Received: 1 June 2021 | Revised: 27 August 2021 | Accepted: 8 September 2021

DOI: 10.1111/ctr.14487

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
WILEY

ORIGINAL ARTICLE

De novo tacrolimus extended-release tablets (LCPT) versus twice-daily tacrolimus in adult heart transplantation: Results of a single-center non-inferiority matched control trial

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Funding information
Veloxis Pharmaceuticals

Abstract

Extended-release tacrolimus for prophylaxis of allograft rejection in orthotopic heart transplant (OHT) recipients is currently not FDA-approved. One such extended-release formulation of tacrolimus known as LCPT allows once-daily dosing and improves bioavailability compared to immediate-release tacrolimus (IR-tacrolimus). We compared the efficacy and safety of LCPT to IR-tacrolimus applied *de novo* in adult OHT recipients. Twenty-five prospective recipients on LCPT at our center from 2017 to 2019 were matched 1:2 with historical control recipients treated with IR-tacrolimus based on age, gender, and baseline creatinine. The primary composite outcome of death, acute cellular rejection, and/or new graft dysfunction within 1 year was compared using non-inferiority analysis. LCPT demonstrated non-inferiority to IR-tacrolimus, with a primary outcome risk reduction of 20% (90% CI: -40%, -.5%; non-inferiority $P = .001$). Tacrolimus trough levels peaked at 2–3 months and were higher in LCPT (median 14.5 vs. 12.7 ng/ml; $P = .03$) with similar dose levels (LCPT vs. IR-tacrolimus: .08 vs. .09 mg/kg/day; $P = .33$). Cardiovascular-related readmissions were reduced by 62% ($P = .046$) in LCPT patients. The complication rate per transplant admission and all-cause readmission rate did not differ significantly. These results suggest that LCPT is non-inferior in efficacy to IR-tacrolimus with a similar safety profile and improved bioavailability in OHT.

KEYWORDS
calcineurin inhibitor, tacrolimus, clinical trial, heart (allograft) function/dysfunction, immunosuppressant, patient survival

1 | INTRODUCTION

Calcineurin inhibitors remain the backbone of maintenance immunosuppressive regimens to prevent donor organ loss to rejection following heart transplantation.[1] Tacrolimus is the most common calcineurin inhibitor used, with approximately 80% of all orthotopic heart transplant (OHT) recipients continuing on tacrolimus at 1 year post-transplantation.[2] Currently, immediate-release tacrolimus (IR-tacrolimus) is the only FDA-approved tacrolimus formulation for the prophylaxis of organ rejection post-OHT and is dosed twice daily.[3,4]

Poor bioavailability, high intra- and inter-patient variability, and need for multiple daily dosing remain a challenge with IR-tacrolimus.[5–8] Recently, once-daily formulations have been achieved in the form of extended-release tacrolimus capsules (ER-tacrolimus; commercial names Astagraf XL and Advagraf, Astellas Pharma, Northbrook, IL, USA) as well as LCPT (Envarsus and Envarsus XR, Veloxis Pharmaceuticals, Cary, NC, USA). Through simplified dosing, once-daily formulations have offered the potential to improve medication adherence. Both have demonstrated non-inferiority in efficacy and safety in kidney transplantation for *de novo* use and conversion from IR-tacrolimus.[9–13] Important pharmacokinetic differences exist between them. ER-tacrolimus exhibits a similar pharmacokinetic profile to IR-tacrolimus, including comparable 24-h area under the curve and maximum concentration.[14] In *de novo* kidney recipients, ER-tacrolimus led to higher mean daily doses to achieve similar troughs compared to IR-tacrolimus and displayed high intra- and inter-patient variability. In contrast, LCPT is formulated by controlled agglomeration,[15] which enhances the bioavailability of medications with poor water solubility by reducing the particle size and delays drug release throughout the gastrointestinal tract, with complete disintegration in the distal tract. Pharmacokinetic studies in kidney and liver transplant recipients have demonstrated longer times to peak, lower peak concentrations, reduced peak-to-trough fluctuations, minimized diurnal variation, and up to 30% decrease in total daily dose requirement to achieve similar area under the curve exposure with LCPT compared to IR-tacrolimus.[11,12,16] LCPT minimizes the pharmacogenomic impact of CYP3A5 expression on Tacrolimus peak level in African-American renal transplant recipients, with a similar drug exposure and lower total daily dose requirement relative to IR-tacrolimus independent of CYP3A5 expression.[17] Studies have also suggested improvement in safety, including neurotoxicity, likely related to lower peak concentrations associated with LCPT.[18]

Studies evaluating once-daily tacrolimus in OHT are limited to ER-tacrolimus and suggest comparable outcomes to IR-tacrolimus.[19–21] Despite its pharmacokinetic profile, currently there is no readily available published data on LCPT in *de novo* OHT.[19,22–25] In the interim since our trial was completed, transitions from IR-tacrolimus to LCPT has been described.[26] The purpose of this study is to evaluate the efficacy and safety of *de novo* LCPT compared to IR-tacrolimus at 1 year post-OHT using non-inferiority analysis.

2 | MATERIALS AND METHODS

2.1 | Study design and patient inclusion

This was a Phase II, single-center, open-label trial with a prospective LCPT interventional cohort (enrolled between December 2017 and January 2019) and matched IR-tacrolimus retrospective control cohort. Upon written informed consent, patients aged ≥18 years listed for OHT at Baylor University Medical Center (Dallas, TX, USA) were offered enrollment into the LCPT arm (ClinicalTrials.gov NCT03373227) if able to comply with the medication regimen and not enrolled in another interventional trial or taking rapamycin or cyclosporine. Patients in the IR-tacrolimus (standard-of-care) arm were retrospectively selected from OHT recipients at the same center during January 2017 to January 2019 and who met the same inclusion/exclusion criteria as the LCPT arm. Given the retrospective nature of the control arm, written informed consent was waived for these patients. The study protocol and informed consent form were approved by the Institutional Review Board of Baylor Scott and White Health Research Institute.

2.2 | Study medication

Given the risk of early renal dysfunction in OHT, an amendment was implemented on December 11, 2017 to reduce the starting dose in the LCPT arm from .17 mg/kg/day (implemented for a single patient) to .01–.02 mg/kg/day for the remainder of the trial. Dosing was scheduled in the morning followed by up-titration when able based on renal function to the institution's standard-of-care trough goals of 10–15 ng/ml in the first 3 months and 6–12 ng/ml between 3 months and 1 year. IR-tacrolimus was administered as two divided doses starting at .01–.02 mg/kg/day, allowing for provider discretion, and titrated to aforementioned target levels. Additionally, patients received 500 mg mycophenolate mofetil twice daily per protocol if ≥60 years of age or weighing < 60 kilograms; otherwise 1000 mg twice daily, except in patients with high-risk cytomegalovirus (CMV) mismatch (CMV donor-positive, recipient-negative serostatus) for whom azathioprine 1 mg/kg/day was prescribed. Corticosteroids were administered as 1000 mg intravenous methylprednisolone intra-operatively, followed by 125 mg every 8 h for three doses and subsequently a weight-based oral prednisone taper. Patients underwent complete steroid withdrawal per protocol by 6 months, unless required for underlying sarcoid or rejection events. Choice of antibody induction was driven by local protocol according to immunological risk category (Table S1). Specifically, no induction in low-risk groups, basiliximab in moderate risk and renal sparing groups, and anti-thymocyte globulin in high-risk groups were given. Local protocols do not include any interacting medications with agents in the immunosuppression regimen.

2.3 | Data collection and definitions

Data were extracted from electronic health records and institutional database of transplant patients. Demographics and baseline comorbidities in were collected at a pre-transplant baseline visit. Baseline labs were recorded within 1 day pre-transplant. eGFR (CKD-EPI) was collected at baseline and 1-year post-transplant. Predicted heart mass (pHM) was calculated accounting for height, weight, age, and gender.[27] Tacrolimus whole-blood trough concentrations were measured as part of standard-of-care visits and at physician discretion. Dose titration of tacrolimus during transplant admission and each subsequent outpatient prescription change were recorded as a total daily dose normalized using bodyweight at transplant. Inpatient readmissions within 1 year post-transplant were classified as cardiovascular-related (Table S2) and all-cause.

Routine standard-of-care visits for the first year post-transplant were scheduled twice-weekly for 4 weeks, then weekly for 2 weeks, then bi-weekly up to 6 months, then monthly to the end of 1-year. Endomyocardial biopsies were performed to assess for rejection per protocol. Graft function was assessed by transthoracic echocardiogram before hospital discharge, at 6–8 weeks and 1 year post-transplant.

2.4 | Primary efficacy outcome

The primary outcome was the composite of all-cause mortality, acute cellular rejection (ACR), and/or new graft dysfunction (NGD) within 1 year post-transplant. Relevant ACR was defined as a grade ≥2R according to the ISHLT-2004 scale,[28] and NGD as a left ventricular ejection fraction (EF) ≤50%, and/or > 20% decrease in EF between two subsequent 2-D echocardiograms 6 weeks to 1 year post-transplant. Antibody-mediated rejection (AMR) defined as AMR ≥ pAMR1, per ISHLT-2013 AMR scale,[29] did not occur in either group of this study.

2.5 | Safety outcomes

Unique complications occurring during the transplant index hospitalization until discharge or transfer were categorized (Table S3) to compare the study safety profiles. Adverse events were recorded prospectively for the study group up to 1 year post-transplant and reviewed by the principal investigator for relatedness to the study drug, severity and categorized as specified in Table S3.

2.6 | Non-inferiority margin

The historical event rate for the composite outcome within 1 year is 38.7% (86/222, 95% Confidence Interval: .32, .46) at our center from 2014 to 2016. The non-inferiority margin was specified pre-analysis as a 40% increase in the historic event rate or, in absolute terms, a margin of 15.5% (38.7% · .4).

2.7 | Power and sample size

Assuming a 10% reduction in the primary composite outcome in LCPT (p_1) compared to IR-tacrolimus (p_0), 75 patients were required with a 2:1 match of IR-tacrolimus to LCPT in order to achieve at least 70% power to detect non-inferiority based on a 95% upper one-sided confidence interval on $p_1 - p_0 < 15.5\%$.

2.8 | Matched control group

For the control arm, nearest-neighbor Mahalanobis distance matching was performed with a 2:1 match of control patients to LCPT patients on gender, age, and pre-transplant creatinine levels as traditional baseline medical condition modification factors.[30] The mean ± standard deviation of paired differences were 0 ± 2 years and .02 ± .27 mg/dl (Figure S1). Matching was implemented using MatchIt in R (version 3.6.1).[31]

2.9 | Statistical analyses

Patient characteristics and outcome measures were reported as means ± standard deviations or medians [quartiles], if skewed, and categorical variables as percentages. Comparisons between study arms were performed using t-tests (Wilcoxon Rank-Sum tests if skewed) for continuous variables, and Chi-Square (Fisher's Exact tests if expected cell counts < 5) for categorical variables.

Non-inferiority in the primary composite outcome was assessed using a Farrington-Manning test based on achieving a one-sided 95%-upper bound (equivalently 90% two-sided) on the difference in proportions comparing LCPT to IR-tacrolimus less than the 15.5% non-inferiority margin.[32] If non-inferiority was achieved, superiority was assessed using a 95% two-tailed confidence interval. A post-hoc analysis of the primary composite outcome by African American race and diabetes mellitus was performed.

Tacrolimus whole-blood troughs were defined as the minimum measurement in a calendar day. An average trough level and average daily dose were calculated for each patient weekly for the first month, then months 2–3, 4–5, and 6–12. The number of Tacrolimus measurements per patient is depicted in Figure S2. The concentration-to-dose ratio was calculated by dividing the patient average tacrolimus trough by daily dose per kilogram. The average number of dose changes per transplant admission day was calculated using the transplant length of stay and average number of outpatient dose changes per patient month using the number of months in follow-up post-transplant. Adverse and Serious Adverse Events (AEs/SAEs) for the LCPT arm were reported descriptively as the number observed and percentage with a suspected relation to the study. The incidence rate ratio (IRR) of complications per transplant-admission and IRR of readmissions per person year (ppy) were estimated with Robust Poisson regression. Kaplan-Meier curves for time to event outcomes were compared using a log-rank test and the hazard ratio estimated using a Cox-proportional hazards model if at least one event occurred in each group. The proportional hazards

assumption was appropriate (Figure S3). Patients were censored at 366 days post-transplant with no loss to follow-up for the study duration.

Statistical tests were evaluated two-sided at a .05 significance threshold with the exception of the non-inferiority analysis, which was calculated one-sided at a .05 threshold. Analyses were performed using R (version 3.6.1 and 4.0.2) and SAS (version 9.4).

3 | RESULTS

In total, 75 OHT recipients were included (50 on IR-tacrolimus retrospectively matched as controls to 25 prospectively enrolled in the LCPT treatment arm). Baseline demographics and clinical characteristics were similar between the groups, except fewer African Americans and patients with diabetes mellitus in the LCPT arm (Table 1). Patients were 80% male with a mean recipient age of 58.7 years, donor age of 34.2 years and BMI of 28.9 kg/m^2. The LCPT arm included two (8%) African Americans and seven (28%) patients with diabetes mellitus relative to 14 (28%) and 21 (42%) in the IR-tacrolimus arm. Other baseline comorbidities that were prevalent in more than a third of the patients included hypertension (69%) and renal disease (52%).

3.1 | Primary composite outcome

The primary outcome of death and/or transplant rejection occurred in 5/25 (20%) patients on LCPT compared to 20/50 (40%) in the control group (risk difference -20%, Figure 1). The 90%-confidence interval on the risk difference spanned from -40% to -.5%, and hence, its upper bound was less than the non-inferiority margin of 15.5%, indicating that LCPT is non-inferior to IR-tacrolimus for the composite outcome (non-inferiority $P = .001$). Despite a non-significant absolute risk reduction of 20% (95%-CI: -41%, 1%) and relative risk reduction of 50% (95%-CI: .21, 1.17) in the composite outcome, superiority was not achieved ($P = .08$).

3.2 | The primary composite outcome by subgroups

When broken down by demographics, the risk difference observed for the primary composite outcome favored LCPT relative to IR-tacrolimus in non-African Americans (-29.8%, 90%-CI: -51%, -8.5%; non-inferiority $P < .001$; Figure S4) and non-diabetes mellitus patients (-23.4%, 90%-CI: -42%, 0%; non-inferiority $P = .002$). There were two African Americans enrolled in the LCPT arm of which one experienced the composite outcome. In the IR-tacrolimus arm, 3/14 (21%) African Americans experienced the composite outcome which was lower relative to the overall event rate of 40% in this treatment arm. In subjects with diabetes mellitus, 3/7 (43%) in the LCPT arm and 10/21 (48%) in the IR-tacrolimus arm experienced the composite outcome.

TABLE 1 Baseline characteristics at transplant

Variables	Study group: BID IR-Tac ($n = 50$)	Study group: Daily LCPT ($n = 25$)	*P*-value
Patient characteristics			
Age (year) [a]	58.8 (8.4)	58.5 (8.7)	.88
BMI (kg·m^{-2})	29.0 (5.0)	28.6 (5.0)	.71
Ethnicity/race			.15
Asian	1 (2%)	1 (4%)	
Black or African American	14 (28%)	2 (8%)	
Hispanic/Latino	3 (6%)	3 (12%)	
White	32 (64%)	19 (76%)	
Gender, male [a]	40 (80%)	20 (80%)	1.00
Heart failure CM etiology			.76
Ischemic	18 (36%)	12 (48%)	
Congenital	1 (2%)	1 (4%)	
Dilated	27 (54%)	11 (44%)	
Hyper-trophic/restrictive	2 (4%)	1 (4%)	
Other	2 (4%)	0 (0%)	
Prior sternotomy	18 (36%)	11 (44%)	.68
Comorbidities			
Diabetes mellitus	21 (42%)	7 (28%)	.35
Hypertension	36 (72%)	16 (64%)	.66
Renal disease	27 (54%)	12 (48%)	.81
Baseline labs			
Creatinine (mg/dl) [a]	1.3 (.3)	1.3 (.4)	.85
eGFR (ml/min/1.73 m^2)	65 [49, 80]	59 [53, 70]	.70
Sodium (mEq/L)	138 [135, 139]	137 [136, 139]	.91
BUN (mg/dl)	21 [17, 25]	21 [16, 27]	.73
Transplant factors			
Donor age (y)	34.2 (10.8)	34.2 (10.7)	.98
Gender mismatch	16 (32%)	7 (28%)	.93
pHM mismatch (%) [b]	1.2 [-9.2, 11.5]	-.7 [-8.8, 5.3]	.40
VAD at transplant	9 (18%)	7 (28%)	.49
Positive retrospective crossmatch	5 (10%)	4 (16%)	.47
DSA at transplant	8 (16%)	6 (24%)	.53
Total ischemic time (min)	184 (53)	180 (62)	.78
Warm ischemic time (min)	53 (13)	53 (11)	.93
Length of stay (d)	17 [9, 29]	13 [10, 25]	.69
CMV status at transplant			.77
D-/R-	5 (10%)	2 (8%)	

(Continues)

TABLE 1 (Continued)

Variables	Study group: BID IR-Tac ($n = 50$)	Study group: Daily LCPT ($n = 25$)	*P*-value
D-/R+	7 (14%)	6 (24%)	
D+/R-	11 (22%)	5 (20%)	
D+/R+	27 (54%)	12 (48%)	
Immunosuppression induction			.65
None	40 (80%)	22 (88%)	
Basiliximab	8 (16%)	3 (12%)	
Antithymocyte globulin	2 (4%)	0 (0%)	
TAC starting dose (mg/kg)	.02 [.01, .04]	.02 [.02, .02]	.48
Time to first dose (d)	2 [1, 3]	2 [2, 2]	.81

Variable summaries are reported as mean (standard deviation), median [quartiles] or absolute counts (%).

Abbreviations: BID, twice-daily; BMI, Body Mass Index; BUN, Blood urea nitrogen; CM, Cardiomyopathy; CMV, Cytomegalovirus; D-, Donor Negative; D+, Donor Positive; DSA, Donor-Specific Antibodies; eGFR, Estimated Glomerular Filtration Rate based on CKD-EPI formula; PHM, Predicted Heart Mass; R-, Recipient Negative; R+, Recipient Positive; TAC, Tacrolimus; VAD, Ventricular Assist Device.

[a]Control group matching variables.

[b]Predicted Heart Mass (pHM) mismatch calculated as (recipient pHM – donor pHM) / recipient pHM * 100.

3.3 | Risk of mortality and transplant rejection or graft failure (ACR≥2, AMR > 0 or NGD)

No deaths were observed for the LCPT group, whereas seven (14%) patients died in the control group within 1 year post-transplant (Table 2). Of the seven deaths, four occurred during the transplant admission, four experienced acute kidney injury or renal failure, and two were preceded by ACR≥2 or NGD (Table 3). The mortality rate ($P = .09$) and Kaplan-Meier survival curves were not significantly different (log-rank $P = .053$). Incidence of ACR≥2R was lower in LCPT compared to control (12% vs. 24%; $P = .36$) as was NGD rates (8% vs. 14%; $P = .71$). However, these reductions were not statistically significant. No patients developed AMR in either group. The risk of transplant rejection or graft failure (ACR/NGD) did not differ significantly (LCPT vs. IR-tacrolimus HR .61, 95%-CI: .22, 1.69). Adherence problems were recorded in two IR-Tac patients that experienced rejection. At 1-year, seven patients (six IR-Tac, one LCPT) remained on steroids for rejection or underlying autoimmune conditions such as sarcoidosis.

3.4 | Tacrolimus trough levels, doses, and dose changes

The median tacrolimus starting dose was .02 mg/kg with a median of 2 days to initiation in both groups (Table 1). The median tacrolimus trough level was 4.2 ng/ml during the first week post-transplant in both groups (Figure 2A and Table 4). Similar therapeutic levels were maintained between weeks 2–4 ($P = .11$) with a median dose of .07 and .08 mg/kg/day for LCPT and IR-tacrolimus, respectively. Tacrolimus levels peaked during months 2–3 with increased levels in

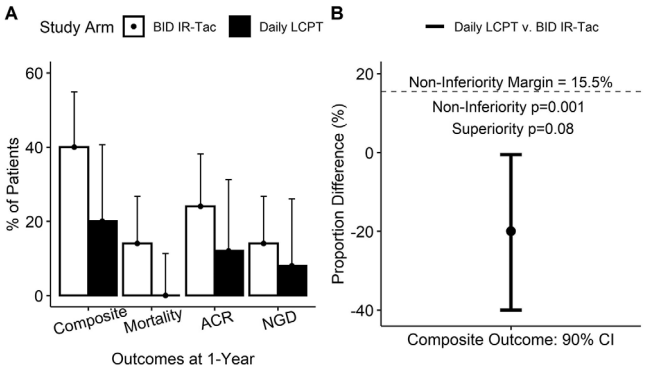

FIGURE 1 Outcomes at 1-year post-transplant. (A) The proportion of patients by study arm experiencing the primary composite outcome and each individual sub-component. Error bars indicate the 95% two-sided Clopper-Pearson Confidence intervals. (B) The error bar indicates the 90% two-sided Farrington-Manning confidence interval on the difference in proportions of the composite outcome comparing daily LCPT to BID IR-Tac. Non-inferiority is established with the upper bound below the non-inferiority margin of 15.5%. ACR, Acute cellular rejection; AMR, antibody-mediated rejection; BID, twice-daily; IR-Tac, immediate release tacrolimus; NGD, new graft dysfunction

TABLE 2 Outcomes at 1-year post-transplant

Outcomes	Study group: BID IR-Tac (n = 50)	Study group: Daily LCPT (n = 25)	*P*-value
AMR (Grade > 0)	0 (0%)	0 (0%)	1.00
Composite	20 (40%)	5 (20%)	.14
ACR≥2R	12 (24%)	3 (12%)	.36
NGD	7 (14%)	2 (8%)	.71
Vital status, expired	7 (14%)	0 (0%)	.09
Dose change per transplant admission day	.5 [.4, .6]	.4 [.3, .6]	.56
Outpatient dose change per month	.7 [.5, .8]	.6 [.5, .8]	.82
Steroid withdrawal [a]	37 (86%)	24 (96%)	.25
eGFR (ml/min/1.73 m^2) [b]	52 [36, 72]	52 [39, 64]	.51
< 15 ml/min/1.73 m^2 [b]	1 (2%)	0 (0%)	1.00

Variable summaries are reported as mean (standard deviation), median [quartiles] or absolute counts (%).

Abbreviations: ACR, Acute cellular rejection; AMR, antibody-mediated rejection; BID, twice-daily; eGFR, Estimated Glomerular Filtration Rate based on CKD-EPI formula; NGD, new graft dysfunction; TAC, Tacrolimus.

[a]Percentage calculated out of the number of patients alive at 1-year of $n = 43$ (IR-Tac) and $n = 25$ (LCPT).

[b]eGFR at 1-year was assessed in $n = 43$ (IR-Tac) and $n = 25$ (LCPT) patients.

TABLE 3 Causes of death in the IR-Tac group

Cause of death	Death during transplant admission	ACR≥2 or NGD	AKI or acute renal failure
Septic shock	Yes	No	No
Septic shock due to mycobacterium avium with biventricular graft dysfunction requiring VA ECMO	No	NGD	Yes
Biventricular PGD	Yes	No	No
PGD-RV with septic shock due to ischemic sigmoid colon	No	No	Yes
PGD-RV with acute renal failure and vancomycin resistant enterococcal bacteremia	Yes	No	Yes
Hemorrhagic shock following chest tube placement for hemothorax with acute pneumonia and acute respiratory failure with intubation	Yes	No	No
Cause unknown with expiration at home	No	ACR≥2	Yes

Abbreviations: ACR, acute cellular rejection; AKI, acute kidney injury; NGD, new graft dysfunction; PGD, primary graft dysfunction; PGD-RV, Right-ventricular PGD; VA ECMO, Veno-Arterial Extracorporeal Membrane Oxygenation.

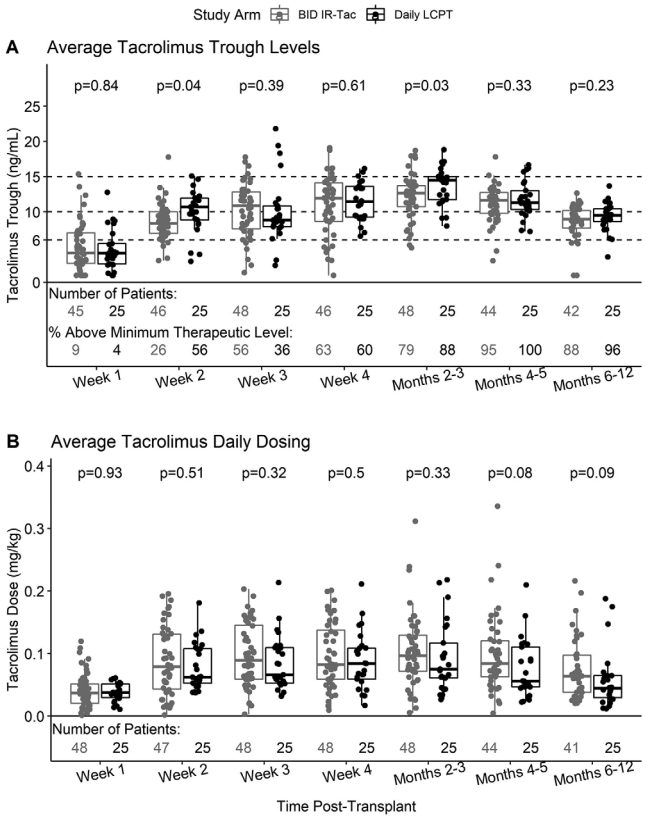

FIGURE 2 Patient Average Whole-Blood Tacrolimus Trough levels and Dosing. Boxplots indicate the study group median and quartiles of (A) the average tacrolimus trough level and (B) average daily dose for each patient calculated weekly for the first month, then months 2–3, 4–5, and 6–12. The 0–3 month and 3–12 month target trough levels of 10 and 6 ng/ml are indicated by dashed lines. BID, twice-daily; IR-Tac, immediate release tacrolimus

LCPT (14.5 vs. 12.7 ng/ml; $P = .03$) where 88% of LCPT patients and 79% of IR-tacrolimus patients exceeded the minimum therapeutic level of 10 ng/ml. These levels were maintained with a similar median dose (LCPT vs. IR-tacrolimus: .08 vs. .09 mg/kg/day; Figure 2B and Table 4). During months 4–12, similar therapeutic levels above 6 ng/ml were maintained with a trend of a lower median dose requirement with LCPT at 4–5 months (.06 vs. .08 mg/kg/day; $P = .08$) and 6–12 months (.04 vs. .06 mg/kg/day; $P = .09$). Moreover, the concentration-to-dose ratio was greater for patients on LCPT in months 4–12 ($P = .04$ and $P = .03$). Finally, the number of dose changes per transplant admission day or per outpatient month did not differ significantly (Table 2).

3.5 | Safety of LCPT

In total, 385 (15.4 pp) adverse events were recorded for patients on LCPT during the first year post-transplant of which 26% were suspected to be related to the study drug. Furthermore, 15 (.6 pp) adverse events were classified as serious of which two (13%) were suspected to be related to the study drug (Table 5). Adverse event categories with > 50% suspected relation to the study drug included hematologic (24 events) and neurological (30 events) groupings. Specific adverse events with more than half of the events with suspected study drug relation included nausea/vomiting (six events), hypertension (30 events), leukopenia (11 events), headaches (10 events), tremors (10 events,), and acute kidney injury or failure (11 events). One acute kidney injury event occurred prior to the protocol change in initial LCPT dosing. Serious adverse events with suspected relation to LCPT included acute appendicitis (one event) and acute renal failure (one event).

TABLE 4 Summary of patient average whole-blood tacrolimus trough levels and dosing

Time post-transplant	BID IR-Tac	Daily LCPT	*P*-value
Tacrolimus serum level (ng/ml)			
Week 1	4.2 [2.7–7.0]	4.2 [2.6–5.5]	.84
Weeks 2–4	10.1 [7.4–11.1]	10.5 [9.5–12.0]	.11
Months 2–3	12.7 [10.7–13.7]	14.5 [11.8–15.0]	.03
Months 4–5	11.7 [9.8–12.7]	11.3 [10.4–13.0]	.33
Months 6–12	9.0 [7.7–10.2]	9.5 [8.6–10.4]	.23
Tacrolimus daily dose (mg/kg/day)			
Week 1	.04 [.02–.05]	.04 [.03–.05]	.93
Weeks 2–4	.08 [.06–.13]	.07 [.06–.11]	.62
Months 2–3	.09 [.07–.13]	.08 [.06–.12]	.33
Months 4–5	.08 [.06–.12]	.06 [.05–.11]	.08
Months 6–12	.06 [.04–.10]	.04 [.03–.06]	.09
Concentration to dose/kg ratio			
Week 1	96 [59–178]	110 [73–160]	.59
Weeks 2–4	115 [70–172]	124 [106–221]	.25
Months 2–3	132 [92–169]	203 [117–236]	.10
Months 4–5	133 [94–174]	187 [138–247]	.04
Months 6–12	151 [82–212]	230 [161–350]	.03

Median [Quartile 1 – Quartile 3] of the average tacrolimus trough level, average daily dose, and ratio of average trough to average dose for each patient calculated for the first week, weeks 2–4, then months 2–3, 4–5, and 6–12.
Abbreviations: BID, twice-daily; Tac, Tacrolimus.

3.6 | Incidence rate of complications and readmissions

The average number of complications that occurred during the transplant admission was 7.5 per person in the IR-Tac group compared to 7.2 in the LCPT group (Table 6) with a comparable incidence rate ($P = .57$). Furthermore, comparable rates were found for acute kidney injury or failure (LCPT vs. IR-Tac: 36% vs. 48%; $P = .45$) and hyperkalemia (LCPT vs. IR-tacrolimus: 16% vs. 14%; $P = .83$). Renal function measured using eGFR at 1-year was comparable (Table 2).

Patients in the LCPT group were readmitted .4 (9/25) times compared to .8 (41/50) in the IR-tacrolimus group (Table 5). The reduction in the readmission rate of 50% ($P = .06$) did not reach statistical significance. Cardiovascular-related readmissions were reduced from .5 (27/50) times in the IR-tacrolimus group to .2 (5/25) in the LCPT group translating to a reduction of 62% ($P = .046$).

4 | DISCUSSION

We evaluated the efficacy and safety of *de novo* immunosuppression with LCPT in OHT compared to matched controls on standard of care IR-tacrolimus. LCPT was found to be comparable to IR-tacrolimus on the composite outcome of death, acute cellular rejection ≥2R (ACR), and/or NGD within 1 year post-transplantation, with a non-inferior reduction in the absolute rate of the composite outcome by 20% (non-inferiority $P = .001$). This is the first report to our knowledge on the comparable efficacy of LCPT with IR-tacrolimus in *de novo* OHT recipients. These results are in line with non-inferiority demonstration on the composite of death or graft failure in kidney transplant recipients.[9]

Outcomes trended towards improvement in the LCPT group relative to control but were not significantly different. Notably, no deaths were observed in the LCPT group compared to seven (14%) in the control group at 1 year with comparable Kaplan-Meier curves of survival. The relatively small sample size precluded us from further analyzing mortality by group. The rate reductions observed for ACR≥2R from 24% to 12% and for NGD from 14% to 8% were comparable. Furthermore, our results align with studies reporting comparable efficacy in mortality and rejection rates comparing daily ER-tacrolimus to IR-tacrolimus in OHT.[19,22,23,25]

Tacrolimus trough levels between weeks 2 and 4 post-transplant were similar between groups. Higher tacrolimus levels were achieved with similar dose levels for LCPT compared to IR-tacrolimus in months 2–3, which may be due to the enhanced bioavailability for LCPT that has been demonstrated in other organ groups,[11,12] further supported by the trend of dose reduction during months 4–5 ($P = .08$) and months 6–12 ($P = .09$) and higher concentration-to-dose ratios ($P = .04$ and $P = .03$). By week 2–4, only a 13% lower median daily dose was

TABLE 5 Adverse events (AEs) for daily LCPT

AE categories	Number of AEs (pp)	AE suspected relation to study drug	Number of SAEs (pp)	SAE suspected relation to study drug
Overall	385 (15.4)	100 (26%)	15 (.6)	2 (13%)
Abdominal/GI	21 (.8)	10 (48%)	1 (.0)	1 (100%)
Diarrhea	7	3 (43%)	0	0
Nausea/vomiting	6	5 (83%)	0	0
Other: < 5 occurrences	8	2 (25%)	1	1 (100%)
Cardiopulmonary	119 (4.8)	32 (27%)	8 (.3)	0
Arrhythmia	14	1 (7%)	2	0
CAV	16	0	1	0
Dyspnea	6	0	1	0
Edema	26	3 (12%)	1	0
Hypertension	30	28 (93%)	0	0
Pericardial/pleural effusion	6	0	0	0
Thrombosis	8	0	0	0
Other: < 5 occurrences	13	0	3	0
Graft function	58 (2.3)	3 (5%)	0 (.0)	0
LV/RV dysfunction	16	2 (13%)	0	0
Cellular rejection = 1R	37	1 (3%)	0	0
Other: < 5 occurrences	5	0	0	0
Hematologic	24 (1.0)	14 (58%)	0 (.0)	0
Leukocytosis	5	0	0	0
Leukopenia	11	8 (73%)	0	0
Other: < 5 occurrences	8	6 (75%)	0	0
Infections	19 (.8)	4 (21%)	1 (.0)	0
CMV viremia	8	3 (38%)	0	0
Other: < 5 occurrences	11	1 (9%)	1	0
Metabolic/endocrine	12 (.5)	5 (42%)	0 (.0)	0
Hyperglycemia	7	1 (14%)	0	0
Other: < 5 occurrences	5	4 (80%)	0	0
Neurologic	30 (1.2)	20 (67%)	1 (.0)	0
Headaches	10	8 (80%)	1	0
Joint/muscle weakness or neuropathy	10	4 (40%)	0	0
Tremors	10	8 (80%)	0	0
Other	102 (4.1)	12 (12%)	4 (.2)	1 (25%)
AKI or acute renal failure	11	8 (73%)	1	1 (100%)
Anxiety and mood disorders	10	0	0	0
Arthritis or joint pain	11	0	1	0
Cold symptoms	5	0	0	0
Fatigue	11	0	0	0
Insomnia	13	3 (23%)	0	0
Muscle pain/cramps	13	1 (8%)	0	0
Other: < 5 occurrences	28	0	2	0

Abbreviations: AEs, adverse events; AKI, acute kidney injury; CAV, coronary artery vasculopathy; CMV, cytomegalovirus; GI, gastrointestinal; LV, left ventricular; pp, per person; RV, right ventricular; SAE, serious adverse event.

TABLE 6 Complications and readmissions

Variables	BID IR-Tac ($n = 50$)	Daily LCPT ($n = 25$)	Incidence Rate Ratio (95% CI)	*P*-value
Total number of complications (pta)	374 (7.5)	181 (7.2)	.94 (.78, 1.15)	.57
Abdominal/GI	39 (.8)	13 (.5)	.67 (.36, 1.25)	.20
Cardiopulmonary	135 (2.7)	72 (2.9)	.87 (.76, 1.38)	.87
Graft function	8 (.2)	4 (.2)	1.00 (.30, 3.32)	1.00
Hematologic	64 (1.3)	35 (1.4)	1.10 (.73, 1.66)	.66
Infections	10 (.2)	7 (.3)	1.51 (.53, 4.25)	.44
Metabolic/endocrine	68 (1.4)	37 (1.5)	1.16 (.77, 1.74)	.48
AKI or acute renal failure	*24 (.5)*	*9 (.4)*	*.75 (.35, 1.60)*	*.45*
Hyperkalemia	*7 (.1)*	*4 (.2)*	*1.14 (.33, 3.91)*	*.83*
Neurologic	7 (.1)	1 (0)	.29 (.04, 2.32)	.24
Other	43 (.9)	12 (.5)	.56 (.29, 1.06)	.07
Total number of readmissions (pp)	41 (.8)	9 (.4)	.50 (.24, 1.03)	.06
Cardiovascular-related	27 (.5)	5 (.2)	.38 (.15, .98)	.046

The incidence rate ratio of complications per patient during the index transplant-admission and readmissions per person year were estimated utilizing robust Poisson regression.

Abbreviations: AKI, Acute Kidney Injury; BID, twice daily; CI, confidence interval; GI, gastrointestinal; pta, per transplant admission; pp, per person.

observed; however, a 25% and 33% lower dose was observed for 4–5 and 6–12 months compared to IR-tacrolimus, respectively, which is similar to the dose reduction recommendations in kidney transplant recipients per FDA label.[33] Further exploration of the impact of pharmacogenomic phenotypes, particularly in the African-Americans, will be required to confirm improved pharmacokinetic profile from the controlled agglomeration formulation, as suggested by the ASERTAA study in this demographic.[17]

Safety of LCPT during the index admission was comparable to IR-tacrolimus with a complication rate per patient of 7.5 in LCPT compared to 7.2 in IR-tacrolimus. Furthermore, a strong safety signal was observed in the sizeable, though not significant, reduction in the all-cause readmission rate from one in two LCPT patients to one in five control patients ($P = .06$). The cardiovascular-related readmission rate was reduced by 62% for LCPT. Previous studies have not compared readmission rates, but rates of acute rejection, infection and nephrotoxicity between IR-tacrolimus and ER-tacrolimus has been reported to be comparable.[19,24] In the LCPT arm, two serious adverse events were prospectively reported of which one was acute renal failure. During the index transplant admission, the rate of kidney injury or failure was comparable between IR-tacrolimus and LCPT. Finally, no adverse events in the LCPT arm resulted in complete discontinuation of treatment, death or graft loss.

The majority of immunosuppression regimens employed in transplantation are currently utilized off-label, particularly in heart transplantation where randomized controlled trials in this population remains limited compared to abdominal transplant. Insurance companies may deny these medications that are necessary for graft and patient survival. Furthermore, the transplant community continues to struggle with the ongoing shortage of immediate-release tacrolimus, which has required us to utilize off-label medications such as LCPT in non-FDA approved organ indications to prevent disruptions in therapy.[34] This report not only provides critical reference data that may be actionable to expand immunosuppression options and access to heart transplant recipients, but also highlights the need to continue to work on prioritization of heart transplant specific trials to ensure optimal use of immunosuppression.

4.1 | Limitations

The primary limitation in our study was lack of randomization. As such, we matched retrospective control patients to prospective study patients, transplanted during an overlapping time period, according to age, gender, and creatinine to account for potential confounding factors at baseline. This design has a potential for self-selection bias with patients consenting for enrollment in the prospective arm. However, baseline characteristics were similar between groups, but numerically fewer patients self-identifying as African American or with a history of diabetes were enrolled in the LCPT group. A subgroup analysis in non-diabetic and non-African American patients suggested non-inferiority consistent with the primary analysis. Future studies with a larger number of patients with diabetes or African American identification are required. Furthermore, while no LCPT patient required switching to IR-tacrolimus during the transplant admission, there is a potential for selection bias with a few patients who were consented for the LCPT arm (i.e., did not receive LCPT) that were unable to finalize enrollment due to oral access barriers precluding *de novo* use of a non-crushable

extended-release formulation. Two of these patients were matched in the IR-tacrolimus arm and analyzed analogous to a modified intention to treat analysis according to receiving at least one dose within the assigned treatment group. Exclusion of these two patients did not alter the significance of the non-inferiority result. Future randomized studies are needed to reduce the potential for selection bias. This study reflects our first implementation of LCPT with our experience, in particular with dose titration, evolving during the course of the trial. Further studies are required to investigate optimal dosing of LCPT in heart transplant.

The retrospective nature of the control group could potentially lead to underreporting bias. However, at our center transplant patients are followed with strict follow-up appointments, well-defined protocols, and established data reporting registries. While we prospectively captured adverse events in the LCPT group, we were not able to do so in our retrospective control group. However, surrogate markers captured and compared included the type and incidence of complications during the transplant admission and subsequent readmissions. Lastly, with our modest sample size we could potentially miss rare events or significance of smaller effects. For the planned study design, we had adequate power to detect non-inferiority with the observed rate difference in the primary composite outcome; however, a larger study would be required to assess superiority, or to allow comparisons on the individual component variables that make up the primary composite outcome.

4.2 | Conclusions

Non-inferiority of LCPT, a once daily, oral, extended-release formulation of tacrolimus, compared to immediate-release tacrolimus for the primary composite outcome of death and graft failure in the first year after OHT is suggested. The rate of cardiovascular-related readmissions was significantly reduced on LCPT. Comparable rates of complications, all-cause readmissions, ACR, and NGD suggest comparable safety and adverse effects. Increased serum tacrolimus trough levels maintained with similar dose levels and higher concentration-to-dose ratios support improved bioavailability of LCPT highlighting a potential for lower dose requirements and fewer side-effects. Larger prospective randomized studies are warranted to confirm these results.

ACKNOWLEDGMENTS

This study was supported by a grant from Veloxis Pharmaceuticals, Cary, NC, USA. Veloxis Pharmaceuticals, however, did not participate in any of the following: data collection, statistical analysis, interpretation of the results, preparation/approval of the manuscript. The decision to submit the trial results for publication was pre-determined by the academically-affiliated authors, independent of trial outcome.

AUTHOR CONTRIBUTION

Conceptualization, design and analysis plans of the trial were undertaken by Johanna S. van Zyl, Teena Sam, Joost Felius, Sandra A. Carey, Robert L. Gottlieb, Cesar Y. Guerrero-Miranda, Parag Kale, and Shelley A. Hall. Management of regulatory approval and patient trial data was done by Aayla K. Jamil. Donna M. Clark, Amanda K. Doss and Sandra A. Carey were involved in prospective patient management, follow-up and recording of data including adverse events. Shelley A. Hall was responsible for overview of the trial and review of adverse events. Kacie R. Kerlee and Zi-On Cheung performed data collection based on patient chart reviews and Kacie R. Kerlee performed classification of readmissions. Data classifications were reviewed by Johanna S. van Zyl, Donna M. Clark, Cesar Y. Guerrero-Miranda, Parag Kale and Shelley A. Hall. Johanna S. van Zyl was responsible for the matching protocol, data management and analysis. Johanna S. van Zyl, Teena Sam, Joost Felius, Robert L. Gottlieb, Cesar Y. Guerrero-Miranda, Parag Kale, and Shelley A. Hall were responsible for data interpretation and manuscript writing. All authors contributed to the manuscript and approved the final version.

CONFLICTS OF INTEREST

Part of the grant from Veloxis Pharmaceuticals was applied to cover proportional salary expenses for Johanna S. van Zyl, Donna M. Clark, Joost Felius, Amanda K. Doss, Katalin Martits-Chalangari and Aayla K. Jamil as outlined by the grant proposal, but did not play a role in employment status or compensation for each.

The remaining authors have no conflicts of interests to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request from the corresponding author (Johanna S. van Zyl) with restriction to adherence to national and state privacy laws and permission from Baylor Scott & White Health.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: van Zyl JS, Sam T, Clark DM, et al. *De novo* Tacrolimus extended-release tablets (LCPT) vs twice-daily tacrolimus in adult heart transplantation: results of a single-center non-inferiority matched control trial. *Clin Transplant*. 2021;35:e14487. https://doi.org/10.1111/ctr.14487