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Efficacy and Safety of Once-Daily LCP-Tacrolimus Versus Twice-Daily Immediate-Release Tacrolimus in Adult Hispanic Stable Kidney Transplant Recipients: Sub-Group Analysis from a Phase 3 Trial

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Data Interpretation D
Manuscript Preparation E
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Background: The pharmacokinetics and metabolism of tacrolimus, an immunosuppressant commonly used to prevent transplant rejection, can differ in specific subpopulations. This analysis examined treatment outcomes and safety of immediate-release tacrolimus (IR-Tac) and LCP-tacrolimus (LCPT) in stable Hispanic kidney transplant recipients.

Material/Methods: This was a post hoc analysis of clinical trial data from Hispanic adult stable kidney transplant recipients randomized to remain on IR-Tac or convert from IR-Tac to a reduced dose of LCPT (NCT00817206). Composite treatment failure was evaluated at 12 months. Estimated glomerular filtration rate and tacrolimus trough concentrations were evaluated over 12 months.

Results: Fifty-five stable (LCPT n=26, IR-Tac n=29) kidney transplant recipients who self-identified as Hispanic or Latino were included in this analysis. Composite treatment failure occurred in 1 patient (4%) who converted to LCPT and 1 (3%) who remained on IR-Tac. The estimated glomerular filtration rate was stable over time and similar in the 2 treatment groups ($P=0.08$). Tacrolimus trough levels for both groups were similar over time in the 2 treatment groups ($P=0.98$). Treatment-emergent adverse events were similar in patients who converted to LCPT and in those who remained on IR-Tac.

Conclusions: Efficacy and safety were similar in Hispanic kidney transplant recipients who converted from IR-Tac to LCPT and in those remaining on IR-Tac.

Keywords: **Glomerular Filtration Rate • Graft Rejection • Kidney Transplantation • Safety • Tacrolimus**

Full-text PDF: <https://www.annalsoftransplantation.com/abstract/index/idArt/929535>



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Background

Tacrolimus, a commonly used immunosuppressive agent for preventing and treating kidney transplant rejection, has a narrow therapeutic window [1,2]. Because of this and substantial intra-patient variability in tacrolimus pharmacokinetics, individualized dosing is needed to ensure efficacy while minimizing toxicity [1-3]. Due to differences in bioavailability, dosing recommendations also differ between tacrolimus formulations, which include twice-daily immediate-release tacrolimus (IR-Tac), a once-daily extended-release capsule formulation, and a once-daily MeltDose® (LCPT) formulation [1]. For example, owing to the approximately 30% greater bioavailability of LCPT than IR-Tac [4,5], the total daily dose (TDD) must be reduced in patients who switch from IR-Tac to LCPT.

The pharmacokinetics and metabolism of tacrolimus can also differ in subpopulations with a CYP3A5*1 allele, and, for instance, can occur at a higher frequency in patients with a West African descent [6-8]. Therefore, these patients may require higher doses of tacrolimus than other individuals to achieve similar trough concentrations [6-9]. A phase 3 trial in de novo transplant recipients found that, although the rate of treatment failure did not differ between LCPT and IR-Tac in the overall population, it was lower with LCPT than IR-Tac in Black patients [10]. This difference was also found in a pooled analysis of phase 3 trials [11].

Analyses from phase 3 data were previously conducted in certain subgroups based on sex, age, and race, to assess the safety and efficacy of LCPT versus IR-tac [10,11]; however, the Hispanic population was not included in these analyses. Research among Hispanics is warranted, since this is the largest minority group in the US (18.3% in 2019) [12], and Hispanics are 1.5 times as likely as non-Hispanics to develop end-stage renal disease [13]; further, they account for an increasing proportion of adults on waiting lists for kidney transplants (20% in 2018) [14]. The CYP3A5*3 allele [15], a loss-of-function mutant [16], is known to slow tacrolimus clearance [17, 18], and the allelic frequency of CYP3A5*3 is lower in Hispanic patients than in White patients. The likelihood of a more rapid metabolism of tacrolimus in Hispanics may predispose these patients to difficulty in attaining trough levels, which can complicate treatment.

Literature currently exists on intravenous tacrolimus and oral IR-Tac, which describes pharmacokinetics, dose requirements, and treatment outcomes compared between Hispanic and non-Hispanic kidney transplant recipients [19-22]. However, dosing and outcomes for IR-Tac and LCPT have not yet been reported in Hispanic kidney transplant recipients [19]. Here, we examined the outcomes, kidney function, and safety of IR-Tac and

LCPT in Hispanic/Latino patients included in a phase 3 clinical trial of stable kidney transplant recipients.

Material and Methods

Study Design

This was a post hoc analysis of data from patients who self-identified as Hispanic or Latino in a phase 3 clinical trial in stable kidney transplant recipients (NCT00817206). The clinical trial was approved by the local health authority and Ethics Committee or Institutional Review Board and was conducted in accordance with the International Council for Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. Informed consent was obtained from all patients.

Details of the study design and overall findings were previously published [23]. Briefly, the study was a 12-month, 2-armed, parallel group, prospective, randomized, open-label, multicenter phase 3 controlled trial to establish the efficacy and safety of switching treatment from IR-Tac to LCPT in stable adult kidney transplant recipients. The study was conducted at 47 sites in the US between December 23, 2008, and February 7, 2011. Stable adult (≥ 18 years) kidney transplant recipients who received a transplant from 3 months to 5 years prior to the time of screening were eligible for enrollment if they were on a stable tacrolimus dose with tacrolimus trough levels within 4 to 15 ng/mL. A stable twice-daily tacrolimus dose was defined as that which was unchanged for ≥ 30 days at the time of screening. Patients were excluded if they had received another organ or bone marrow transplant; had an estimated glomerular filtration rate (eGFR) < 30 mL/min at screening; a white blood cell count $\leq 2.8 \times 10^9$ /L (unless the white blood cell count had been stable for at least 2 weeks); had received sirolimus or everolimus 3 months prior to enrollment; or had results that were outside of laboratory reference ranges.

Eligible patients with a stable target trough concentration of 4 to 15 ng/mL for IR-Tac at enrollment were randomized to either remain on IR-Tac or to switch from IR-Tac to LCPT for up to 12 months. For non-Black patients, initial dosing of LCPT was 0.7 times the TDD of tacrolimus being taken before conversion to account for the increased bioavailability of LCPT. For Black patients, initial dosing of LCPT was 0.85 times the TDD of tacrolimus being taken before conversion to account for the higher doses of tacrolimus needed to achieve comparable blood concentrations in Black patients [9]. During the study, tacrolimus trough concentrations were used to adjust the dose to maintain trough levels of 4 to 15 ng/mL.

Tacrolimus trough concentrations were measured by a central laboratory in whole blood samples drawn ≤ 30 min before

morning doses of study medication. Following protein precipitation of whole blood samples and solid-phase chromatography, tacrolimus concentrations were measured by reverse-phase high performance liquid chromatography-tandem mass spectroscopy. An XTerra MS C8, 2.1×100 mm, 5- μ m column (Waters, Millford, MA, USA) was used, and the mobile phase was 90:10 (v/v) methanol: 0.002 M ammonium acetate in 0.1% formic acid. Rapamycin was used as the internal standard. Detection was in positive ion mode (m/z 821.500→768.450 for tacrolimus and m/z 931.570→864.480 for rapamycin). Results were quantified using the peak area ratio method. The TDD of tacrolimus was calculated as the sum in milligrams of LCPT or IR-Tac.

Study Endpoints

The primary endpoint of this analysis was composite treatment failure, and secondary endpoints included individual components of the composite, TDD, renal function, and safety outcomes. Composite treatment failure was defined as an occurrence of one of the following within 12 months: biopsy-proven acute rejection (BPAR), death, graft loss, or loss to follow-up within 12 months after the randomization date. BPAR was assessed by a blinded central pathologist and defined as Banff grade $\geq 1A$, based on Banff 2007 criteria [24]. Renal function was estimated by eGFR using the Modification of Diet in Renal Disease 7 formula [25,26].

Safety assessments included the incidence of treatment-emergent adverse events (TEAEs), treatment-related TEAEs (in the opinion of the investigator), and post-transplant diabetes mellitus in patients without evidence of preexisting diabetes (diabetes at baseline or a medical history of diabetes, baseline fasting plasma glucose ≥ 126 mg/dL, prior use of a hypoglycemic agent or insulin for diabetes, or HbA1c $\geq 6.5\%$ before transplantation).

Statistical Analyses

This post hoc analysis was limited to patients in the trial who self-identified as Hispanic or Latino and who received at least 1 dose of study drug. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Categorical variables were compared by chi-square test, and continuous variables by analysis of variance. Composite treatment failure and individual components of it (BPAR, death, graft loss, and loss to follow-up) were compared between LCPT and IR-Tac groups by Fisher's exact test. Mean tacrolimus daily dose, trough concentrations, and eGFR over time were compared between treatment groups using a general linear model for repeated measures. The general linear model was used to evaluate treatment and the day of evaluation as independent variables, which was used to compute a P value for the interaction between these 2 variables (treatment*day). A P value

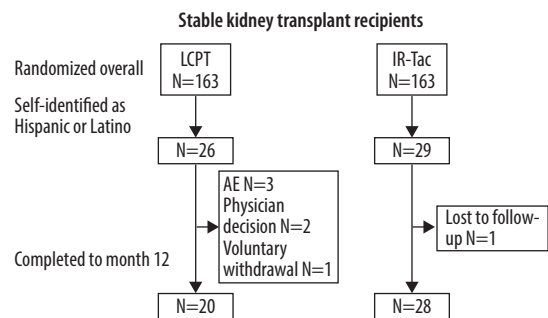


Figure 1. Patient disposition. AE – adverse event; IR-Tac – immediate-release tacrolimus; LCPT – LCP-tacrolimus.

<0.05 was considered to be statistically significant. For eGFR, timepoints after death or graft loss were assigned a value of zero. For all other outcomes, missing data were not replaced.

Results

Patients

Of the 326 patients randomized in the stable transplant recipient study, 55 self-identified as Hispanic or Latino (26 were randomized to LCPT and 29 were randomized to IR-Tac), 48 of whom completed the study (Figure 1). Baseline demographics and clinical characteristics for the study are summarized in Table 1. Briefly, most participants in the Hispanic/Latino subpopulations were men, and the average age was 46.2 ± 13.0 years. The average time between transplant to enrollment was 21.0 ± 15.6 months, and 66% received a transplanted kidney from a deceased donor. Baseline characteristics within the Hispanic subpopulation did not differ significantly between patients in the LCPT and IR-Tac groups.

TDD and Tacrolimus Trough Levels

The mean TDD of tacrolimus at enrollment was similar in patients who switched from IR-Tac to LCPT (5.79 ± 4.24 mg) and in those who remained on IR-Tac (5.45 ± 4.21 mg). In both groups, TDD decreased gradually over time: at month 12, the mean TDD had decreased to 4.26 ± 4.76 mg for patients who switched from IR-Tac to LCPT and to 4.70 ± 3.34 mg for patients who remained on IR-Tac (Figure 2A). The trends in TDD over time did not significantly differ between the LCPT and IR-Tac groups ($P=0.94$). Tacrolimus trough levels for both groups were also similar over time in the 2 treatment groups ($P=0.98$) (Figure 2B), and there were no significant trends over the 12-month study period ($P=0.84$) (Figure 2C).

Table 1. Within each study, no significant differences were detected between Hispanic/Latino patients in the LCPT and IR-Tac groups.

Characteristic	Switched to LCPT	Remained on IR-Tac	Total	P-value
	N=26	N=29	N=55	
Age (years), mean (SD)	44.1 (12.6)	48.1 (13.2)	46.2 (13.0)	0.25
Male, n (%)	20 (77)	22 (76)	42 (76)	0.93
Body mass index (kg/m ²), mean (SD)	29.2 (6.0)	27.8 (5.9)	28.5 (5.9)	0.81
Deceased donor, n (%)	17 (65)	19 (66)	36 (66)	0.99
Diabetes at time of transplant, n (%)	12 (46)	9 (31)	21 (38)	0.25
Panel reactive antibody, n (%)				0.80
<5%	14 (54)	15 (52)	29 (53)	
5-20%	4 (15)	4 (14)	8 (15)	
>20%	3 (12)	6 (21)	9 (16)	
Missing	5 (19)	4 (14)	9 (16)	
Previous kidney transplant, n (%)	1 (4)	3 (10)	4 (7)	0.35
Time of transplant to enrollment (months), mean (SD)	24.3 (17.7)	18.1 (13.0)	21.0 (15.6)	0.14

IR-Tac – immediate-release tacrolimus; LCPT – LCP-tacrolimus; SD – standard deviation.

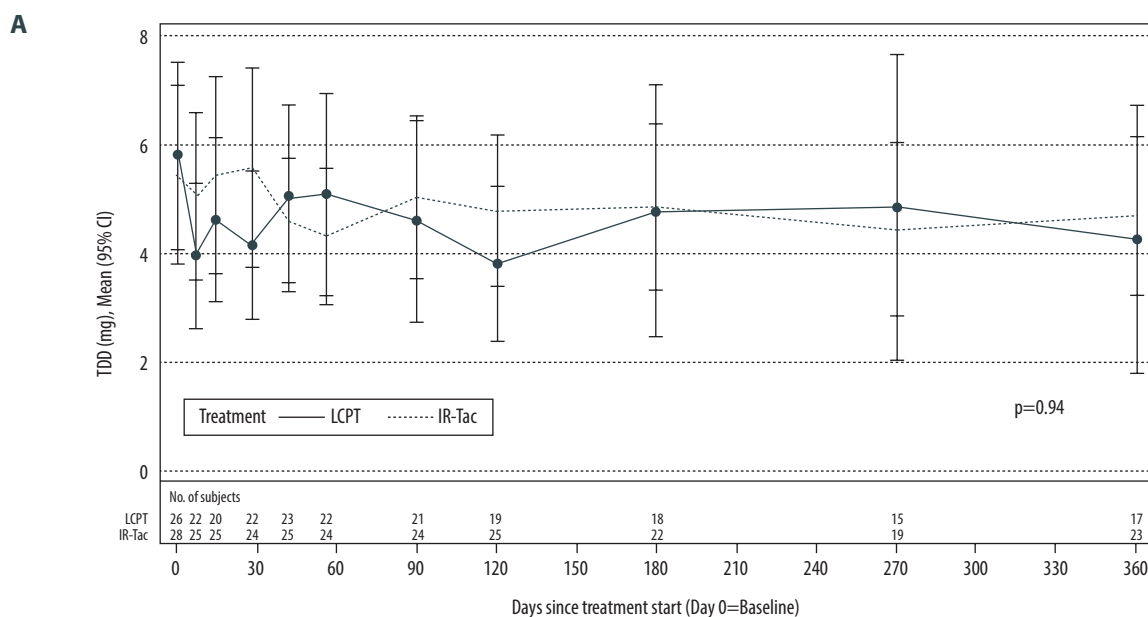
Renal Function

Renal function, approximated using the eGFR, changed little and was similar over time in the 2 treatment groups ($P=0.08$) (Figure 3).

Efficacy Outcomes

Treatment failure occurred in 1 (4%) Hispanic/Latino patient in the LCPT group, due to BPAR, and in 1 (3%) in the IR-Tac

group, due to loss to follow-up (Table 2). One LCPT patient experienced a grade 1B acute cellular rejection episode at study day 57 with a tacrolimus concentration of 3.4 ng/mL just prior to BPAR diagnosis; 1 IR-Tac patient was lost to follow-up at 357 days after randomization. A forest plot depicting composite treatment failure and individual efficacy endpoints for LCPT versus IR-Tac among Hispanic and non-Hispanic groups is shown in the Supplementary Figure 1.



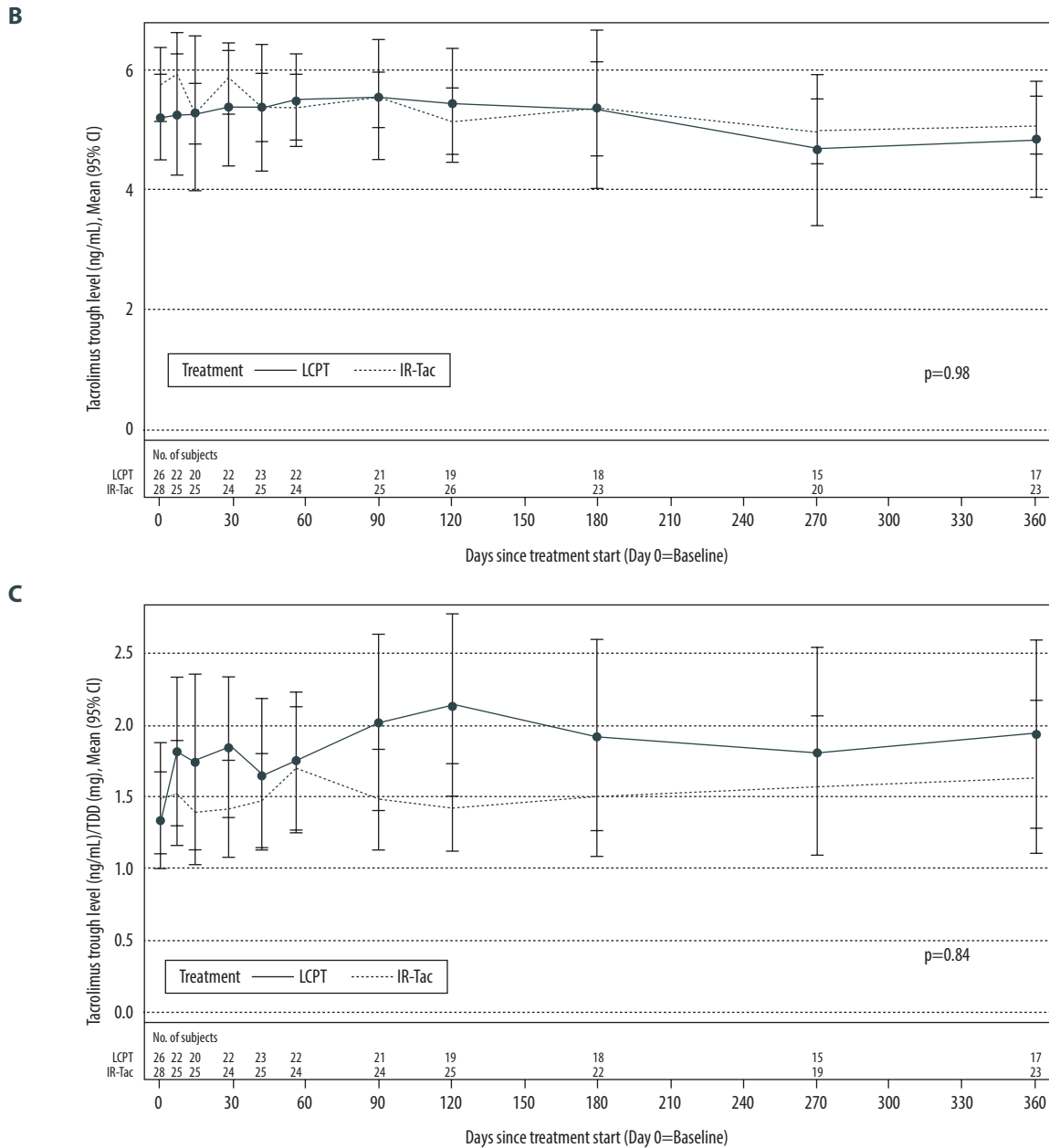


Figure 2. TDD (A), tacrolimus trough concentration (B), and the ratio of tacrolimus trough concentration to TDD (C) in Hispanic/Latino stable kidney transplant recipients. *P* values were calculated by general linear model for fixed effect of treatment×time. CI – confidence interval; IR-Tac – immediate-release tacrolimus; LCPT – LCP-tacrolimus; TDD – total daily dose.

Safety

Drug-related TEAEs were reported for 7 Hispanic/Latino patients (27%) in the LCPT group and 4 (14%) in the IR-Tac group. The most common drug-related TEAEs were urinary tract infection (n=1 [4%] LCPT, n=2 [7%] IR-Tac), diarrhea (n=1 [4%] LCPT, n=1 [3%] IR-Tac), and increased serum creatinine (n=1 [4%] LCPT, n=1 [3%] IR-Tac) (Table 3). In patients without a prior history

of diabetes, post-transplant diabetes mellitus occurred in 0% (0/13) of patients in the LCPT group and 6% (1/18) of patients in the IR-Tac group. No deaths or malignancies occurred in either treatment group.

According to the study investigators, 3 patients on LCPT discontinued for the following reasons: intubation prevented

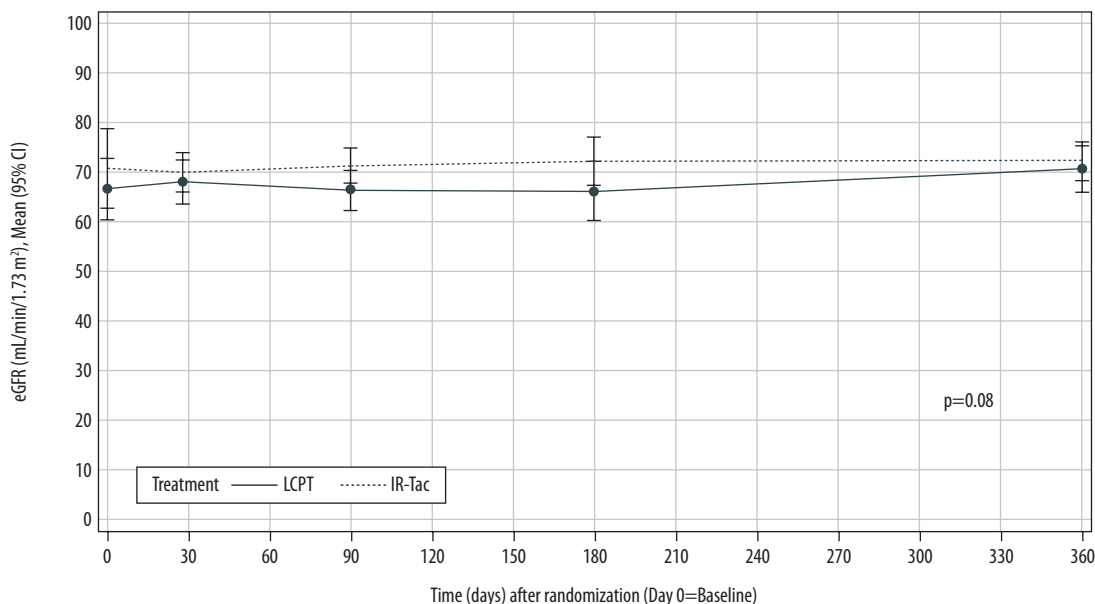


Figure 3. Renal function in Hispanic/Latino stable kidney transplant recipients. eGFR – estimated glomerular filtration rate; IR-Tac – immediate-release tacrolimus; LCPT – LCP-tacrolimus.

Table 2. Rates of treatment failure at 12 months.

Outcome	Switched to LCPT	Remained on IR-Tac	P-value*
	N=26	N=29	
Composite treatment failure, n (%)	1 (4)	1 (3)	1.0000
Treatment failure due to:			
BPAR n (%)	1 (4)	0	0.4727
Death, n (%)	0	0	–
Graft failure, n (%)	0	0	–
Lost to follow up, n (%)	0	1 (3)	1.0000

BPAR – biopsy-proven acute rejection; IR-Tac – immediate-release tacrolimus; LCPT – LCP-tacrolimus. * P values were calculated by Fisher's exact test.

administration of oral medications (1), mild tacrolimus toxicity (1), and acute rejection (1).

Discussion

Hispanics are at higher risk than non-Hispanics for developing kidney failure [13] and are therefore more likely to require kidney transplantation. The current analysis showed that treatment failure rates, kidney function, and safety were similar in Hispanic kidney transplant recipients that either converted from IR-Tac to LCPT or remained on IR-Tac. This aligns with results from the full population from the same trial [23] and in the full population in a trial in de novo kidney transplant

recipients [10,11]. Further, new post-transplant diabetes mellitus, an infrequent but serious adverse effect associated with tacrolimus [27], was not observed in Hispanic transplant recipients who converted to LCPT. These differences in development of new-onset diabetes after transplantation were not significantly different between the 2 groups.

Owing to the greater bioavailability of LCPT than IR-Tac, a reduced TDD is usually observed in patients who convert from IR-Tac to LCPT. A recent retrospective study of stable kidney recipients who switched from IR-Tac to LCPT found 34% greater bioavailability of LCPT [5]. Similarly, a randomized clinical trial in de novo kidney transplant recipients found 30% greater bioavailability for LCPT [4]. In the current study, to account

Table 3. Fisher's exact test was performed to compare the proportion of patients who either did or did not experience the adverse event.

Event, n (%)	Switched to LCPT	Remained on IR-Tac
	N=26	N=29
Urinary tract infection	1 (4)	2 (7)
Diarrhea	1 (4)	1 (3)
Blood creatinine increased	1 (4)	1 (3)
Anemia	1 (4)	0
Drug level increased	1 (4)	0
Dyspepsia	1 (4)	0
Hyperkalemia	1 (4)	0
Leukopenia	1 (4)	0
Nausea	1 (4)	0
Nephropathy toxic	1 (4)	0
Oral candidiasis	0	1 (3)
Renal function test abnormal	1 (4)	0
Urosepsis	0	1 (3)
Vomiting	1 (4)	0

IR-Tac – immediate-release tacrolimus; LCPT – LCP-tacrolimus.

for the greater bioavailability of LCPT, conversion to LCPT occurred at 0.7 to 0.85 times that of the IR-tac dose taken prior to conversion. This resulted in similar tacrolimus trough concentrations in the LCPT and IR-Tac treatment groups throughout the study.

Although the current study did not determine the frequency of CYP3A5*1 and CYP3A5*3 alleles occurring in transplant recipients, other studies have examined tacrolimus dose requirements in Mexican patients with these polymorphisms. CYP3A5*1, the wild-type allele, occurs in 25% of Hispanic patients [28] and these individuals may require a higher dose of tacrolimus [21]. For instance, the median dose of tacrolimus

0.16 mg/kg/day was required for patients with the CYP3A5*1*1 genotype, and the median dose of 0.07 mg/kg/day was needed for patients with CYP3A5*3*3 [21]. Compared to non-Hispanic patients, over half of Mexican renal patients (N=291) had the CYP3A5*3*3 genotype and required a lower tacrolimus dose than did patients with the CYP3A5*1 allele. Further research is needed to confirm these results in Hispanic/Latino kidney transplant recipients to guide dosing practices among clinicians.

This study has some limitations. The study included a small sample of transplant recipients who were stable at 2 years after transplantation, and the small sample limited the ability to detect differences and make inferences; however, the current study suggests that Hispanic kidney transplant recipients can be safely converted from LCPT to IR-Tac. This study did not compare Hispanic/Latino patients with non-Hispanic subpopulations, and patients were included in the analysis based on self-reported Hispanic/Latino ethnicity. However, these limitations should not have affected the conclusions of this study. Of the small numbers of patients, 5 IR-Tac and 3 LCPT patients were missing tacrolimus levels at several of the later timepoints, and the study did not assess the potential effects of genetic (CYP3A5 alleles) factors, although they are known to impact outcomes in patients treated with tacrolimus. Future research may include conducting a study with genotyping among a larger sample of Hispanic transplant recipients to further explain tacrolimus dose requirements.

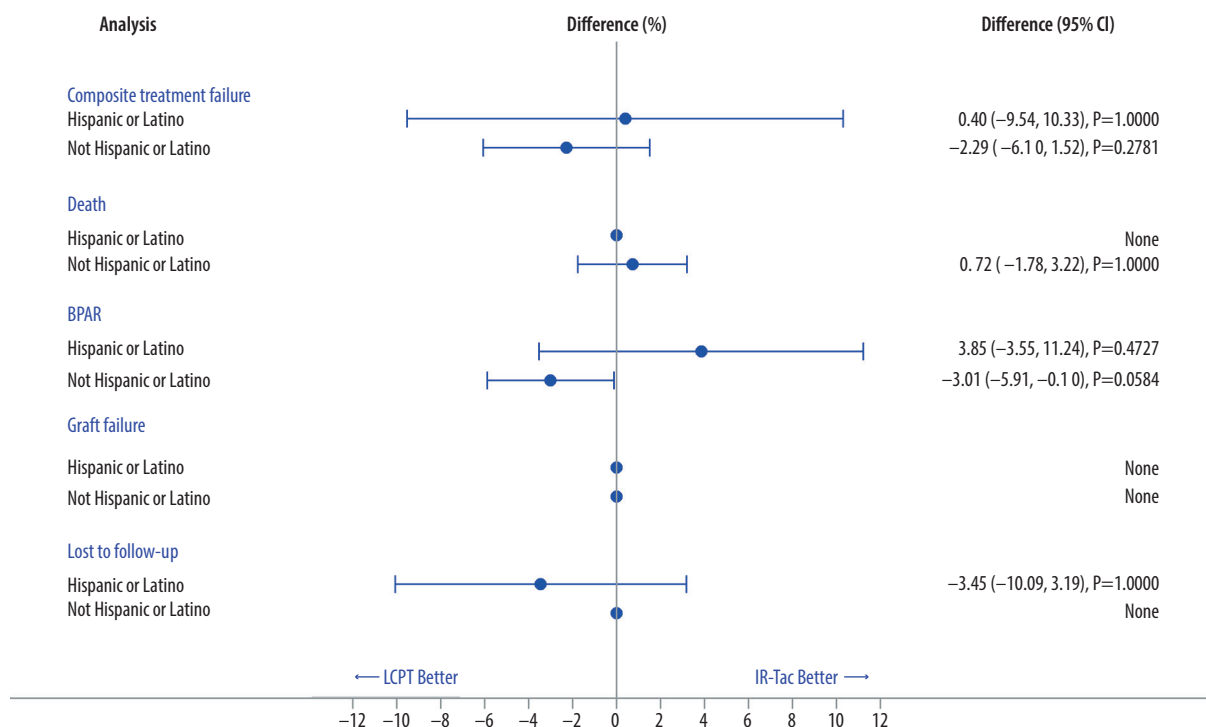
Conclusions

In conclusion, this post hoc analysis suggested that in stable Hispanic/Latino kidney transplant recipients, switching from LCPT is as effective and safe as remaining on IR-Tac for preventing treatment failure. This information should help guide clinicians on switching their kidney transplant recipients from twice-daily IR-Tac to once-daily LCPT.

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Supplementary Data



Supplementary Figure 1. Comparison of efficacy endpoints in Hispanic and non-Hispanic kidney transplant recipients 12 months after treatment randomization.

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