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Authors

Momper, Jeremiah

Venkataramanan, Raman

Jantz, Arin

et al.

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Evaluation of Effective Half-Life and Its Impact on Time to Steady State for Oral MeltDose Tacrolimus (LCPT) in De Novo Kidney Transplant Recipients

Jeremiah D. Momper, PharmD, PhD, Raman Venkataramanan, MS, PhD,† Arin S. Jantz, PharmD,‡ Diane M. Cibrik, MD,§ Kelly Birdwell, MD, MSCI,¶ Tk Nguyen, PharmD,* Brian M. Masters, PharmD,‖ and Samir J. Patel, PharmD, MPH‖*

Background: For extended-release drug formulations, effective half-life ($t_{1/2eff}$) is a relevant pharmacokinetic parameter to inform dosing strategies and time to reach steady state. Tacrolimus, an immunosuppressant commonly used for the prophylaxis of organ rejection in transplant patients, is available as both immediate- and extended-release formulations. To the best of our knowledge, the $t_{1/2eff}$ of tacrolimus from these different formulations has not yet been assessed. The objective of this study was to characterize the $t_{1/2eff}$ and terminal half-life ($t_{1/2z}$) of an extended-release once-daily tacrolimus formulation (LCPT) and twice-daily immediate-release tacrolimus (IR-Tac).

Methods: A noncompartmental analysis of pharmacokinetic data obtained from a phase 2 study in de novo kidney transplant recipients receiving either LCPT or IR-Tac was conducted. Intensive blood sampling was performed on days 1, 7, and 14, and tacrolimus whole blood concentrations were measured using a validated liquid chromatography with tandem mass spectrometry method. $T_{1/2eff}$ was estimated using within-participant accumulation ratios. $T_{1/2z}$ was estimated by linear regression of the terminal phase of the concentration versus time profile.

Results: The median accumulation ratios of LCPT and IR-Tac on day 14 were 3.18 and 2.06, respectively. The median (interquartile range; IQR) $t_{1/2eff}$ for LCPT at day 14 of dosing was 48.4 (37.4–77.9) hours, whereas the $t_{1/2z}$ was 20.3 (17.6–22.9) hours. For IR-Tac, the median (IQR) $t_{1/2eff}$ and $t_{1/2z}$ on day 14 were 12.5 (8.8–23.0) hours and 12.2 (9.2–15.7) hours, respectively.

Conclusions: Consistent with its prolonged release of tacrolimus, LCPT demonstrated a higher accumulation ratio and a longer $t_{1/2eff}$ compared with IR-Tac. These findings underscore the pharmacokinetic differences between different drug formulations of the same moiety and may help inform dose adjustments for LCPT in kidney transplantation.

Key Words: tacrolimus, LCPT, half-life, kidney transplant, steady state

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INTRODUCTION

In pharmacology, half-life typically refers to the terminal disposition half-life, defined as the time interval over which the concentration of a drug in blood or plasma decreases by half through redistribution and elimination.[1,2] Half-life is an important pharmacokinetic parameter that informs dosing intervals (eg, once-daily vs. twice-daily regimens) and the time to reach steady state upon multiple dosing.[1–3] Importantly, for drugs that exhibit multicompartment distribution, several half-life parameters can be defined.[1,2] Terminal half-life ($t_{1/2z}$) is the half-life value most often considered by clinicians to guide drug dosing and is most frequently reported in the prescribing information of medications.[1]

$T_{1/2z}$ is an appropriate and relevant parameter for drugs with linear, single-compartment pharmacokinetics, as it informs dosing intervals and helps estimate the time to steady state.[1,3] However, for certain drugs and/or formulations, such as those with modified release, prolonged absorption, and multicompartment distribution, $t_{1/2z}$ may not accurately reflect how long the drug persists in the body or the actual time required to reach steady state. In these situations, $t_{1/2z}$ represents only a fraction of the concentration–time curve and may not adequately describe drug accumulation after multiple dosing.[1,2]

Effective half-life ($t_{1/2eff}$) has been proposed as a clinically relevant pharmacokinetic parameter for drug formulations that exhibit complex drug release and absorption, including extended-release formulations and drugs with multicompartment pharmacokinetics.[4] Whereas $t_{1/2z}$ is estimated

From the *Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, La Jolla, California; †School of Pharmacy and Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; ‡Department of Pharmacy, Henry Ford Health, Detroit, Michigan; §Department of Medicine, University of Kansas Health System, Kansas City, Kansas; ¶Division of Nephrology, Vanderbilt University Medical Center, Nashville, Tennessee; and ‖Medical Affairs, Veloxis Pharmaceuticals, Inc., Cary, North Carolina.

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Correspondence: Jeremiah D. Momper, PharmD, PhD, University of California, San Diego 9500, Gilman Drive, MC 0657, La Jolla, CA 92093 (e-mail: jmomper@health.ucsd.edu)

based on the terminal slope of the concentration versus time profile (either from single dose or multiple dose data), $t_{1/2eff}$ considers the concentration–time profile of a drug after single and multiple dosing. The estimation of $t_{1/2eff}$ utilizes the ratio of drug exposure at steady state to drug exposure after the first dose (accumulation ratio, or R_{ac}), with a higher R_{ac} indicating greater drug accumulation. The concept of $t_{1/2eff}$ has been described for antiepileptic drugs, where formulations have been designed to blunt high peak plasma concentrations, reduce peak-to-trough fluctuations, and improve adherence.[1,3,5]

LCP tacrolimus (LCPT, Envarsus XR, Veloxis Pharmaceuticals, Cary, NC) is a once-daily, extended-release tacrolimus formulation approved for the prophylaxis of organ rejection in patients with a kidney transplant. LCPT presents a proprietary MeltDose technology that enhances oral bioavailability through a process known as "controlled agglomeration".[6,7] This results in prolonged absorption, with initial disintegration of the formulation in the stomach and proximal small bowel and more complete disintegration in the colon.[8] Pharmacokinetic data have demonstrated a markedly lower peak (maximum concentration, or C_{max}) concentration, delayed time to maximum concentration (T_{max}), lower peak-to-trough fluctuation, and increased bioavailability with LCPT compared with twice-daily immediate-release tacrolimus (IR-Tac).[7,9] Although exhibiting prolonged absorption and multicompartmental pharmacokinetics, $t_{1/2eff}$ has not previously been explored for tacrolimus from LCPT.[6,10] The objective of this study was to compare the $t_{1/2z}$ and $t_{1/2eff}$ for both IR-Tac and LCPT using robust pharmacokinetic data in de novo kidney transplant recipients.

METHODS

Pharmacokinetic data were obtained from a phase 2, open-label, randomized study in which adult patients undergoing de novo kidney transplant were randomized 1:1 to receive either once-daily LCPT at a starting dose of 0.14 mg/kg/d for non-Black patients and 0.17 mg/kg/d for Black patients or twice-daily IR-Tac capsules at a starting dose of 0.2 mg/kg/d. LCPT and IR-Tac doses were titrated based on clinical assessments and tolerability to achieve whole-blood trough concentrations of 7–20 ng/mL. Day 1 was defined as the day in which the first morning dose of the study drug was administered, within 48 hours of transplantation. Intensive blood sampling was performed on days 1, 7, and 14. For participants receiving once-daily LCPT, blood samples were collected at 0 (predose) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 14, 16, 20, and 24 hours postdose. For participants receiving twice-daily IR-Tac, blood samples were collected at 0 (predose) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 12.5, 13, 13.5, 14, 15, 16, 20, and 24 hours postdose. Tacrolimus concentrations in whole blood were quantified using a validated liquid chromatography-tandem mass spectrometry method.

Pharmacokinetic parameters were determined by noncompartmental analysis using the Phoenix WinNonlin software (version 8.1; Certara, Princeton, NJ). The maximum and minimum concentrations (C_{max}, C_{min}) and the corresponding time points (T_{max}, T_{min}) were observed directly. Area under the concentration versus time curve during the dosing interval ($AUC_{0-\ \tau}$) was determined using the linear trapezoidal method. Half-life during the elimination phase ($t_{1/2z}$) was calculated as ln(2)/k, where k is the elimination rate constant derived from the terminal linear slope of the log concentration versus time curve.

The dose-adjusted within-participant accumulation ratio (R_{ac}) was calculated using participant matched day 1 and 7 data and day 1 and 14 data, as follows: ($AUC_{0-\ \tau,\ Day\ 7}$/Day 7 Dose)/($AUC_{0-\ \tau,\ Day\ 1}$/Day 1 Dose) and ($AUC_{0-\ \tau,\ Day\ 14}$/Day 14 Dose)/($AUC_{0-\ \tau,\ Day\ 1}$/Day 1 Dose). The effective elimination rate constant (K_{eff}) and $t_{1/2eff}$ were estimated for each participant as:

$$t_{1/2eff} = \frac{\ln(2)}{K_{eff}}$$

The percentage of steady-state reached versus time was determined as $100 \times (1–½^{i})$, where i is the number of effective half-lives elapsed.

RESULTS

Participant Characteristics

Pharmacokinetic data were available for 31, 29, and 28 participants receiving LCPT at days 1, 7, and 14, respectively. A total of 26 participants had matched day 1 and day 7 data for LCPT, whereas 27 participants had matched day 1 and day 14 data. For IR-Tac, data were available for 30, 28, and 28 participants at days 1, 7, and 14, respectively. A total of 27 participants on IR-Tac had matched data for both days 1 and 7, and days 1 and 14. Participant characteristics are summarized in Table 1.

LCPT Pharmacokinetics

The median (interquartile range, IQR) daily dose of LCPT at days 1, 7, and 14 was 12 mg (10.25–14), 10 mg (8–14), and 10 mg (7–13.25), respectively (Table 2). The median (IQR) dose normalized trough concentration increased from 0.4 ng/mL/mg (0.3–0.6) on day 1 to 0.9 ng/mL/mg (0.6–1.4) on day 7 and 1.1 ng/mL/mg (0.6–1.6) on day 14.

On days 7 and 14, the median (IQR) R_{ac} values were 3.15 (2.69–4.21) and 3.18 (2.02–4.50), respectively. The tacrolimus AUC and C_{min} normalized to the median dose of 10 mg in participants receiving LCPT are displayed in Figure 1. The median (IQR) $t_{1/2eff}$ was 43.6 hours (35.8–61.3) using matched day 1 and 7 data and 48.4 hours (37.4–77.9) using matched day 1 and 14 data (Table 2). The time to steady state for LCPT based on $t_{1/2eff}$ is shown in Figure 2. The estimated $t_{1/2z}$ of tacrolimus administered as LCPT was similar at each time point and was approximately half of $t_{1/2eff}$.

IR-Tac Pharmacokinetics

The median (IQR) total daily doses of IR-Tac on days 1, 7, and 14 were 16.5 mg (14.0–18.75), 10 mg (7.75–12), and 8 mg (5.75–10.5), respectively (Table 3). The median

TABLE 1. Participant Characteristics

	LCPT (n = 31)	IR-Tac (n = 30)
Age, years, mean (SD)	49.1 (12.2)	46.2 (14.1)
Male, sex, n (%)	21 (67.7)	21 (70.0)
Race, n (%)		
White	25 (80.6)	20 (66.7)
African American	5 (16.1)	8 (26.7)
Other	1 (3.2)	2 (6.7)
Weight, kg, mean (SD)	87.4 (19.0)	89.6 (19.3)
BMI, mean (SD)	28.7 (4.4)	29.1 (5.2)

BMI, body mass index.

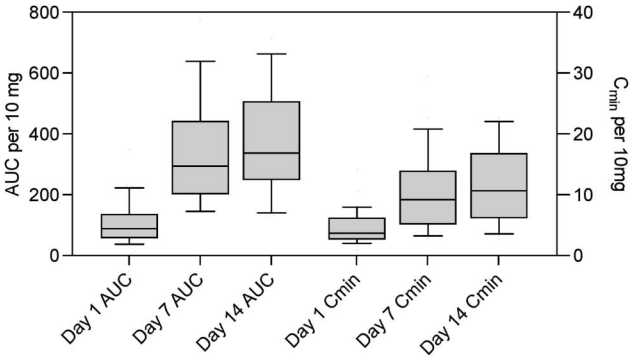

FIGURE 1. LCPT dose-normalized exposure (AUC) and trough concentration (C_{min}). Box plots display the 25th and 75th percentiles at the end of each box, with whiskers extending to the 10th and 90th percentiles. The horizontal lines within each box represent the median values.

(IQR) dose normalized trough concentration increased from 0.5 ng/mL/mg at day 1 to 0.9 ng/mL/mg (0.7–1.5) at both days 7 and 14. On days 7 and 14, the median (IQR) R_{ac} values were 2.11 (1.46–2.55) and 2.06 (1.64–3.29), respectively. The estimated $t_{1/2z}$ of tacrolimus when administered as IR-Tac was comparable to the $t_{1/2eff}$ (12.2 hours (9.2–15.7) and 12.5 hours (8.8–23.0), respectively, at day 14), and each was lower than the $t_{1/2eff}$ for LCPT (48.4 (37.4–77.9) h). The time to steady state for IR-Tac based on $t_{1/2eff}$ is shown in Figure 2.

DISCUSSION

For drug formulations that exhibit modified release characteristics and prolonged absorption, $t_{1/2z}$ may not adequately predict accumulation or the time required to reach steady state. In such instances, the effective half-life ($t_{1/2eff}$) —defined a priori based on accumulation ratio—has been proposed as a more relevant half-life parameter.[1] In this pharmacokinetic analysis, we showed that the $t_{1/2eff}$ of tacrolimus was markedly different between LCPT and IR-Tac in kidney transplant patients. This finding is consistent with the literature on extended-versus immediate-release formulations of antiepileptic drugs.[1,3,5]

To the best of our knowledge, this is the first study to evaluate the concept of $t_{1/2eff}$ with an immunosuppressant medication. Using the AUC after the first LCPT dose and upon multiple LCPT dosing in a de novo kidney transplant population, we estimated the median $t_{1/2eff}$ to be approximately 43–48 hours after 7–14 days of dosing. The estimated $t_{1/2eff}$ was similar when C_{max} and C_{min} were used from the first dose and multiple doses instead of the AUC (data not shown). The $t_{1/2eff}$ value for LCPT was more than twice the calculated $t_{1/2z}$. As expected, the $t_{1/2eff}$ for LCPT was longer than that for IR-Tac. Based on a median (IQR) $t_{1/2eff}$ of 48.4 (37.4–77.9) h for LCPT, achieving 93.75% of steady state (representing 4 $t_{1/2eff}$) would require a median (IQR) of 8.1 (6.2–13.0) days.

The main practical implications of these findings are related to monitoring and making more informed dose adjustments based on tacrolimus formulations. As tacrolimus has a narrow therapeutic window, frequent monitoring of whole blood concentrations in early postoperative settings is essential to optimize dosing.[11] The time to steady state, which is a function of $t_{1/2eff}$, is an important consideration in determining appropriate dose adjustments for patients receiving tacrolimus. The present study demonstrated that the $t_{1/2eff}$ and time to steady state differed between IR-Tac and LCPT; therefore, the tacrolimus formulation must also be considered when dosing adjustments are made. LCPT labelling states that the time to achieve steady state is approximately 7 days after initiating or changing the dose. By comparison, the data presented here show that

TABLE 2. LCPT Pharmacokinetic Data

Parameter, Median (IQR)	Day 1 (n = 31)	Day 7 (n = 29)	Day 14 (n = 28)
Dose (mg)	12 (10.25–14)	10 (8–14)	10 (7–13.25)
$AUC_{(0-\tau)}$ (ng × h/mL)	106.0 (86.0–194.2)	320.2 (217.9–406.1)	330.9 (268.3–434.9)
$AUC_{(0-\tau)}$/Dose (ng × h/ml/mg)	8.8 (6.8–13.2)	30.1 (21.6–44.2)	33.7 (25.7–47.6)
C_{max} (ng/mL)	10.2 (7.3–17.4)	21.6 (15.7–33.2)	23.1 (19.3–32.1)
C_{max}/Dose (ng/mL/mg)	0.8 (0.6–1.2)	2.5 (2.0–3.2)	2.7 (2.0–3.6)
T_{max} (h)	12.0 (7.0–15.0)	6.0 (3.1–6.0)	4.0 (2.8–6.0)
C_{min} (ng/mL)	4.8 (3.3–6.6)	9.0 (5.2–12.4)	9.5 (7.5–13.0)
C_{min}/Dose (ng/mL/mg)	0.4 (0.3–0.6)	0.9 (0.6–1.4)	1.1 (0.6–1.6)
$t_{1/2z}$ (h)	17.5 (13.6–20.8)	19.7 (15.3–21.7)	20.3 (17.6–22.9)
Accumulation ratio	—	3.15 (2.69–4.21)	3.18 (2.02–4.50)
$t_{1/2eff}$ (h)	—	43.6 (35.8–61.3)	48.4 (37.4–77.9)

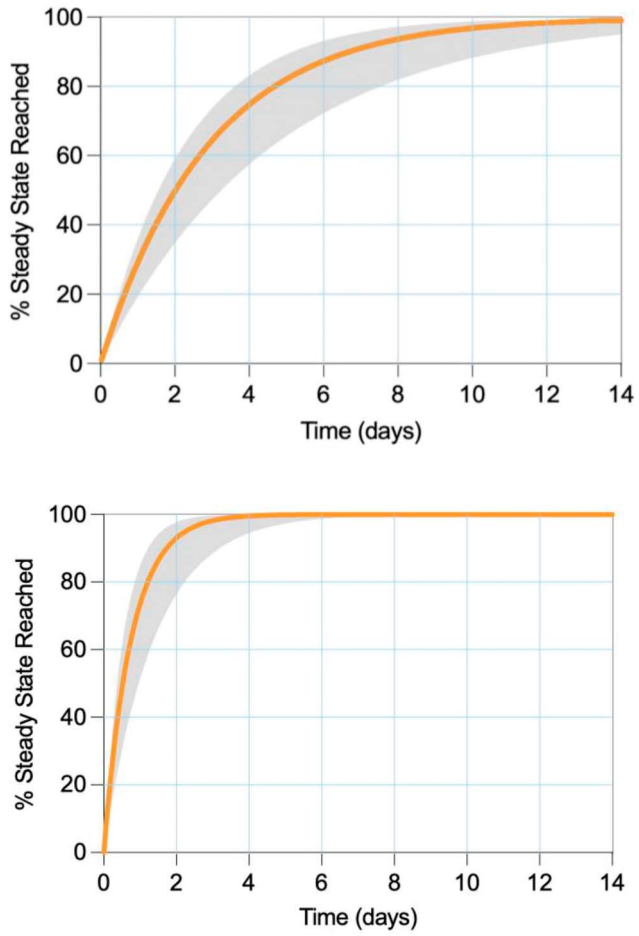

FIGURE 2. Estimated percentage of steady state achieved based on effective half-life ($t_{1/2eff}$) for LCPT (top) and IR-Tac (bottom). Solid line represents the median, and the shaded area shows the interquartile range (25th–75th percentile).

approximately 91% of LCPT steady state is reached at 7 days, and in fact, for a quarter of patients, only 78% or less of steady state is achieved on day 7. These results differ from those of IR-Tac, which exhibits less accumulation owing to its shorter $t_{1/2eff}$, indicating that the full impact of LCPT dose changes may be different from what clinicians are accustomed to with IR-Tac. This indicates that when considering dose adjustments for LCPT before steady state, clinical judgement must take into account additional accumulation expected to occur. This information may be considered to better inform the timing and/or magnitude of potential dose adjustments for patients receiving LCPT, particularly in the early transplantation period when frequent monitoring and dose adjustments occur.

Notably, the $t_{1/2z}$ values for both LCPT and IR-Tac in this study were lower than those reported in product labelling (Prograf and LCPT PIs).[6,12] This finding may be explained by differences in the sampling window, methods used to calculate the half-life, and the population in which $t_{1/2z}$ was determined. Half-life estimates may be influenced by the sampling duration.[13,14] Calculations based on shorter intervals may provide different estimates of $t_{1/2z}$ compared with studies with longer sampling windows.[13,14] In addition, the shorter half-life of tacrolimus among kidney transplant recipients compared with healthy volunteers has also been demonstrated with IR-Tac,[13] and a similar observation was made in the current study. The current study, which is the first to estimate the $t_{1/2z}$ for LCPT in adult kidney transplant recipients, approximated $t_{1/2z}$ at 20 hours compared with previous studies in healthy volunteers, where $t_{1/2z}$ estimates were reported to be approximately 31 hours.[6,10]

The current study has some limitations. The analysis was performed in de novo kidney transplant recipients but not in stable kidney transplant recipients. Second, the analysis was performed in patients enrolled in a phase 2 trial, in which patients with certain factors influencing tacrolimus pharmacokinetics, such as the concomitant use of interacting medications or liver dysfunction, were excluded from enrollment. Similarly, genotyping was not performed; therefore, the impact of the CYP3A4/5 polymorphisms could not be determined. It is worth noting that CYP3A5*1 expressors have been shown to require higher doses of LCPT to achieve therapeutic concentrations.[15,16] This analysis assumes that tacrolimus follows linear pharmacokinetics (dose- and time-independent) when administered as LCPT or IR-Tac and that exposure changes proportionally with dose; however, there is no evidence for nonlinear kinetics for tacrolimus. Finally, given that clinician-driven dose changes were allowed for

TABLE 3. IR-Tac Pharmacokinetic Data

Parameter, Median (IQR)	Day 1 (n = 30)	Day 7 (n = 28)	Day 14 (n = 28)
Dose (mg)	16.5 (14.0–18.75)	10 (7.75–12)	8 (5.75–10.5)
$AUC_{(0-\tau)}$ (ng × h/mL)	241.0 (185.4–308.3)	296.7 (214.1–360.9)	271.0 (188.9–334.5)
$AUC_{(0-\tau)}$/Dose (ng × h/ml/mg)	15.8 (13.4–18.5)	28.9 (17.1–39.6)	30.8 (25.1–45.9)
C_{max} (ng/mL)	22.3 (13.6–32.2)	21.4 (13.9–33.6)	18.9 (15.8–25.3)
C_{max}/Dose (ng/mL/mg)	1.5 (0.9–2.0)	2.7 (1.4–3.2)	3.0 (1.9–3.5)
T_{max} (h)	4.0 (1.5–13.9)	1.6 (1.0–3.8)	1.9 (1.5–3.0)
C_{min} (ng/mL)	8.1 (6.6–10.4)	9.0 (7.8–11.8)	8.1 (5.7–10.5)
C_{min}/Dose (ng/mL/mg)	0.5 (0.4–0.7)	0.9 (0.7–1.5)	0.9 (0.7–1.5)
$t_{1/2z}$ (h)	9.6 (7.9–11.0)	10.7 (8.8–14.6)	12.2 (9.2–15.7)
Accumulation ratio	—	2.11 (1.46–2.55)	2.06 (1.64–3.29)
$t_{1/2eff}$ (h)	—	12.9 (7.2–16.7)	12.5 (8.8–23.0)

participants on both IR-Tac and LCPT, some participants may not have been at steady state on day 7 or 14, which may have underestimated $t_{1/2eff}$.

The key strengths of this study were the availability of intensive pharmacokinetic data to estimate $t_{1/2z}$ and $t_{1/2eff}$, and the ability to analyze half-life in a population of de novo kidney transplant recipients rather than in healthy volunteers or stable kidney transplant recipients. This is the first study to evaluate the concept of $t_{1/2eff}$ for immunosuppressant medications, providing unique pharmacokinetic data for LCPT.

CONCLUSION

The $t_{1/2eff}$ is considered a more clinically relevant pharmacokinetic parameter for extended-release drug formulations than for immediate-release formulations of the same active substance. The present analysis demonstrated differences in $t_{1/2z}$ and $t_{1/2eff}$ for LCPT, and differences in $t_{1/2z}$ and $t_{1/2eff}$ for LCPT, compared with the immediate-release formulation, IR-Tac. These findings provide insights into the interpretation of tacrolimus concentrations and inform clinical decision making when administering LCPT to kidney transplant recipients.

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