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## Prospective Study

# Dosing strategies for *de novo* once-daily extended release tacrolimus in kidney transplant recipients based on *CYP3A5* genotype

Adam Diamond, Sunil Karhadkar, Kenneth Chavin, Serban Constantinescu, Kwan N. Lau, Oscar Perez-Leal, Kerry Mohrien, Nicole Sifontis, Antonio Di Carlo

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## Abstract

### BACKGROUND

Tacrolimus extended-release tablets have been Food and Drug Administration-approved for use in the *de novo* kidney transplant population. Dosing requirements often vary for tacrolimus based on several factors including variation in metabolism based on *CYP3A5* expression. Patients who express *CYP3A5* often require higher dosing of immediate-release tacrolimus, but this has not been established for tacrolimus extended-release tablets in the *de novo* setting.

### AIM

To obtain target trough concentrations of extended-release tacrolimus in *de novo* kidney transplant recipients according to *CYP3A5* genotype.

### METHODS

Single-arm, prospective, single-center, open-label, observational study (Clinical-

Trials.gov: NCT037-13645). Life cycle pharma tacrolimus (LCPT) orally once daily at a starting dose of 0.13 mg/kg/day based on actual body weight. If weight is more than 120% of ideal body weight, an adjusted body weight was used. LCPT dose was adjusted to maintain tacrolimus trough concentrations of 8-10 ng/mL. Pharmacogenetic analysis of *CYP3A5* genotype was performed at study conclusion.

## RESULTS

Mean time to therapeutic tacrolimus trough concentration was longer in *CYP3A5* intermediate and extensive metabolizers vs *CYP3A5* non-expressers (6 d vs 13.5 d vs 4.5 d;  $P = 0.025$ ). Mean tacrolimus doses and weight-based doses to achieve therapeutic concentration were higher in *CYP3A5* intermediate and extensive metabolizers vs *CYP3A5* non-expressers (16 mg vs 16 mg vs 12 mg;  $P = 0.010$ ) (0.20 mg/kg vs 0.19 mg/kg vs 0.13 mg/kg;  $P = 0.018$ ). *CYP3A5* extensive metabolizers experienced lower mean tacrolimus trough concentrations throughout the study period compared to *CYP3A5* intermediate metabolizers and non-expressers (7.98 ng/mL vs 9.18 ng/mL vs 10.78 ng/mL;  $P = 0.008$ ). No differences were identified with regards to kidney graft function at 30-d post-transplant. Serious adverse events were reported for 13 (36%) patients.

## CONCLUSION

Expression of *CYP3A5* leads to higher starting doses and incremental dosage titration of extended-release tacrolimus to achieve target trough concentrations. We suggest a higher starting dose of 0.2 mg/kg/d for *CYP3A5* expressers.

**Key Words:** Immunosuppression; Kidney transplant; Dosing; Tacrolimus; Therapeutic drug monitoring; Genotype

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**Core Tip:** In this single-arm, prospective, observational study we study once-daily, extended release tacrolimus dosing. Here we find that the expression of the cytochrome P450 enzyme, *CYP3A5*, is an important clinical factor to determine optimal dosage requirements after kidney transplantation. In kidney transplant recipients who express *CYP3A5* activity, higher doses of extended-release tacrolimus are required to attain therapeutic trough concentrations. Delays in achieving therapeutic trough concentrations has been linked to increase rates of acute rejection which highlights the importance of this research in identifying dosing considerations for extended-release tacrolimus in the *de novo* kidney transplant setting.

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## INTRODUCTION

Outcomes after kidney transplantation have been significantly improved with advances in immunosuppressive therapies. Tacrolimus is currently marketed in various formulations that have proven to be highly effective in preventing acute rejection after kidney transplantation[1-3]. Compared to immediate release tacrolimus, once daily extended-release formulations have demonstrated similar efficacy and safety in the *de novo* kidney transplant setting leading to increased utilization[1,2,4,5]. Life cycle pharma tacrolimus (LCPT) (Envarsus®; Veloxis Pharmaceuticals) was designed to enhance the bioavailability of tacrolimus[6]. In published studies, utilization of LCPT has been shown to provide rapid achievement of target trough concentrations following kidney transplantation[1,2,7]. In addition, a once daily LCPT dosing regimen results in lower peak concentrations with equivalent overall exposure compared to immediate-release and other extended-release tacrolimus formulations[3]. Similar efficacy and safety profiles have been demonstrated when comparing LCPT to other available tacrolimus formulations[1-3,7,8].

The use of LCPT has been Food and Drug Administration (FDA)-approved for the prophylaxis of organ rejection in *de novo* kidney transplant patients and in kidney transplant patients converted from tacrolimus immediate-release formulations[6]. The recommended FDA-approved dosing for *de novo* kidney transplant recipients is 0.14 mg/kg/d, however various starting doses have been evaluated in clinical trials[1,2,6]. Some kidney transplant recipients are known to metabolize tacrolimus at a higher or lower rate due to the presence of genetic polymorphisms that affect its metabolism [9]. The metabolism of LCPT occurs primarily within the cytochrome P450 (CYP) system, of which approximately 55 different genes have been identified in the human genome[10]. A multitude of CYP enzymes exist, including *CYP3A5* which is known to be an integral component of tacrolimus metabolism. In addition, genetic variation affecting *CYP3A5* function is known to impact overall tacrolimus exposure as well as dosing requirements to attain therapeutic concentrations[11,12]. The most common genetic variants (*CYP3A5\*3* and *CYP3A5\*6*) of *CYP3A5* in the general population

produce non-functional versions of the enzyme[13,14]. On the other hand, the presence of at least one *CYP3A5*\*1 allele would confer activity to *CYP3A5* (commonly known as an expresser) which has been shown to lead to higher dosage requirements of tacrolimus to attain therapeutic concentrations[9]. Previous data has illustrated that *CYP3A5* expressers can require up to 2-fold higher tacrolimus doses to achieve similar trough concentrations compared to *CYP3A5* non-expressers[15]. *CYP3A5* genetic variation may also lead to delays in time to achievement of target trough concentrations, which has been linked to higher rates of acute rejection. Furthermore, knowledge of *CYP3A5* genetic variants in transplant patients may lead to prevention of subtherapeutic and suprathreshold concentrations in the early post-transplant period potentially lowering the risks of acute rejection and drug toxicities[16,17].

The primary objective of this study was to identify the time to therapeutic trough concentration of *de novo* once-daily LCPT in kidney transplant recipients according to *CYP3A5* expresser status. Secondary objectives include the description of the distribution of common *CYP3A5* variants in our population and to identify the dose required (total and weight-based) to obtain target trough concentrations according to expresser status.

## MATERIALS AND METHODS

### Study design and patient population

We conducted a single-arm, prospective, open-label, single-center, observational study (ClinicalTrials.gov: NCT03-713645). Adult *de novo* recipients of a living or deceased donor kidney transplant capable of providing consent from November 15, 2018 to April 23, 2021 were consented for inclusion in the study. Patients who were scheduled for multiple organ transplants at enrollment, non-English speaking, pregnant, or diagnosed with moderate to severe hepatic impairment (Child Pugh > 10 or bilirubin > 2 mg/dL) were excluded from the study. In addition, patients who had existing contraindications to tacrolimus-based products including hypersensitivity to tacrolimus or any other component of the formulation or who were receiving concomitant medications known to have strong drug-drug interaction potential with tacrolimus were excluded from the study. The post-transplant observation period was 30 d.

### Intervention

All patients received LCPT tablets orally once daily at a starting dose of 0.13 mg/kg/day based on actual body weight. If a patient weighed more than 120% of their ideal body weight, an adjusted body weight was calculated for initial drug dosing[18]. All doses were rounded to the nearest 1 mg increment and adjusted to maintain a tacrolimus trough concentration of 8-10 ng/mL for the first 30 d after kidney transplant. No dose adjustments were performed during the first 48 h after the initial dose or subsequent dose adjustments to allow steady state concentrations to be achieved. All patients received additional immunosuppression with antithymocyte globulin (Thymoglobulin®; Sanofi Pharmaceuticals) or basiliximab (Simulect®, Novartis Pharmaceuticals) induction and mycophenolate sodium 720 mg by mouth every 12 h. Antithymocyte globulin dosing ranged between 4-6 mg/kg based on immunologic risk and was dosed by actual body weight unless the patient was greater than 120% of their ideal body weight, for which an adjusted body weight was utilized. Adjustments to mycophenolate sodium dosing was at the discretion of the treating physician, based on adverse effects, lab abnormalities, and other clinical considerations. All patients received daily pulse-dose methylprednisolone for 5 d according to institutional protocol. Prednisone maintenance immunosuppression was utilized in some recipients based on immunologic risk and the presence of an autoimmune kidney disease at the time of kidney transplant. Patients requiring prednisone received a maintenance dose of prednisone 5-10 mg by mouth daily.

### *CYP3A5* genotype sample collection and analysis

Two buccal swab samples were collected from each patient using DNA/RNA Shield™ collection tubes (Zymo Research Corporation). The samples were stored frozen at -20 °C until obtaining samples from all patients included in the study. The DNA extraction was performed with NucleoMag® DNA Swab extraction kit (Takara Bio Inc.) following the manufacturer's recommendations. A Tecan Spark Plate Reader was used to determine the DNA concentration using the NanoQuant Plate™. The DNA concentration was normalized at 5 ng/L for all the samples with molecular biology grade water for real-time PCR analysis.

We processed all the patient's DNA samples on the same day for DNA genotyping. We performed DNA single nucleotide polymorphism (SNP) analysis of these *CYP3A5* variants: *CYP3A5*\*3 (rs776746), *CYP3A5*\*6 (rs10264272), and *CYP3A5*\*7 (rs41303343). We used three TaqMan™ probes for variant detection *via* real-time PCR (Catalog ID 4362691, 4362691, 4362691) following the manufacturer's recommendations (Thermo Fisher Scientific). As positive controls, we used nine commercially available DNA samples containing all possible combinations of the *CYP3A5* variants analyzed in this study. The positive control samples were obtained from the Coriell Institute with the following catalog numbers: *CYP3A5* \*1\*1 (HG01190), \*1\*3 (NA07000), \*1\*6 (NA19226) \*1\*7 (NA19035), \*3\*3 (NA17660), \*3\*6 (NA18855), \*3\*7 (NA19207), \*6\*7 (NA19143), \*7\*7 (NA19920). The real-time PCR assay was performed at the Genetics Core Facility of the University of Arizona. The variant detection data analysis was done single-blinded to corroborate the correct identification of the control samples' genotypes. Upon receipt of *CYP3A5* genotype results, patients were then classified by *CYP3A5* phenotype as a *CYP3A5* non-expresser (individual carries two non-functional alleles), *CYP3A5* intermediate metabolizer (individual carrying one functional allele and one non-functional allele), or *CYP3A5* extensive metabolizer (individual carrying two functional alleles)[19].

### Clinical and safety endpoints

The primary efficacy endpoint was the time to therapeutic tacrolimus trough concentration during the first 30 d after kidney transplantation. Therapeutic tacrolimus trough concentration was defined as tacrolimus trough concentration 8 ng/mL. Secondary efficacy endpoints included the tacrolimus dose and weight-based tacrolimus dose required to achieve an initial therapeutic trough concentration. Safety outcomes measured included incidence of hyperkalemia (serum potassium > 5.5 mEq/L) and incidence of tremor. Tremor was assessed utilizing the quality of life in essential tremor (QUEST) questionnaire and was completed at 30 d post-kidney transplant[20]. Incidence of serious adverse events (SAEs) and drug discontinuation due to adverse events (AEs) were also reported.

### Statistical methods and analysis

Descriptive statistics were used to characterize the baseline demographics of the entire cohort (intent to treat population). Continuous parametric data are presented as mean  $\pm$  SD while continuous non-parametric data are presented as median (25%-75% interquartile range). Analysis of outcomes according to CYP3A5 expresser status within the modified intent-to-treat (ITT) population were completed using the Kruskal-Wallis or ANOVA test for continuous data and the chi-squared test for categorical data. Tests were corrected for multiple comparisons as necessary utilizing the Bonferroni method. All tests were two-tailed, and  $P < 0.05$  was used to represent statistical significance. Time to therapeutic tacrolimus trough concentration was analyzed using a Kaplan-Meier time-to-event analysis. All analyses were performed using SPSS, version 26 for windows (Armonk, NY; IBM Inc.).

## RESULTS

A total of 36 patients (ITT population) were enrolled and 35 patients completed the entire 30-d treatment period. One patient withdrew prior to the end of the study time period due to neurologic toxicity and tremors. Patients who were able to complete genotype testing were included in the final analysis [ $n = 34$ ; modified ITT (mITT) population]. All 34 patients were included in the mITT analysis and patients were stratified based on CYP3A5 phenotype. Of the 34 total patients, 15 (44.1%) were found to be non-expressers of CYP3A5, while 13 (38.2%) and 6 (17.6%) were found to be intermediate and extensive metabolizers, respectively. The population was predominantly black (66.7%), male (55.6%), and recipients of a deceased donor kidney transplant (69.4%) with a mean age of 55.5 years (Table 1). Baseline characteristics were similar between groups except for a higher percentage of black patients (92.3% vs 83.3% vs 46.7%;  $P = 0.026$ ) in the CYP3A5 intermediate and extensive metabolizer groups compared to CYP3A5 non-expressers (Table 2).

Mean time to therapeutic tacrolimus trough concentration was longer in CYP3A5 intermediate and extensive metabolizers compared to CYP3A5 non-expressers ( $P = 0.025$ ). A Kaplan Meier analysis demonstrated that the highest incidence of patients not achieving therapeutic tacrolimus trough concentration by 7 d post-transplant were CYP3A5 extensive metabolizers followed by CYP3A5 intermediate metabolizers. Only 13.3% of CYP3A5 non-expressers failed to achieve a therapeutic tacrolimus trough by 7 d post-transplant compared to approximately 30.8% of CYP3A5 intermediate metabolizers and 83.3% of CYP3A5 extensive metabolizers (Figure 1). Mean tacrolimus doses to achieve therapeutic concentration were higher in CYP3A5 intermediate and extensive metabolizers compared to CYP3A5 non-expressers (16 mg vs 16 mg vs 12 mg;  $P = 0.010$ ). Mean weight-based tacrolimus doses to achieve therapeutic tacrolimus trough concentrations were also higher in CYP3A5 intermediate and extensive metabolizers compared to CYP3A5 non-expressers (0.20 mg/kg vs 0.19 mg/kg vs 0.13 mg/kg;  $P = 0.018$ ) (Table 3).

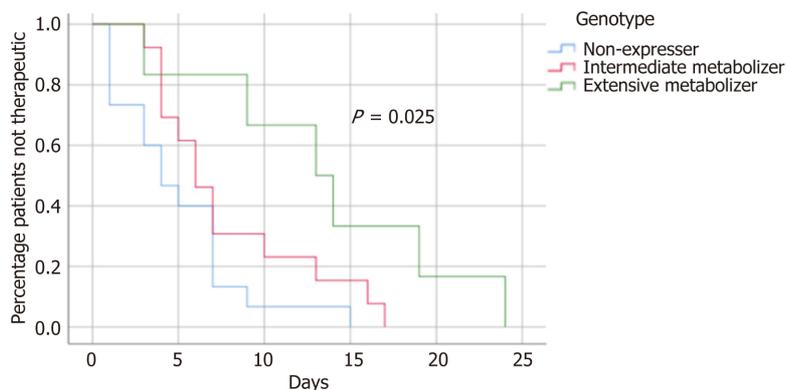
Mean daily tacrolimus dose, daily weight-based tacrolimus dose, and tacrolimus trough concentrations throughout the 30-d study period were compared amongst the three groups. A higher mean daily tacrolimus dose was seen in CYP3A5 intermediate and extensive metabolizers compared to poor metabolizers (12.5 mg vs 13.8 mg vs 9.6 mg;  $P = 0.011$ ). While not statistically significant, a higher daily weight-based tacrolimus dose was seen in CYP3A5 intermediate and extensive metabolizers compared to CYP3A5 non-expressers (0.136 mg/kg vs 0.176 mg/kg vs 0.128 mg/kg;  $P = 0.074$ ). CYP3A5 extensive metabolizers experienced lower mean tacrolimus trough concentrations throughout the study period compared to CYP3A5 intermediate metabolizers and non-expressers (7.98 ng/mL vs 9.18 ng/mL vs 10.78 ng/mL;  $P = 0.008$ ). No statistically significant differences in kidney graft function at 30-d post-transplant were observed between CYP3A5 extensive metabolizers, intermediate metabolizers, and non-expressers measured by mean serum creatinine (1.94 mg/dL vs 1.76 mg/dL vs 1.76 mg/dL;  $P = 0.906$ ) and mean estimated glomerular filtration rate (31.5 mL/min/1.73 m<sup>2</sup> vs 46 mL/min/1.73 m<sup>2</sup> vs 40 mL/min/1.73 m<sup>2</sup>;  $P = 0.701$ ) (Table 3).

Safety endpoints were evaluated as part of the ITT analysis. SAEs were reported for 13 (36%) patients with 1 SAE (2.8%) attributed to study drug. The one patient who experienced a SAE attributed to study drug resulted in neurotoxicity which led to study drug discontinuation. Assessment of tremor using the QUEST questionnaire revealed that the majority of patients experienced no significant impact of tremor on their quality of life. A further description of patient responses to the QUEST questionnaire are summarized in Figure 2. A total of 11 (31%) patients enrolled experienced at least one potassium value above 5.5 mEq/L. Mean potassium values did differ throughout the 30-d study period between extensive metabolizer, intermediate metabolizer, and non-expresser groups, but were not clinically significant (4.35 vs 4.68 vs 4.29;  $P = 0.041$ ).

**Table 1 Baseline Characteristics (intent to treat population)**

All patients (n = 36)	
Age (yr), mean ± SD	55.5 ± 13.7
Male, n (%)	20 (55.6)
Race, n (%)	
White	9 (25.0)
Black	24 (66.7)
Hispanic	2 (5.6)
Transplant type, n (%)	
Deceased donor	25 (69.4)
Living donor	11 (30.6)
Hypertension, n (%)	28 (77.8)
Diabetes mellitus, n (%)	9 (25.0)
Focal segmental glomerulosclerosis, n (%)	1 (2.8)
Polycystic kidney disease, n (%)	1 (2.8)
HIV-associated nephropathy, n (%)	1 (2.8)
Lupus nephritis, n (%)	1 (2.8)
Transplant number, n (%)	
One	35 (97.2)
Two	1 (2.8)
cPRA (%), median (IQR)	0 (0-10.0)
Actual body weight (kg), mean ± SD	87.4 ± 18.4
Dosing weight, n (%)	
Actual	16 (44.4)
Adjusted	20 (55.6)
BMI (kg/m <sup>2</sup> ), mean ± SD	30.0 ± 5.5

BMI: Body mass index; cPRA: Calculated panel reactive antibody; IQR: Interquartile range; HIV: Human immunodeficiency virus.



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**Figure 1 Time to therapeutic tacrolimus trough concentration (Kaplan Meier analysis).**

**Table 2 Baseline characteristics (modified intent to treat population)**

	Non-expresser (n = 15)	Intermediate metabolizer (n = 13)	Extensive metabolizer (n = 6)	P value
Age (yr), mean ± SD	53.8 ± 12.6	49.0 ± 14.0	58.3 ± 14.1	0.354
Male, n (%)	9 (60.0)	8 (61.5)	2 (33.3)	0.470
Race, n (%)				0.026
White	7 (46.7)	1 (7.7)	0	
Black	7 (46.7)	12 (92.3)	5 (83.3)	
Hispanic	1 (6.7)	0	0	
Transplant type, n (%)				0.550
Deceased donor	12 (80.0)	8 (61.5)	4 (66.7)	
Living donor	3 (20.0)	5 (38.5)	2 (33.3)	
Hypertension, n (%)	12 (80.0)	9 (69.2)	6 (100.0)	0.304
Diabetes mellitus, n (%)	2 (13.3)	4 (30.8)	2 (33.3)	0.457
Focal segmental glomerulosclerosis, n (%)	1 (6.7)	0	0	0.521
Polycystic kidney disease, n (%)	0	1 (7.7)	0	0.435
HIV-associated nephropathy, n (%)	1 (6.7)	0	0	0.521
Lupus nephritis, n (%)	0	1 (7.7)	0	0.435
Transplant number, n (%)				0.435
One	15 (100.0)	12 (92.3)	6 (100.0)	
Two	0	1 (7.7)	0	
cPRA (%), median (IQR)	0 (0-20.8)	10.0 (0-10.0)	0 (0-20.8)	0.732
Actual body weight (kg), mean ± SD	85.5 ± 16.8	91.8 ± 22.2	77.4 ± 10.5	0.286
Dosing weight, n (%)				0.987
Actual	7 (53.3)	6 (53.8)	3 (50.0)	
Adjusted	8 (46.7)	7 (46.2)	3 (50.0)	
BMI (kg/m <sup>2</sup> ), mean ± SD	29.68 ± 5.0	30.68 ± 6.9	28.88 ± 4.5	0.805

BMI: Body mass index; cPRA: Calculated panel reactive antibody; IQR: Interquartile range; HIV: Human immunodeficiency virus.

## DISCUSSION

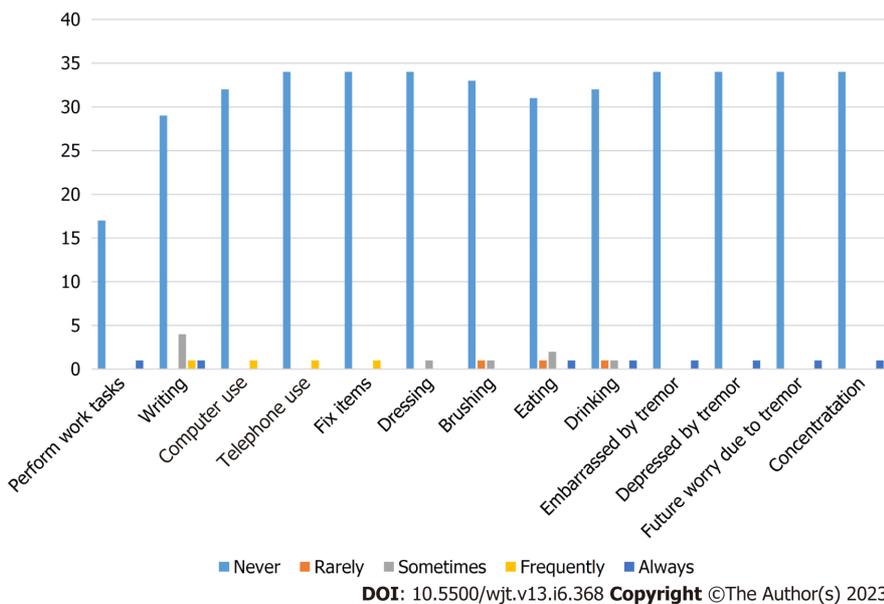
To our knowledge, this is the first prospective observational study to provide outcomes data for the *de novo* dosing of extended-release tacrolimus, LCPT, in a predominant *CYP3A5\*1* expresser kidney transplant population. This research evaluates a lower initial LCPT dose of 0.13 mg/kg/d compared with the FDA-approved initial LCPT dosing of 0.14 mg/kg/d. A starting LCPT dose of 0.17 mg/kg/d was commonly evaluated in other *de novo* kidney transplant populations[1, 2]. Genetic polymorphisms have been shown in numerous studies to directly affect dosage requirements of extended-release tacrolimus preparations, including LCPT[8,12]. In addition, several other patient specific factors may affect tacrolimus absorption including age, ethnicity, body weight, hepatic function, drug-drug interactions, and oral intake[15, 21]. The incorporation of a *CYP3A5* genotype testing variable provides a clearer understanding of LCPT dosage requirements in this study given its significant impact on individual metabolism and tacrolimus interpatient variability[12,19].

Delayed time to therapeutic tacrolimus trough concentrations results in higher rates of acute cellular rejection[15-17]. The expression of at least one *CYP3A5\*1* allele is associated with a delayed time to achieve initial therapeutic tacrolimus trough concentration as well as a decreased time within therapeutic tacrolimus trough concentration range after kidney transplantation[12,15]. The significant impact of *CYP3A5* activity on tacrolimus metabolism warrants investigation into dosing of once daily tacrolimus formulations in *CYP3A5* expressers. Participants in this study who expressed at least one *CYP3A5\*1* allele or two *CYP3A5\*1* alleles had significant increases in LCPT dosing requirements compared to those who did not express any *CYP3A5\*1* alleles. Higher dosing requirements in *CYP3A5* expressers noted in this study leads to the consideration of a need for higher initial LCPT *de novo* dosing in this population to avoid delays in attainment of therapeutic tacrolimus trough concentrations.

**Table 3 Primary and secondary efficacy endpoints**

	Non-expressers (n = 15)	Intermediate metabolizer (n = 13)	Extensive metabolizer (n = 6)	P value
Time (d) to therapeutic tacrolimus concentration, median (IQR)	4.5 (1.0-7.0)	6.0 (4.0-11.5)	13.5 (7.5-20.25)	0.025
Tacrolimus dose (mg) at therapeutic concentration, median (IQR)	12 (10-14)	16 (13-20)	16 (11-20.5)	0.010
Weight-based tacrolimus dose (mg/kg) at therapeutic concentration, median (IQR)	0.13 (0.12-0.165)	0.20 (0.125-0.25)	0.19 (0.138-0.265)	0.018
Tacrolimus dose (mg), median (IQR)	9.6 (9.2-10.1)	12.5 (10.6-14.5)	13.8 (10.4-14.4)	0.011
Weight-based tacrolimus dose (mg/kg), median (IQR)	0.128 (0.102-0.142)	0.136 (0.108-0.169)	0.176 (0.128-0.217)	0.074
Tacrolimus trough concentration (ng/mL), mean ± SD	10.78 ± 2.1	9.18 ± 1.6	7.98 ± 1.3	0.008
Weight-based tacrolimus dose at day 30 (mg/kg), mean ± SD	0.103 ± 0.429	0.154 ± 0.620	0.167 ± 0.590	0.022
Potassium (mEq/L), mean ± SD	4.29 ± 0.36	4.68 ± 0.35	4.35 ± 0.59	0.041
Serum creatinine (mg/dL) at day 30, median (IQR)	1.76 (1.29-2.62)	1.75 (1.27-2.65)	1.94 (1.2-3.0)	0.906
eGFR (mL/min/1.73 m <sup>2</sup> ) at day 30, median (IQR)	40.0 (27.0-58.0)	46.0 (30.0-58.5)	31.5 (25.0-56.3)	0.701

eGFR: Estimated glomerular filtration rate; IQR: Interquartile range.



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**Figure 2 Quality of life in essential tremor questionnaire lifestyle self-assessment.**

Since LCPT dosing has not been evaluated in prior studies based on CYP3A5 genotype, it is worthwhile to compare the results of our study to a different once daily tacrolimus formulation (Advagraf®, Astagraf®; Astellas Pharmaceuticals). De Meyer *et al*[12] showed that CYP3A5 expressers, both intermediate and extensive metabolizers, required higher tacrolimus extended-release doses by day 30 compared to CYP3A5 non-expressers (CYP3A5 intermediate metabolizer: 0.30 mg/kg/d vs CYP3A5 extensive metabolizer: 0.46 mg/kg/d vs CYP3A5 non-expresser: 0.15 mg/kg/d; P < 0.001). We identified a similar trend as De Meyer *et al*[12] in which CYP3A5 expressers regardless of intermediate or extensive metabolizer phenotype, require higher LCPT dosing than CYP3A5 non-expressers. However, lower doses of LCPT appear to be required for CYP3A5 expressers in our study compared to other available once daily tacrolimus formulations (Astagraf®) when comparing dosing at day 30 post-kidney transplant (CYP3A5 intermediate metabolizer: 0.17 mg/kg/d vs 0.30 mg/kg/d; CYP3A5 extensive metabolizer: 0.16 mg/kg/d vs 0.46 mg/kg/d). One limitation to this comparison is the goal tacrolimus trough concentration, since in De Meyer *et al*[12] it was 8-12 ng/mL at day 30 compared to our study goal of 8-10 ng/mL, although median trough concentrations were similar at day 30 for both studies.

Guidelines from the Clinical Pharmacogenetics Implementation Consortium for CYP3A5 Genotype and Tacrolimus Dosing provide clinical recommendations for dosing based on CYP3A5 genotype[19]. These guidelines provide clinical

evidence for dose adjustments required for immediate-release tacrolimus dosing, but do not discuss the implications for dose adjustments for tacrolimus extended-release formulations, such as LCPT. Recommendations for all *CYP3A5* expressers is to provide initial tacrolimus dosing of 1.5-2 times the recommended starting dose and to not exceed a starting dose of 0.3 mg/kg/d. *CYP3A5* expressers in our study required approximately 1.5 times the recommended FDA-approved 0.14 mg/kg/d starting dose for LCPT to achieve therapeutic tacrolimus trough concentrations[6]. The majority of *CYP3A5* expressers in this study required an approximate 20% reduction in the mean LCPT dose at day 30 from the time of attainment of therapeutic tacrolimus trough concentrations. The delayed time to achieve therapeutic tacrolimus trough concentration for *CYP3A5* expressers compared to *CYP3A5* non-expressers leads to *CYP3A5* expressers requiring higher initial starting doses of LCPT. However, patients may require dose reduction over time to maintain therapeutic tacrolimus concentrations. Patients in this study identified as *CYP3A5* intermediate metabolizers required a mean of 0.2 mg/kg/d to achieve therapeutic tacrolimus concentration *vs* 0.19 mg/kg/d for *CYP3A5* extensive metabolizers. Given the similarity in doses required to achieve therapeutic tacrolimus concentrations between these two groups, a similar dosing strategy for all *CYP3A5* expressers could be utilized. Two large sample size studies evaluated clinical outcomes associated with *de novo* use of LCPT in kidney transplant recipients. Budde *et al*[1] evaluated the incidence of biopsy-proven acute rejection, graft failure, patient survival, and AEs at 12 mo while Rostaing *et al*[2] evaluated similar outcomes at both 12 and 24 mo after kidney transplantation. Both of these studies evaluated an initial starting dose of 0.17 mg/kg/d, which is the maximum dose of LCPT evaluated in clinical studies with at least 12 mo efficacy and safety outcomes. *CYP3A5* genotype was not performed for these studies and our study provides additional data regarding initial *de novo* LCPT dosing based on *CYP3A5* genotype. Based on these findings, we suggest that *CYP3A5* expressers may require higher initial starting doses of approximately 0.2 mg/kg/d. In order to avoid delays in attaining therapeutic tacrolimus trough concentrations, 0.2 mg/kg/d may be used as an initial starting LCPT dose for *CYP3A5* expressers barring no other clinical barriers to higher starting doses.

This study has several limitations to the interpretation and generalizability of its findings. The single-center design of this study reflects the clinical approach of one institution which may not be applicable to all kidney transplant recipients. *CYP3A5* genotype may not be the only genetic consideration when determining an individual's genetic predisposition to the metabolism of tacrolimus. Genetic differences in *CYP3A4* activity and other SNPs within the *CYP* system could play a role in determining the metabolic rate of tacrolimus which is not captured in our study[12]. Our study evaluated dose requirements and other clinical outcomes through the first 30 d after kidney transplantation. This follow-up period only provides information on short-term LCPT dosing outcomes and future studies with long-term follow-up periods should be performed. This study is also limited by its open-label design and relatively smaller number of patients enrolled. In addition, the single-arm design of this study did not allow for a comparator arm and future randomized controlled studies should be performed to further evaluate dosing requirements of LCPT in the *de novo* kidney transplant population.

## CONCLUSION

Expression of *CYP3A5* metabolic activity is an important clinical factor needed to determine optimal LCPT dosage requirements in the *de novo* kidney transplant recipient. It is expected that *CYP3A5* expressers would require a higher initial starting dose as well as higher incremental dosage titration to achieve therapeutic tacrolimus trough concentrations in a reasonable timeframe. Prospective identification of *CYP3A5* genotype may lead to optimized dosing of LCPT in the *de novo* kidney transplant setting. Future, randomized, larger-scale studies should be conducted to determine the optimal *de novo* dosing of LCPT after kidney transplantation.

## ARTICLE HIGHLIGHTS

### Research background

Tacrolimus has been extensively studied and shown to require significant dose adjustments in *CYP3A5* expressers compared to non-expressers. Data regarding the impact of *CYP3A5* expresser status on the dosing of tacrolimus extended-release tablets has not been published and is important to understand given the vastly different pharmacokinetic profile of this tacrolimus formulation. There is an increased use of tacrolimus extended-release tablets in the *de novo* setting warranting further investigation into this clinical question.

### Research motivation

The main concerns when initiating tacrolimus in the *de novo* kidney transplant setting is to achieve therapeutic tacrolimus trough concentrations in a reasonable timeframe while also avoiding drug toxicity. The rationale behind this research is to identify dosing strategies that should be considered when initiating tacrolimus extended-release immediately after kidney transplant. Particular, research evaluating dosing strategies in patients known to have higher tacrolimus dose requirements (*i.e.* *CYP3A5* expressers) will provide data for transplant centers to make educated clinical decisions surrounding dosing and dosing adjustments for tacrolimus extended-release tablet formulations.

### Research objectives

The main objectives of this research was to identify the time to therapeutic tacrolimus trough concentration as well as the dose required to obtain that trough concentration. These objectives were realized as well as the differences in dosing requirements amongst CYP3A5 expressers compared to non-expressers. The significance of these objectives warrant further investigation towards linking clinical outcomes such as acute rejection and graft function outside of the first month after transplant in patients receiving tacrolimus extended-release tablets in the *de novo* kidney transplant setting.

### Research methods

Patients ( $n = 36$ ) were consented to receive tacrolimus extended-release tablets at a dose of 0.13 mg/kg/d at the time of kidney transplantation. Dosing was adjusted to maintain therapeutic trough concentrations of 8-10 ng/mL which assisted in identifying the primary objective of time to therapeutic concentration. In addition, all patients that consented to CYP3A5 genotype testing ( $n = 34$ ) were included in additional data analysis to describe dosing requirements for tacrolimus extended-release tablets in patients that were CYP3A5 expressers compared to CYP3A5 non-expressers. These methods allowed the authors to describe initial dosing requirements as well as the impact of CYP3A5 metabolism on tacrolimus extended-release dosing and attainment of target trough concentrations.

### Research results

This research demonstrated that kidney transplant recipients who are expressers of CYP3A5 exhibited higher dose requirements for tacrolimus extended-release tablets and also experienced delays in attaining therapeutic trough concentrations compared to CYP3A5 non-expressers. These findings are pertinent to the field of solid organ transplant since transplant centers that utilize tacrolimus extended-release tablets in the *de novo* setting should be aware of the higher dosing needs in this patient population. In addition, transplant recipients suspected to or known to be CYP3A5 expressers may require more aggressive dose titration to achieve and maintain target tacrolimus trough concentrations. Future research in this area should focus on clinical outcomes beyond our study period of 30 d to determine the impact on acute rejection and kidney graft function.

### Research conclusions

Overall, this study provides additional clinical information regarding the dosing requirements of tacrolimus extended-release tablets in the *de novo* kidney transplant setting. To our knowledge, this is the first prospective observational study to provide outcomes data for the *de novo* dosing of tacrolimus extended-release tablets. The findings from this research validate that the impact of CYP3A5 expression has a clinical impact on the pharmacokinetic profile of tacrolimus extended-release tablets similar to findings published with tacrolimus immediate-release. New approaches to dosing and dose titration for tacrolimus extended-release tablets have been proposed by this research in the *de novo* kidney transplant setting and can be used as a guide when making clinical decisions in this patient population.

### Research perspectives

Future research should aim to randomize patients to various doses of tacrolimus extended-release tablets to offer a more advanced comparison of different initial dosing strategies. Conducting CYP3A5 genotype analyses prior to study drug initiation would be beneficial in future studies in order to further assess the impact of pharmacokinetic variations in metabolism on tacrolimus extended-release tablets.

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## FOOTNOTES

**Author contributions:** Diamond A and Di Carlo A participated in design and oversight of the study, data collection, data analysis, and drafted and finalized the manuscript; Karhadkar S and Lau KN, participated in design and oversight of the study, and assisted with data analysis; Chavin K drafted the manuscript and assisted with data analysis; Constantinescu S participated in design and oversight of the study, drafted the manuscript, and assisted with data analysis; Mohrien K performed statistical analysis in conjunction with Temple University Center for Biostatistics & Epidemiology, participated in data analysis, and drafted the manuscript; Perez-Leal O conducted DNA analysis for genotype samples and analyzed genotype data, and drafted the manuscript; Sifontis N participated in design and oversight of the study, assisted with data analysis, and drafted the manuscript; all authors read and approved the final manuscript.

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