Tacrolimus Formulations and African American Kidney Transplant Recipients: When Do Details Matter?

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Poorer outcomes after kidney transplantation in African Americans compared with other ethnicities have been attributed to clinical (eg, cardiovascular disease), genetic (eg, *APOL1* gene variants), and socioeconomic (eg, financial) factors.[1-3] Better understanding of the causes underlying these disparities has led to several initiatives striving to improve outcomes in African American kidney transplant recipients (KTRs).[4,5] The *CYP3A5*1* allele, known to confer faster metabolism of tacrolimus in KTRs and predominantly present in individuals of sub-Saharan African ancestry, has been shown to cause subtherapeutic exposure in African Americans, a group having higher acute rejection rates and inferior graft outcomes.[6,7] The effects of CYP3A5 on conventional twice-daily tacrolimus (IR-Tac [Prograf; Astellas Pharma US, Inc]) and extended-release once-daily tacrolimus (ER-Tac [Astagraf XL; Astellas Pharma US, Inc]) formulations in terms of exposure, dose requirements, and dose conversion ratios are well established in whites.[8,9] A randomized prospective study in which most participants were white demonstrated no clinical benefit of *CYP3A5* genotype–based IR-Tac dosing in de novo kidney transplantation.[10]

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The once-daily tacrolimus formulation referred to as LCPT (Envarsus XR; Veloxis Pharmaceuticals) has higher bioavailability by design (using the Veloxis MeltDose drug delivery technology) than IR-Tac and ER-Tac in whites, with ratios of the geometric mean values of the 24-hour area under the curve ($AUC_{0\text{-}24h}$) of 117% (90% confidence interval [CI], 107.9%-127%) and 125.7% (90% CI, 114.1%-138.5%), respectively.[11] The bioavailability of the different tacrolimus formulations has not been formally evaluated in African American KTRs, although the majority are carriers of at least 1 *CYP3A5*1* allele.[11] Hypothetically, a tacrolimus formulation with higher oral bioavailability could benefit patients who constitutionally (ie, genetically) have higher dose requirements because this phenotype has been associated with both nephrotoxicity and subtherapeutic exposure leading to acute rejection.[7,12] Direct comparative prospective studies between IR-Tac and ER-Tac or LCPT have not demonstrated meaningful differences in primary clinical end points (eg, acute rejection and graft survival) or secondary end points (eg, donor-specific anti-HLA antibody formation). In this issue of *AJKD*, Trofe-Clark et al[13] showed in a prospective randomized comparative crossover pharmacokinetic study (ASERTAA [A Study of Extended Release Tacrolimus in African Americans]) that achieving therapeutic trough concentrations (C_0) with IR-Tac in CYP3A5-expressing African American KTRs was accompanied by significantly higher peak concentrations (C_{max}), an effect that was attenuated when using the LCPT formulation.[13]

Among CYP3A5 expressors (76% of patients were carrying at least 1 *CYP3A5*1* allele), IR-Tac weight-normalized dose requirements were, as expected, higher (0.12 ± 0.05 mg/kg/d) compared with CYP3A5 nonexpressors (0.06 ± 0.02 mg/kg/d). Interestingly, IR-Tac C_{max} was significantly higher (33.9%; 90% CI, 6.2%-68.8%) in CYP3A5 expressors versus nonexpressors; this difference between *CYP3A5* genotypes was not observed during LCPT treatment. The authors applied a 1 mg to 0.85 mg dose conversion factor when switching from IR-Tac to LCPT treatment in the crossover $AUC_{0\text{-}24h}$ measurements. This conversion ratio was based on LCPT pharmacokinetic data from comparative studies in white KTRs.[14,15] Despite the preemptive dose adaptations, LCPT $AUC_{0\text{-}24h}$ was still 12.2% higher than during IR-Tac treatment, while LCPT C_{max} was 31.4% lower. These differences were observed only in KTRs carrying at least 1 *CYP3A5*1* allele. In CYP3A5 nonexpressors, the minimum concentration (C_0) was still significantly higher with LCPT than with IR-Tac, indicating that the estimated preemptive dose conversion ratio was too low. The authors found that on a milligram-to-milligram basis, LCPT oral bioavailability was 32.6% and 35.8% higher than IR-Tac in African American CYP3A5 expressors and nonexpressors, respectively.

Recently, Tremblay et al[11] established total daily dose conversion rates between IR-Tac, ER-Tac, and LCPT based on results of a 2-sequence 3-period crossover pharmacokinetics study. Although the ER-Tac dose needed augmentation by 8% when switching from IR-Tac, the daily LCPT dose needed lowering by 30% when converting from IR-Tac and by 36% when switching from ER-Tac.[11] The authors of the current *AJKD* study explain the higher bioavailability (and thus lower dose requirements) of LCPT versus IR-Tac because CYP3A4/CYP3A5 concentration in the intestinal mucosa decreases from the proximal toward distal parts of the gut, leading to slower tacrolimus metabolism in the distal gut (colon), where LCPT is mainly released from its formulation.[16] In contrast, IR-Tac is released immediately in the proximal intestine and hence metabolized faster by intestinal CYP3A4/5.[16] The lower C_{max} (and slower T_{max} [time to C_{max}]) of LCPT compared to IR-Tac fits with this hypothesis. However, in a study of healthy volunteers, when a tacrolimus solution in polyethylene glycol 400 was released at specific parts of the gastrointestinal tract (stomach, proximal and distal

small bowel, and ascending colon), tacrolimus $AUC_{0\text{-}24h}$ and C_{max} did not differ significantly between sites.[17] In physiologically based pharmacokinetic modeling, a controlled-release (CR) formulation of tacrolimus (which is classified as a BCS [Biopharmaceutics Classification System] class 2 drug [ie, low solubility and high permeability]) would have an expected absorption lower than its immediate-release formulation.[18] However, overall relative bioavailability of a CR formulation would not be affected because the fraction of the drug that escapes from first-pass metabolism in the proximal gut wall would also increase.[18] Most CR formulations therefore have decreased or unchanged relative bioavailability compared with their immediate-release counterparts, as is the case for ER-Tac. What makes LCPT different? Most likely, the biopharmaceutical characteristics of the formulation (MeltDose drug delivery technology) enable tacrolimus to very effectively circumvent proximal first-pass metabolism and allow for slower absorption in the distal gut.

How should we interpret the 33.9% higher C_{max} for IR-Tac in African American CYP3A5 expressors? Tacrolimus exposure has been implicated in infectious complications, neurologic symptoms, and reduced creatinine clearance, but in contrast to cyclosporine, not with arterial graft perfusion.[19-21] LCPT, characterized by a "flattened" $AUC_{0\text{-}24h}$ compared with IR-Tac and ER-Tac, seems to attenuate this pharmacogenetic effect in African Americans carrying at least 1 *CYP3A5*1* allele. However, the authors failed to stratify their observations according to the presence of diabetes (54% of participants had pre-existing diabetes), which can cause slower and lower peak absorption of tacrolimus. In addition, although the IR-Tac formulations used in the study were bioequivalent, small differences in dissolution characteristics and the use of corticosteroids could have affected C_{max}.[22] Whether LCPT will protect African American *CYP3A5*1* carriers from the previously mentioned adverse effects and other disadvantages (eg, posttransplantation diabetes) potentially related to a higher C_{max} remains to be determined in prospective studies. Second, intra- and interpatient variability of C_{max} was high, irrespective of *CYP3A5* genotype, which further brings into question its relevance in clinical practice. Tremor was shown to be less prevalent in patients treated with LCPT compared to IR-Tac in one study, but without notable differences in C_0 (C_{max} was not measured).[20]

Of potentially more clinical relevance are the significantly lower tacrolimus daily dose requirements for LCPT compared with IR-Tac and ER-Tac. We and others have demonstrated that high tacrolimus dose requirements in white populations are associated with histologic signs of nephrotoxicity, poor graft function, and more graft loss, even in KTRs not expressing CYP3A5.[12,23] Although other variants such as *CYP3A5*6* and *CYP3A5*7* also play a role, the *CYP3A5*1* allele still confers the largest effect on tacrolimus dose requirements in African American KTRs.[24] In contrast to whites, African American KTRs are less likely to achieve therapeutic target concentrations and have higher risk for acute rejection, but exhibit a slightly lower propensity to develop interstitial fibrosis and tubular atrophy.[7] Thus, it seems that ethnicity also determines, at least to a certain extent, the repercussions of high tacrolimus dose requirements for the graft beyond the pure pharmacogenetic effects of CYP3A5 on drug disposition.

Intrapatient variability (IPV) in tacrolimus exposure has emerged as a very important modifiable clinical determinant of graft (dys)function, (late) acute rejection, and graft loss.[25] High tacrolimus IPV has recently also been associated with the development of donor-specific anti-HLA antibodies and the progression of graft fibrosis.[26,27] IPV is a cumulative index of many variables, including medication (non)adherence, drug-drug interactions, food effects, chronobiology, gastrointestinal function, etc.[28] In a recent observational study by Taber et al,[29] tacrolimus IPV was not only shown to be higher in African American versus non–African American KTRs, but also a 10% increase in IPV augmented the risk for acute rejection by 20% in only the former. CR formulations are often developed to achieve lower peak-to-trough fluctuations and allow once-daily dosing, which can translate into better side-effect profiles and better adherence. A tacrolimus formulation that could significantly lower IPV could provide an important additional clinical benefit for patients, especially African American KTRs. For ER-Tac, small improvements in $AUC_{0\text{-}24h}$ IPV (−3.2%) have been demonstrated under controlled study conditions by Stifft et al,[8] but without changes in the concurrent IPV of corresponding C_0 values. Although Trofe-Clark et al[13] report that estimated intrapatient coefficients of variation for $AUC_{0\text{-}24h}$, C_0, and C_{max} for LCPT and IR-Tac were all <30%, comparative data between formulations, stratified per *CYP3A5* genotype, were not shown. One can deduce from the results of recent large studies, including data from African American KTRs, that tacrolimus IPV in real-life settings is even higher than observed during pharmacokinetic studies.[26,30] It will be interesting to see how the LCPT formulation performs in terms of IPV compared with IR-Tac and ER-Tac, especially because the reported differences in percent peak-to-trough fluctuation and swing have not been linked to a better clinical profile.[13]

Another unanswered question is the susceptibility of the different tacrolimus formulations to drug-drug interactions with potent CYP3A inhibitors such as azole antifungals. Theoretically, one could assume that LCPT, being absorbed in more distal parts of the gastrointestinal tract, would be less affected by CYP3A inhibitors, which act mainly in the upper parts of the gut, where CYP3A4 (and CYP3A5) are abundantly expressed and involved in first-pass metabolism.[16] Because CYP3A5 expressors are already less susceptible for the effects of CYP3A inhibitors, LCPT could potentially be of interest for KTRs not carrying a *CYP3A5*1* allele and treated with CYP3A inhibitors.[30]