus Dose and Trough Variability, *CYP3A5* Genotype, and Acute Rejection in African American and European American Kidney Recipients

Seibert SR, BS[1]; Schladt DP, MS[2]; Wu B, PhD[3]; Guan W, PhD[3]; Dorr C, PhD[2,7]; Berglund D, BS[1]; Remmel RP, PhD[4]; Matas AJ, MD[5]; Mannon R, MD[6]; Israni AK, MD[2,7]; Oetting WS, PhD[1]; Jacobson PA, PharmD[1] for the DeKAF Investigators

[1]Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, MPLS, MN; [2]Chronic Disease Research Group, Minneapolis Medical Research Foundation, MPLS, MN, [3]Division of Biostatistics, School of Public Health, University of Minnesota, MPLS, MN; [4]Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, MPLS, MN; [5]Division of Transplantation, Department of Surgery, School of Medicine, University of Minnesota, MPLS, MN; [6]Department of Nephrology, University of Alabama, Birmingham, AL; [7]Department of Medicine, Hennepin County Medical Center, University of Minnesota, MPLS, MN.

Introduction

Non-optimal immunosuppression with tacrolimus (TAC, initial goal trough concentration 8–12 ng/mL) after kidney transplantation contributes to the development of toxicity and loss of efficacy. This is especially problematic in African American (AA) patients, partially due to variation in *CYP3A4/5* genes that form proteins responsible for TAC metabolism.[1-4] Long-term graft function remains a significant problem in the field and half or more of all kidney recipients lose their allografts by 10 years post-transplant.[5] We aimed to associated intra-patient TAC pharmacokinetic variability with acute rejection (AR) in adult AA and European American (EA) kidney transplant recipients and to evaluate if TAC variability is associated with *CYP3A5* loss of function (LOF) alleles.

Methods

Coefficients of variation (CV) of TAC trough concentrations (CVTT) and of TAC doses (CVTD) in the first 6 months after transplantation of adult recipients enrolled in DeKAF Genomics[6] (clinicaltrials.gov NCT00270712) were tested for association with AR and *CYP3A5* LOF variants (**3, *6, *7*) in 246 AA and 1226 EA recipients separately. Due to unequal timing and frequency of measurements among recipients, CVs were calculated for each 5 consecutive measurements. This resulted in 2975 CVs of each kind in AA and 15883 CVs of each kind in EA. Longitudinal mixed effects models adjusted for center and time post-transplant were used to test for association with LOF alleles. Multivariate Cox proportional hazard models were used to test for association with time to AR, retaining covariates of SKP transplant, HLA mismatches, B/T cell crossmatch, donor age, and *CYP3A5* LOFs.

Results

Table 1. Patient Demographics and Clinical Characteristics

Variable	Number with Characteristic or Median (% or interquartile range)	
	African American (n = 246)	European American (n = 1226)
Male Recipient	162 (65.9)	774 (63.1)
Age at Transplant, years	49 (37 – 57)	53 (43 – 61)
Donor Age at Transplant, years	36 (25 – 45)	43 (31 – 52)
Deceased Donor Status	180 (73.2)	426 (34.8)
HLA Mismatches		
0	17 (6.9)	156 (12.7)
1 or 2	19 (7.7)	218 (17.8)
3 or 4	110 (44.7)	478 (39.0)
5 or 6	100 (40.7)	372 (30.3)
Unknown	0 (0)	2 (0.2)
B- or T-Cell Crossmatch	19 (7.7)	85 (7.0)
No. of CYP3A5 LOF Alleles (*3, *6, *7)		
0	54 (22.0)	6 (0.5)
1	126 (51.2)	163 (13.3)
2	66 (26.8)	1057 (86.2)
TAC in First 6 Months Posttransplant		
Daily Dose, mg	8.00 (6.00 – 10.00)*	5.60 (3.80 – 8.00)*
Trough Concentration, ng/mL	6.80 (5.40 – 8.40)*	8.94 (7.66 – 10.22)*
CV of TAC Trough (CVTT), %	27.10 (18.37 – 37.87)*	22.37 (15.36 – 32.23)*
CV of TAC Dose (CVTD), %	8.60 (0.00 – 19.44)*	13.98 (6.21 – 24.41)*
Recipients with AR by 6 Months	14 (5.7)	83 (6.8)

HLA – Human Leukocyte Antigen, LOF – Loss of Function
*All p-values < 0.0001 for comparisons between AA and EA

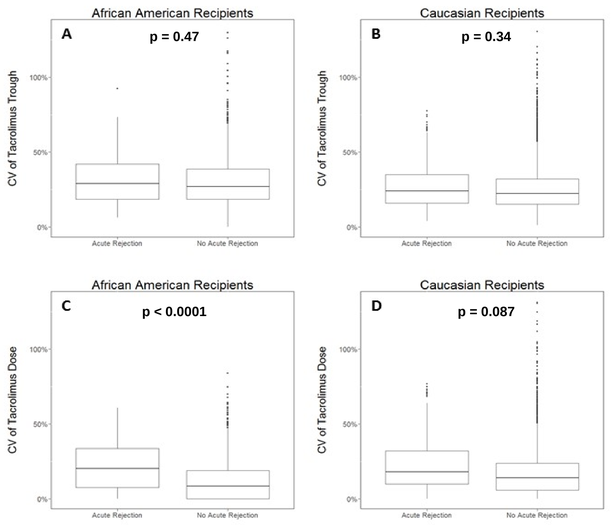

Figure 1. TAC trough and dose variability in patients with and without AR. A) CVTT in AA. B) CVTT in EA. C) CVTD in AA. D) CVTD in EA. Variability of TAC dose is significantly higher in AA recipients who experienced acute rejection.

Table 2. Multivariate Model for Association with Acute Rejection[a]

Variable	African American		European American	
	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P
CV of TAC Dose (Highest quartile)[b]	33.5 (5.54 to 202.85)	0.0001	1.81 (1.14 to 2.86)	0.012
No. of CYP3A5 Loss of Function Alleles	0.16 (0.05 to 0.49)	0.0015	1.51 (0.74 to 3.11)	0.26
No. of HLA Mismatches		0.85		0.0073
1 or 2	0.30 (0.01 to 6.42)		3.15 (0.87 to 11.37)	
3 or 4	0.37 (0.04 to 3.71)		3.64 (1.11 to 11.96)	
5 or 6	0.39 (0.03 to 4.30)		5.95 (1.82 to 19.41)	
B- or T-Cell Crossmatch	3.01 (0.46 to 19.65)	0.25	2.25 (1.13 to 4.50)	0.022
Donor Age at Transplant	1.01 (0.97 to 1.06)	0.65	1.02 (1.00 to 1.04)	0.039

[a] After backwards selection with retention p-value of 0.10
[b] Highest CVTD quartile is >19% for AA and >24% for EA

Table 3. Change in TAC Variability per Additional *CYP3A5* LOF Allele

Variable	African American		European American	
	Absolute Change, % (95% CI)	P	Absolute Change, % (95% CI)	P
CV of TAC Trough	-1.61 (-3.36 to 0.14)	0.07	-1.82 (-3.06 to -0.57)	0.0042
CV of TAC Dose	1.09 (-0.30 to 2.49)	0.13	2.57 (1.31 to 3.84)	< 0.0001

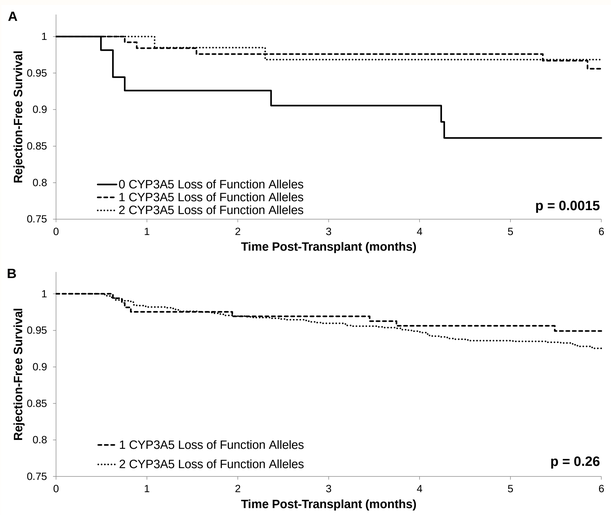

Figure 2. Kaplan-Meier curves for acute rejection in AA patients (A) and EA patients (B) according to number of *CYP3A5* loss of function alleles.

Conclusions

- In AA recipients, variability in TAC dose was significantly higher in those with AR (20.9%) vs no AR (11.2%) (Figure 1), and remained significant in multivariate analysis (Table 2).
- In EA recipients, variability in TAC dose trended towards higher in those with AR (21.5%) vs no AR (16.4%) (Figure 1) and but was significant in multivariate analysis after adjusting for clinical factors (Table 2).
- In AA and EA recipients, we found no association of variability in TAC trough with AR (Figure 1).
- AA with at least one *CYP3A5* LOF allele are less likely to experience acute rejection compared to those with no LOF alleles (Figure 2).
- In EA recipients, there is a reduction in TAC trough variability for each LOF but an increase in TAC dose variability (Table 3).
- AA received significantly higher TAC doses (8.0 vs 5.6 mg/day) and achieved lower troughs (6.80 vs 8.94 ng/mL) (Table 1).
- AA had significantly higher variability in TAC troughs while EA had significantly higher variability in doses (Table 1).

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