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Short Communication

Pharmacokinetic Differences Corroborate Observed Low Tacrolimus Dosage in Native American Renal Transplant Patients

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ABSTRACT:

We have observed in clinical practice that Native Americans require lower dosages of tacrolimus to attain similar target blood trough levels compared to whites after renal transplant. Because there are no pharmacokinetic studies of tacrolimus in this ethnic group, we investigated whether this clinical observation could be corroborated by pharmacokinetic differences between Native Americans and other ethnic and racial groups. We recruited 24 adult Native American kidney transplant recipients on stable oral doses of tacrolimus for at least 1 month posttransplant. We conducted a 12-h steady-state pharmacokinetic profile for all of the patients and estimated pharmacokinetic parameters using NONMEM. The concentration-time data were fit to a linear two compartment model with first-order absorption and lag time using an empirical Bayesian approach. The mean estimate of oral clearance (CL/F) was 11.1 l/h. Compared with previously reported data in other ethnic and racial groups, the Native American cohort has approximately one third the clearance of other groups. Our pharmacokinetic study reveals the clinically observed low dose of tacrolimus in Native American renal transplant patients is associated with a decreased oral tacrolimus clearance. There is scant information available on the genetic or environmental characteristics unique to this ethnic group that affect pharmacokinetics compared to other, better-studied groups, and elucidation of these factors will provide information to further facilitate individualized drug treatment for tacrolimus and a wide range of other drugs with similar clearance processes.

Introduction

The calcineurin inhibitor tacrolimus (FK506) is widely used for primary immunosuppression after renal transplantation. Tacrolimus has a narrow therapeutic index and large interindividual variability, thereby requiring close therapeutic drug monitoring to maintain blood concentrations. It has been established that the area under the concentration-time curve of tacrolimus correlates well with its trough blood levels, so therapeutic drug monitoring is performed using trough concentrations at the end of the 12-h dosing interval (Masuda and Inui, 2006). Racial differences in the pharmacokinetics of tacrolimus have been reported, namely that African Americans require higher doses of tacrolimus than whites to achieve similar trough levels (Neylan, 1998). This variation in the pharmacokinetics of tacrolimus among individuals has been attributed largely to the activity of both metabolizing enzymes (namely cytochromes P450 CYP3A4 and CYP3A5) and drug transporters including P-glycoprotein, encoded by the gene *MDR1* (Masuda and Inui, 2006). Both CYP3A4/5 and P-glycoprotein are expressed in the enterocytes of the small intestine and the hepatocytes of the liver where they act in concert to prevent absorption of the active drug into the systemic circulation from the gastrointestinal tract and to facilitate elimination of the drug from the body.

In clinical practice, we observed that Native American renal transplant patients require lower twice-daily doses of tacrolimus to attain similar trough levels in comparison to white patients. Because there are no pharmacokinetic studies of tacrolimus in this group, we investigated whether this clinical observation could be corroborated by pharmacokinetic differences between Native Americans and other ethnic and racial groups as reported in the literature.

Materials and Methods

Study Cohort. After institutional review board approval, we identified the study cohort by conducting a systematic chart review of adult Native American kidney transplant recipients on stable doses of tacrolimus for at least 1 month posttransplant. Hospital target trough levels are based on time since transplant: 10 to 12 ng/ml within the 1st month posttransplant, 8 to 10 ng/ml between the 1st and 4th months, and 5 to 8 ng/ml after 4 months. No patients were on medications, supplements, or foods known to interact with tacrolimus, such as antifungals, antiepileptics, macrolide antibiotics, St. John's wort, or grapefruit.

Pharmacokinetic Study. We conducted a 12-h pharmacokinetic profile for all patients. After an overnight fast, patients' morning tacrolimus dose was administered in capsules, and serial blood samples were drawn over the course of the dosing interval at times 0 (predose), and 0.5, 1, 2, 4, 6, 8, and 12 h

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ABBREVIATIONS: MDR1, multidrug resistance 1; OFV, objective function value; BMI, body mass index; CL, clearance; F, bioavailability; *V*, central compartment volume; *Q*, intercompartmental clearance; V_{ss}, steady-state volume of distribution; k_a, first-order absorption rate; t_{lag}, absorption lag time; V_2, peripheral compartment volume; $t_{1/2,\alpha}$, alpha half-life; $t_{1/2,\beta}$, beta half-life.

postdose. EDTA whole-blood samples were analyzed either fresh at room temperature or after being frozen at −80°C via whole-blood immunoassay [Architect tacrolimus in whole blood (Bazin et al., 2010), Mayo Clinic Arizona, Phoenix, AZ].

Pharmacokinetic and Statistical Analyses. Pharmacokinetic parameters were estimated using NONMEM (version 7.1; Icon Development Solutions, Dublin, Ireland) using an empirical Bayesian approach. Linear one-compartment and two-compartment pharmacokinetic models with first-order absorption, with and without an absorptive lag time, were evaluated based on the objective function value (OFV). A decrease in OFV of 3.8 (with the addition of lag time) or 5.99 (with addition of the second compartment), corresponding to a χ^2 p value of 0.05 with one or two degrees of freedom, respectively, was considered significant. Goodness-of-fit was also assessed through visual inspection. The necessity of testing a lag time was based on visual inspection of the concentration-time data. Linear regression analyses between pharmacokinetic parameters and demographic characteristics (total daily dose, age, gender, weight, body mass index (BMI), and total days on therapy) were performed in GraphPad Prism (version 4; GraphPad Software Inc., San Diego, CA). A p value less than 0.05 was considered significant after correcting for multiple testing within the linear regression with a Holm test.

Results and Discussion

Descriptive Analyses of Study Cohort. The baseline demographics for the 24 patients recruited to the study are shown in Table 1. Family data demonstrated that all subjects had both parents and both sets of grandparents that belonged to an American Indian tribal group. Excluding only one patient who had been on therapy less than 4 months such that target trough levels were higher than those of the rest of the patients (per hospital protocol), the average total daily tacrolimus dose was 2.54 ± 1.22 mg/day or 0.033 ± 0.021 mg/kg per day, and average trough levels were 6.53 ± 2.43 ng/ml. The pharmacokinetic parameters for this patient were within the range of the other patients'.

Pharmacokinetics. The pharmacokinetic profiles of all 24 patients are shown in Fig. 1. A linear two-compartment model with first-order absorption and lag time was selected based on OFV. It has been previously noted that oral tacrolimus may be modeled with a lag time (Benkali et al., 2009). Population parameter estimates and interindividual variability estimates for oral clearance (CL/F), central compartment volume (V/F), intercompartmental clearance (Q/F), steady-state distribution volume (V_{ss}/F), absorption rate (k_a), and absorption lag time (t_{lag}) were estimated in NONMEM, whereas mean parameter estimates and S.D.s were calculated from each individual's Bayesian estimates. The secondary pharmacokinetic parameters [peripheral compartment volume (V_2), alpha half-life ($t_{1/2,\alpha}$), and beta half-life ($t_{1/2,\beta}$)] were also calculated from each individual's Bayesian estimates. Pharmacokinetic parameters and variability estimates in our cohort are shown in Table 2.

TABLE 1

Descriptive analyses of study cohort

Age, mean ± S.D.	52 ± 13 years
Sex	63% male
BMI, mean ± S.D.	29.9 ± 5 kg/m^2
Weight, mean ± S.D.	83.6 ± 19.3 kg
Tribal affiliation	
Navajo	58%
Hopi	21%
Other	21%
Duration posttransplant, mean ± S.D.	30 ± 23 months
Twice daily dose, mean ± S.D.[a]	1.27 ± 0.644 mg (0.016 ± 0.010 mg/kg)
Presence of diabetes mellitus before transplant	67%
Presence of acute rejection	25%
Presence of new onset diabetes mellitus	13%

[a] Excluding one patient who had been on therapy less than 4 months, such that, per hospital protocol, the target trough level was higher for this patient.

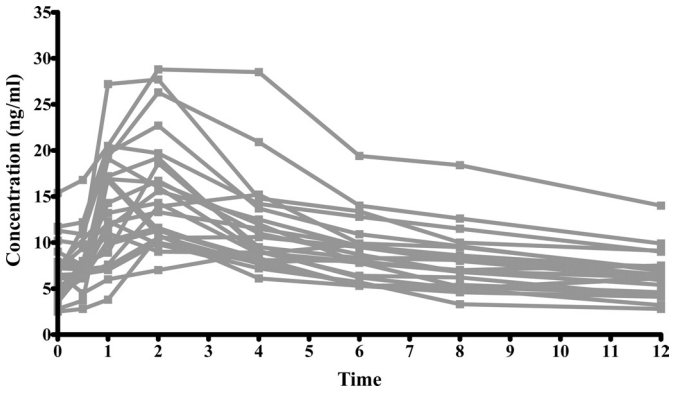

FIG. 1. Tacrolimus pharmacokinetic profiles of 24 Native American renal transplant patients over 12 h.

The interindividual variability in steady-state distribution volume (V_{ss}/F) could not be estimated in NONMEM with our limited sample size; all patients were estimated to have the same NONMEM population V_{ss}/F value of 462 l. The population oral clearance estimate is 10.1 l/h, and the average oral clearance value in our cohort is 11.1 l/h (range, 5.19–27.5 l/h) or 0.139 $l \cdot h^{-1} \cdot kg^{-1}$. At steady state, clearance is inversely associated with blood concentrations such that a higher clearance is associated with lower concentrations. Within the 23 patients in our cohort that had been on therapy for more than 4 months such that the target trough level was 5 to 8 ng/ml, CL/F was significantly associated with patients' total daily tacrolimus dose (linear regression p value = 0.0013) such that each clearance increase of 1 l/h is associated with a 0.138-mg increase in tacrolimus daily dose. Within all 24 patients, no other demographic characteristics (age, gender, weight, BMI, or total days on therapy) were associated with clearance or other pharmacokinetic parameters.

Comparison to Other Groups. A survey of the literature revealed a number of tacrolimus pharmacokinetic studies in various racial and ethnic groups. As shown in Table 3, the oral clearance estimate in our Native American cohort (11.1 l/h or 0.139 $l \cdot h^{-1} \cdot kg^{-1}$) is approximately one third of clearance values in other groups. Our analyses also corroborated the clinical observation that Native Americans require lower doses of tacrolimus: in a comparable study of white (~80%), African (~10%), and Oriental (~10%) renal transplant patients, the average tacrolimus dose at 1 year posttransplant was 0.076 mg/kg per day, leading to an average trough concentration of 7.7 ± 1.6 ng/ml (Scholten et al., 2005). In contrast, the average tacrolimus dose in our cohort was 0.033 mg/kg per day, approximately 40% of the non-Native American dose, but leads to a comparable average trough concentration of 6.53 ± 2.43 ng/ml. Our pharmacokinetic study reveals that the clinically observed low dose of tacrolimus in Native American renal transplant patients is associated with a decreased oral tacrolimus clearance.

This pharmacokinetic study is the first of its kind in Native American patients. There is scant information available on genetic and/or environmental characteristics unique to this ethnic group that affect pharmacokinetics in comparison to other, better-studied groups, and elucidation of these factors will provide information to further facilitate individualized drug treatment. Polymorphisms in *CYP3A5*, namely the **3* reduced function variant, and polymorphisms in *MDR1* (which encodes P-glycoprotein), including *C3435T* and *G2677T/A*, have been shown to affect tacrolimus pharmacokinetics (Masuda and Inui, 2006), but have not been evaluated in Native Americans. In

TABLE 2

Pharmacokinetic parameter estimates for tacrolimus in Native American patients

	NONMEM Parameter Estimates						Secondary (Calculated) Parameters		
	CL/F	*V*/F	*Q*/F	V_{ss}/F	k_a	t_{lag}	V_2/F	$t_{1/2,\alpha}$	$t_{1/2,\beta}$
	l/h	*liter*	*l/h*	*liter*	hr^{-1}	*hr*	*liter*	*hr*	*hr*
Population estimate	10.1	73.3	27.1	462	1.38	0.573			
Interindividual variability	43.5%	36.9%	50.4%	n.e.	46.0%	13.3%			
Mean estimate	11.1	71.5	30.3	462	1.55	0.613	391	1.18	40.2
S.D.	5.53	18.6	13.2	n.e.	0.641	0.149	18.6	0.416	15.7

n.e., not estimated.

TABLE 3

Comparative tacrolimus oral clearance estimates

Clearance estimates are provided as mean ± S.D., where S.D.s were provided in the reference study.

Group	Patient Type	Clearance/F	Clearance/F
		l/h	$l \cdot h^{-1} \cdot kg^{-1}$
Native American, $n = 24$	Renal transplant	11.1 ± 5.53	0.139 ± 0.072
White/African/Oriental, $n = 17$	Renal transplant		0.405 (Scholten et al., 2005)
Australian, $n = 70$	Renal transplant	33.0 ± 11.3 (Staatz et al., 2002)	
French, $n = 32$	Renal transplant	28 (Benkali et al., 2009)	
Japanese, $n = 39$	Renal transplant	25.1 ± 9.2–35.0 ± 13.3, depending on CYP3A5 genotype (Tada et al., 2005)	
Japanese, $n = 30$	Renal transplant		0.467 ± 0.176–0.644 ± 0.226, depending on CYP3A5 genotype (Tsuchiya et al., 2004)
Blacks, $n = 13$	Renal transplant		1.0 (Fitzsimmons et al., 1998)
Nonblacks, $n = 41$	Renal transplant		0.47 (Fitzsimmons et al., 1998)
African American, $n = 10$	Healthy		0.37 (Mancinelli et al., 2001)
White, $n = 12$	Healthy		0.25 (Mancinelli et al., 2001)
Latin American, $n = 12$	Healthy		0.31 (Mancinelli et al., 2001)

addition, clearance processes for a wide range of other drugs with narrow therapeutic indices, including chemotherapeutic agents, calcium channel antagonists, HIV protease inhibitors, hormones, and other immunosuppressive agents such as cyclosporine and sirolimus, are also mediated by CYP3A and P-glycoprotein (Zhang and Benet, 2001). Given these similarities, it is possible that Native American patients will also exhibit lower clearances for these classes of drugs, such that they may require lower doses to avoid the toxicities associated with narrow therapeutic index drugs. Therefore, future directions include developing an understanding of these specific characteristics that may affect pharmacokinetics in Native American patients toward a goal of optimizing therapy and minimizing the reliance on therapeutic drug monitoring.

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