Results of ASERTAA, a Randomized Prospective Crossover Pharmacogenetic Study of Immediate-Release Versus Extended-Release Tacrolimus in African American Kidney Transplant Recipients

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Background: Differences in tacrolimus dosing across ancestries is partly attributable to polymorphisms in *CYP3A5* genes that encode tacrolimus-metabolizing cytochrome P450 3A5 enzymes. The *CYP3A5*1* allele, preponderant in African Americans, is associated with rapid metabolism, subtherapeutic concentrations, and higher dose requirements for tacrolimus, all contributing to worse outcomes. Little is known about the relationship between *CYP3A5* genotype and the tacrolimus pharmacokinetic area under the curve (AUC) profile in African Americans or whether pharmacogenetic differences exist between conventional twice-daily, rapidly absorbed, immediate-release tacrolimus (IR-Tac) and once-daily extended-release tacrolimus (LifeCycle Pharma Tac [LCPT]) with a delayed absorption profile.

Study Design: Randomized prospective crossover study.

Setting & Participants: 50 African American maintenance kidney recipients on stable IR-Tac dosing.

Intervention: Recipients were randomly assigned to continue IR-Tac on days 1 to 7 and then switch to LCPT on day 8 or receive LCPT on days 1 to 7 and then switch to IR-Tac on day 8. The LCPT dose was 85% of the IR-Tac total daily dose.

Outcomes: Tacrolimus 24-hour AUC ($AUC_{0\text{-}24}$), peak and trough concentrations (C_{max} and C_{min}), time to peak concentration, and bioavailability of LCPT versus IR-Tac, according to *CYP3A5* genotype.

Measurements: *CYP3A5* genotype, 24-hour tacrolimus pharmacokinetic profiles.

Results: ~80% of participants carried the *CYP3A5*1* allele (*CYP3A5* expressers). There were no significant differences in $AUC_{0\text{-}24}$ or C_{min} between *CYP3A5* expressers and nonexpressers during administration of either IR-Tac or LCPT. With IR-Tac, tacrolimus C_{max} was 33% higher in *CYP3A5* expressers compared with nonexpressers ($P = 0.04$): With LCPT, this difference was 11% ($P = 0.4$).

Limitations: This was primarily a pharmacogenetic study rather than an efficacy study; the follow-up period was too short to capture clinical outcomes.

Conclusions: Achieving therapeutic tacrolimus trough concentrations with IR-Tac in most African Americans results in significantly higher peak concentrations, potentially magnifying the risk for toxicity and adverse outcomes. This pharmacogenetic effect is attenuated by delayed tacrolimus absorption with LCPT.

Trial Registration: Registered at ClinicalTrials.gov, with study number NCT01962922.

Complete author and article information provided before references.

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Individuals of African ancestry accounted for one-third of US deceased donor kidney recipients in 2015 despite constituting 13% of the population.[1] Because African Americans are inadequately represented in most immunosuppression trials,[2,3] findings from such studies cannot necessarily be extrapolated to this subpopulation. Rates of rejection[4] and transplant loss[4–7] are greater in African Americans compared with Americans of European ancestry due to immunologic and nonimmunologic factors.[8] Recently, the contribution of genetics to these disparate outcomes has become an area of focus.[9,10] Among contemporary therapies, the widely used tacrolimus[11,12] exemplifies a drug for which patient genotype affects dosing.

Factors that affect tacrolimus pharmacokinetics include sex, ethnicity, concomitant medications, and genetic polymorphisms.[13–16] Although tacrolimus is metabolized via CYP3A4 and CYP3A5 enzymes primarily in the gut and liver, the intrinsic tacrolimus clearance capacity of CYP3A5 predominates over CYP3A4.[17] Loss-of-function alleles *CYP3A5*6*, *CYP3A5*7* (found only in individuals of African ancestry), and *CYP3A5*3* (present in most Americans of European ancestry and Asians) result in marked diminution of CYP3A5 enzyme activity (*CYP3A5* nonexpressers).[18] The *CYP3A5*1* allele, found predominantly but not exclusively in individuals of black African descent,[18] encodes CYP3A5 enzymes that are associated with rapid tacrolimus disposition (*CYP3A5* expressers), leading to subtherapeutic concentrations and increased dose requirements.[19]

In the Deterioration of Kidney Allograft Function (DeKAF) Study, the *CYP3A5*1* allele was found to be the most important allele associated with subtherapeutic tacrolimus concentrations in African Americans,[15,20] supporting tacrolimus underexposure as an inferior transplant outcome determinant in this population.[21]

Pharmacogenetic studies of tacrolimus in African Americans (such as DeKAF) have been limited by: (1) tacrolimus assays being performed at individual centers rather than a centralized laboratory, (2) lack of standardized tacrolimus dosing,[22] and (3) measurement of trough concentrations rather than steady-state pharmacokinetic area-under-the-curve (AUC) profiles.[15,20] This latter limitation is especially important because investigations into the association between pharmacokinetic profile and adverse effects of calcineurin inhibitors suggest that their toxicities[23-25] are related to peak concentration (C_{max}), with improvement when the dose is reduced or withdrawn.[26-28]

CYP3A5 enzyme activity is greatest in the foregut and progressively decreases downstream through the bowel.[29] Conventional twice-daily tacrolimus (ie, immediate-release tacrolimus [IR-Tac]) undergoes immediate capsular release and rapid absorption in the proximal small bowel, leading to peak blood concentrations 90 to 120 minutes after administration (t_{max}). LCPT (originally LifeCycle Pharma Tacrolimus [Envarsus XR in the United States]) is a once-daily tacrolimus formulation with similar efficacy and safety to IR-Tac. LCPT's drug delivery technology results in delayed tacrolimus absorption throughout the gastrointestinal tract,[30,31] leading to longer t_{max} and increased bioavailability compared to IR-Tac. Studies have demonstrated that LCPT has a lower dose requirement than IR-Tac to achieve similar tacrolimus trough concentrations.[32,33] Whereas Clinical Pharmacogenetics Implementation Consortium guidelines for *CYP3A5* genotype and tacrolimus dosing are available for IR-Tac, there are currently no guidelines for once-daily tacrolimus. Given the pharmacokinetic differences of LCPT compared to IR-Tac, it is unlikely that the same recommendations are applicable.[34]

The purpose of this study was to advance understanding of the differences in tacrolimus exposure between African American *CYP3A5* expressers and *CYP3A5* nonexpressers using steady-state 24-hour pharmacokinetic profiling and to explore the hypothesis that pharmacogenetic differences between *CYP3A5* expressers and nonexpressers would be attenuated by delayed tacrolimus absorption with LCPT compared to immediate absorption with IR-Tac.

Methods

Study Design and Objectives

ASERTAA (A Study of Extended Release Tacrolimus in African Americans) was an open-label, prospective, randomized, 2-sequence, 3-period, crossover, pharmacogenetic study conducted at the University of Pennsylvania, University of Illinois, and Washington University School of Medicine (St. Louis) between November 25, 2013, and July 30, 2015 (Fig 1). The main study objective was to compare steady-state pharmacokinetics of once-daily LCPT tablets (dosed 15% lower than total daily IR-Tac dose) with evenly divided twice-daily IR-Tac capsules (Prograf [Astellas Pharma US, Inc] or its generic formulations [predominately Sandoz, Dr Reddy, and Accord formulations], for which the systemic exposure differs minimally compared to Prograf[35-37]) in stable African American kidney recipients, according to *CYP3A5* genotype. Secondary objectives were to confirm the total daily dose reduction in the LCPT group following conversion from IR-Tac and compare the safety and short-term efficacy of the 2 formulations. After completing the pharmacokinetic phase, patients had an option to enter a 5-month extended-use phase with their second assigned treatment.

Eligible patients were randomly assigned in a 1:1 ratio using a fixed-block randomization scheme, generated by an independent statistician before study initiation, to one of 2 sequences (Fig 1): sequence I: patients continued their current IR-Tac dose until study day 7, then switched to LCPT; sequence II: patients started on LCPT at 15% lower total daily dose than IR-Tac until study day 7, then switched to IR-Tac at its previous twice-daily dose. Each participant received the second assigned treatment from days 8 to 21. Twenty-four–hour pharmacokinetic profiles were obtained at days 7, 14, and 21. No immunosuppression dose adjustment was permitted during the pharmacokinetic phase. Patients continued concomitant immunosuppression (mycophenolate mofetil/mycophenolate sodium and corticosteroids) throughout the study per each institution's standard of care. Safety assessments were completed approximately 30 days after administration of the last study treatment for all patients. The study was reviewed and approved by the institutional review board (approval numbers: University of Pennsylvania: 818642; University of Illinois: 2014-0494; and Washington University: 201406026) in each center. This study was conducted in accordance with the Declaration of Helsinki; all participants provided informed consent.

Participants

Male or female deceased or living donor kidney recipients aged 18 to 70 years of African ancestry were invited to participate. Participants were at least 6 months posttransplantation (2 exceptions were granted: 1 patient, 5.9 months, and another, 4.7 months posttransplantation), with therapeutic tacrolimus concentrations (per center practice) on a stable IR-Tac dose and formulation. Eight patients at enrollment were taking medications known to have drug-drug interactions with tacrolimus and were required to continue the same dose of these medications (diltiazem hydrochloride, n = 1; azithromycin, n = 6; and amiodarone, n = 1) during the pharmacokinetics