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ORIGINAL ARTICLE

Comparative pharmacokinetics of tacrolimus in stable pediatric allograft recipients converted from immediate-release tacrolimus to prolonged-release tacrolimus formulation

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Abstract

This study was a Phase II, open-label, multicenter, single-arm, cross-over study comparing the pharmacokinetics (PK) of tacrolimus in stable pediatric kidney, liver, or heart allograft recipients converted from immediate-release tacrolimus (IR-T) to prolonged-release tacrolimus (PR-T). In Days −30 to −1 of screening period, patients received their IR-T-based regimen; during Days 1-7, patients received study IR-T (same dose as screening). On Day 7, the first 24-hours PK profile was taken; patients were then converted to PR-T (1 mg:1 mg), with a second 24-hours PK profile taken on Day 14. The primary end-point was tacrolimus area under the blood concentration–time curve over 24 hours (AUC_{24}); secondary end-points were maximum concentration

Abbreviations: AUC, area under the blood concentration–time curve; AUC_{24}, area under the blood concentration–time curve over 24 hours; C_{24}, concentration at 24 hours; CI, confidence interval; C_{max}, maximum concentration; HPLC/MS/MS, high-performance liquid chromatography tandem mass-spectrometry; LSM, least squares mean; MMF, mycophenolate mofetil; PKAS, pharmacokinetics analysis set; PK, pharmacokinetics; SD, standard deviation; T_{max}, time to maximum concentration.

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$C_{max}$and concentration at 24 hours C_{24}. The predefined similarity interval for confidence intervals (CIs) of least squares mean (LSM) ratios was 80%-125%. The PK analysis set comprised 74 pediatric transplant recipients (kidney, n = 45; liver, n = 28; heart, n = 1). PR-T:IR-T LSM ratio (90% CI) was similar overall for $AUC_{24,\ max}$, and C_{24}, and for kidney and liver recipients for AUC_{24} (LSM ratio, kidney 91.8%; liver 104.1%) and C_{24} (kidney 90.5%; liver 89.9%). Linear relationship was similar between AUC_{24} and C_{24}, and between PR-T and IR-T (rho 0.89 and 0.84, respectively), suggesting that stable pediatric transplant recipients can be converted from IR-T to PR-T at the same total daily dose, using the same therapeutic drug monitoring method.

KEYWORDS

heart transplantation, kidney transplantation, liver transplantation, pediatrics, pharmacokinetics, tacrolimus

1 | INTRODUCTION

Following solid organ transplantation, tacrolimus-based immunosuppression is the most commonly used treatment regimen to prevent allograft rejection.[1] As tacrolimus has a narrow therapeutic index, it is important that exposure to the drug is maintained within a tightly defined range, as overexposure can cause drug-related adverse effects and toxicity,[2] while underexposure is associated with poor transplant outcomes.[3,4] Oral bioavailability of tacrolimus exhibits large interpatient variability[5] and, therefore, the dose of tacrolimus is optimized on the basis of maintaining the patients' systemic exposure within a narrow range. As the AUC for tacrolimus is significantly associated with efficacy,[2,6] therapy is optimized on an individual patient basis by monitoring tacrolimus trough concentrations as a surrogate marker of AUC.

Available formulations of tacrolimus include twice-daily, immediate-release capsules and once-daily, prolonged-release capsules. While immediate-release tacrolimus is approved for the prophylaxis of transplant rejection in adult and pediatric liver, kidney, and heart allograft recipients,[7] the prolonged-release formulation is approved for the prophylaxis of transplant rejection in adult liver and kidney allograft recipients only. Evidence suggests that converting patients from immediate- to prolonged-release tacrolimus maintenance immunosuppression can increase treatment adherence and reduce intrapatient variability in tacrolimus exposure,[8-10] which could potentially improve long-term transplant outcomes.[3,11]

Extensive clinical experience suggests that stable adult transplant recipients can be safely converted from immediate- to prolonged-release tacrolimus on a 1 mg:1 mg total daily dose basis.[12-15] However, after conversion, trough concentrations of tacrolimus should be monitored, and the dose adjusted as required to ensure that adequate exposure to tacrolimus is maintained.

Currently, clinical experience with prolonged-release tacrolimus in pediatric patients is limited. In the pediatric studies reported to date, patients were converted on a 1 mg:1 mg basis. Heffron et al reported data from a study performed in 18 stable pediatric liver transplant patients, which suggested that the mean exposure to tacrolimus over 24 hours (AUC_{24}) was similar between prolonged- and immediate-release tacrolimus.[16] Min et al reported data from 34 Korean pediatric renal transplant patients and showed that AUC_{24} 7 days after conversion was approximately 15% lower with prolonged- vs immediate-release tacrolimus.[17] However, following dose adjustments during a further 2-week period, tacrolimus exposure was similar between the formulations, with a comparable mean overall dose.[17] Additionally, in a study by Lapeyraque et al, data from 19 pediatric kidney transplant patients suggested that the median tacrolimus AUC_{24} was approximately 10% lower with the prolonged-release vs the immediate-release formulation.[18] However, these were small-scale studies and warrant further research to confirm that stable pediatric transplant recipients can be safely converted from immediate-release to prolonged-release tacrolimus at the same total daily dose. We therefore undertook the current larger study to compare the PK of tacrolimus before and after conversion from immediate- to prolonged-release tacrolimus in stable pediatric kidney, liver, and heart allograft recipients.

2 | PATIENTS AND METHODS

2.1 | Study design

This was a 6-week, Phase II, open-label, multicenter, single-arm, one-way, cross-over study that compared the PK of tacrolimus in stable pediatric transplant recipients converted from an immediate-release tacrolimus- (Prograf®, Astellas Pharma Ltd, Chertsey, UK) to a prolonged-release tacrolimus-based regimen (Advagraf®, Astellas Pharma Europe BV, Netherlands). Patients were enrolled from 14 centers in seven countries across Europe between June 2011 and October 2015 (ClinicalTrials.gov identifier: NCT01294020).

The study was conducted in accordance with Good Clinical Practice, International Council on Harmonisation guidelines, and the Declaration of Helsinki. The respective Ethics Committees of each contributing

center approved the study protocol. Prior to study commencement, written informed consent was obtained from all individual participants included in the study (if appropriately aged to provide consent) or their guardian. Patients could withdraw from the study at any time.

2.2 | Patients

Patients were included if they were aged ≥5 and ≤16 years, able to swallow intact drug capsules, had received a heart, liver, or kidney transplant ≥6 months before the study, were maintained on an immediate-release tacrolimus-based immunosuppressive regimen for ≥3 months, and were clinically stable in the opinion of the investigator. Patients included were required to have had stable whole-blood tacrolimus trough levels between 3.5 and 15.0 ng/mL, measured on at least two separate occasions, ≥6 days apart, and within 30 days of study commencement.

Key exclusion criteria were multiple organ transplantation, and any rejection episode either <3 months before the study, or <6 months before the study if antibody therapy was required. Patients could not be receiving sirolimus, everolimus, or formulations of mycophenolic acid (other than MMF). While generic formulations of MMF were not excluded, they were not used by any of the participating centers. Patients were also excluded if they required treatment with medications known to inhibit or induce tacrolimus metabolism during, or within 28 days prior to, the study.

2.3 | Study treatment

All eligible patients entered a 30-day screening period (Day −30 to Day −1) during which they continued to receive their immediate-release tacrolimus-based regimen. On Days 1-7, patients received twice-daily, immediate-release tacrolimus capsules, orally, as study medication, at the same dose as received during the screening period. A 24-hour PK profile was taken on Day 7 (ending predose on Day 8). Following completion of the PK profile, all eligible patients were converted from immediate-release tacrolimus to a single morning dose of once-daily, prolonged-release tacrolimus on a 1 mg:1 mg total daily dose basis, with no rounding of doses. The dose of prolonged-release tacrolimus was maintained until Day 14 (the day of the second 24-hour PK profile, which ended predose on Day 15). Dose adjustments of tacrolimus were not permitted during the study, until after the Day 14 PK profile had been taken.

Patients could continue to receive steroids, azathioprine, or MMF throughout the study period, at constant dose, if they had been taking these treatments before enrollment.

2.4 | Pharmacokinetic profiles assessment

For the PK analysis, the first blood sample was taken after a fasting period of at least 6 hours, before study drug administration. Patients were not fasted during the 24-hour PK sampling period. Whole-blood samples were collected before the morning dose (0 hours), and 1, 2, 4, 6, 12, 13, 14, 16, 18, and 24 hours post-dose on Day 7 (immediate-release tacrolimus) and on Day 14 (prolonged-release tacrolimus). On Day 7, 12-hour blood sampling commenced before the evening dose of immediate-release tacrolimus.

As described previously,[12] 2 mL aliquots of blood were mixed with ethylenediaminetetraacetic acid and frozen at −20°C within 2 hours of collection. Samples were stored until shipment to the central laboratory for bioanalysis. Tacrolimus concentrations were then measured using a validated (HPLC/MS/MS) assay (lower limit of quantification, 0.059 ng/mL), based on the methodology by Alak et al[19] Study samples, whole-blood calibrators, and quality-control samples were thawed, and 1 mL aliquots were taken. Internal standard (tacrolimus analog FR900520; 20 μL, 50 ng/mL) was added and mixed. Aliquots were extracted by protein precipitation and solid-phase extraction using C18 200 mg/3 mL cartridges. Elutes were then evaporated to dryness under a stream of nitrogen at 40°C, and residues were redissolved in a 50:50 mix (vol/vol) of acetonitrile and water, mixed, and centrifuged. Following this process, samples were submitted for HPLC/MS/MS.[12] The between-day and within-day precision of the assay at concentrations of 0.3, 4.0, and 8.0 ng/mL was <5.0% coefficient of variation.[19] All procedures were performed in compliance with the principles of Good Laboratory Practice.

The primary end-point was the AUC_{24} of tacrolimus on Days 7 and 14. Secondary end-points were maximum tacrolimus concentration (C_{max}), time to C_{max} (T_{max}), and tacrolimus C_{24}, on Days 7 and 14.

Other end-points included tacrolimus dose and trough levels, and the proportion of patients within the recommended whole-blood tacrolimus trough range (3.5-15.0 ng/mL) on Days 7 and 14.

2.5 | Statistical analyses and sample size calculation

Sample size was calculated using a significance level of $p = 0.05$, assuming a steady-state AUC_{24} ratio of geometric LSM of 0.9, and a SD; log scale of 0.18, irrespective of the organ transplanted and age group. Using these parameters, 72 patients with two complete PK profiles provided 97% power to assess similarity of exposure. This was based on a two-sided 90% CI for the ratio of geometric LSM, and a similarity interval of 80%-125%.

The PKAS included all patients who received at least one dose of study medication and provided two complete PK profiles. Analyses were stratified by treatment and transplanted organ type (kidney, liver, or heart). To estimate the PK parameters, standard non-compartmental methods were used. AUC_{24} was calculated using the linear-log trapezoidal rule. AUC_{24}, C_{max}, and C_{24} were compared between prolonged- and immediate-release formulations using a mixed-effects model on log-transformed PK parameters, with treatment and organ transplanted included as fixed effects, age at baseline as a continuous covariate, and patient as a random effect. The difference of LSM of log-transformed PK parameters between formulations, and its 90% CI, was back-transformed to the raw scale and was expressed as percentages. If the 90% CI for the ratio of geometric LSM was within the predefined

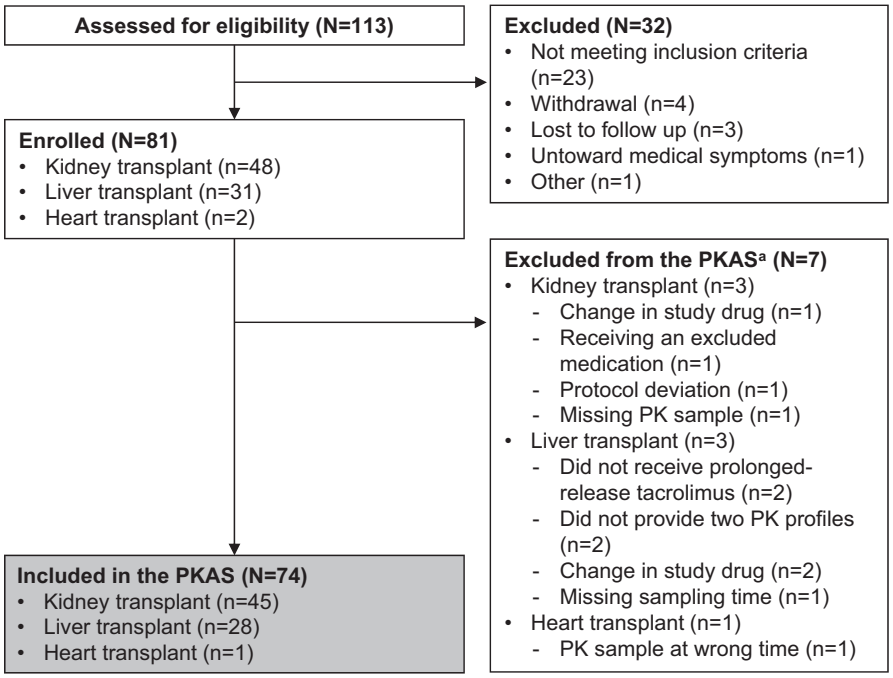

FIGURE 1 Patient flow through the study. [a]More than one reason for exclusion can apply to a patient. PK, pharmacokinetics; PKAS, pharmacokinetics analysis set

similarity interval of 80%-125%, then the PK parameter was considered to be similar between tacrolimus formulations. Treatment-by-age and treatment-by-organ-transplant interactions were assessed for PK parameters using a mixed-effects model, with interactions deemed significant at an associated *p* value ≤0.10.

For both treatments, the correlation between C_{24} and AUC_{24} was assessed using regression analysis, and by calculating the Pearson correlation coefficient (rho). The correlation was classified as "strong" if it was greater than 0.7, and "moderate" if between 0.3 and 0.7 inclusive; below 0.3, the correlation was deemed "weak." SAS® Version 9.3 or higher was used for all data processing, summarization, and analyses.

3 | RESULTS

3.1 | Study population

Of 113 screened patients, 81 were enrolled and received study medication, of whom 74 (kidney, n = 45; liver, n = 28; heart, n = 1) were included in the PKAS (Figure 1). Patient baseline demographics and characteristics are presented in Table 1; due to the small patient numbers, statistical comparisons between organ types were not performed. In the overall PKAS, over half of patients (59.5%) were male, and the mean ± SD age was 11.5 ± 2.8 years (range 5-16 years). Overall, 43.2% of patients were children (aged ≥5 to ≤11 years) and 56.8% were adolescents (aged ≥12 to ≤16 years). The mean ± SD height and weight were 144.4 ± 17.8 cm and 41.8 ± 15.6 kg, respectively, but there was wide variation, due to the age range of the patients.

3.2 | Dosage and trough levels

As per protocol, patients included in the PKAS did not have dose adjustments, and all were converted from immediate- to prolonged-release tacrolimus on a 1 mg:1 mg total daily dose basis. Therefore, the mean ± SD tacrolimus daily dose (mg) was the same with immediate-release tacrolimus on Day 7 and prolonged-release tacrolimus on Day 14 (7.99 ± 4.94, 8.67 ± 5.66, 6.96 ± 3.42, and 6.00 (no SD) overall, and for kidney, liver, and heart recipients, respectively). The mean ± SD weight-adjusted tacrolimus daily doses (mg/kg) were also similar with immediate- and prolonged-release tacrolimus on Days 7 and 14, respectively, for the overall PKAS, and by organ transplanted (Figure 2A).

The mean ± SD tacrolimus trough levels were slightly lower with prolonged-release tacrolimus on Day 14 compared with immediate-release tacrolimus on Day 7 (Figure 2B). Mean tacrolimus trough levels were approximately 20% lower in liver than in kidney recipients, irrespective of tacrolimus formulation. As data are available for only one patient, the higher tacrolimus trough level observed in the heart recipient (8.1 and 8.3 ng/mL on Days 7 and 14, respectively) vs other organ types cannot be interpreted.

Tacrolimus trough levels from routine monitoring were generally within target range on Day 7 for liver and kidney transplant patients receiving immediate-release tacrolimus (95.6% and 89.3% of patients, respectively); 2.2% and 3.6% of patients, respectively, were below the target range. Following conversion to prolonged-release tacrolimus, there was an increase in the proportion of kidney and liver patients with trough tacrolimus levels below the target range on Day 14 (8.9% and 28.6% below target, respectively). No patients were above the target range with either formulation on Days 7 and 14.

3.3 | Tacrolimus blood concentration–time profile

The mean whole-blood concentration–time curve of tacrolimus for the 24 hours after administration of the two formulations is

TABLE 1 Patient baseline demographics and characteristics for the overall population and stratified by organ type (PKAS)

Parameter	Kidney transplant (n = 45)	Liver transplant (n = 28)	Heart transplant (n = 1)	Overall (n = 74)
Age, y				
Mean ± SD[a]	10.8 ± 2.9	12.5 ± 2.2	13.0	11.5 ± 2.8
Median	11.0	13.0	–	12.0
Minimum, maximum	5, 16	7, 16	–	5, 16
Age category, n (%)				
≥5 to ≤11 y (children)	24 (53.3)	8 (28.6)	0	32 (43.2)
≥12 to ≤16 y (adolescents)	21 (46.7)	20 (71.4)	1 (100.0)	42 (56.8)
Gender, male, n (%)	28 (62.2)	15 (53.6)	1 (100.0)	44 (59.5)
Race, n (%)				
White	42 (93.3)	23 (82.1)	1 (100.0)	66 (89.2)
Black/African American	0 (0)	1 (3.6)	0	1 (1.4)
Asian	2 (4.4)	0	0	2 (2.7)
Other	1 (2.2)	4 (14.3)	0	5 (6.8)
Weight, kg				
Mean ± SD[a]	38.7 ± 17.5	46.1 ± 10.5	62.0	41.8 ± 15.6
Median	35.0	47.7	–	40.3
Minimum, maximum	17, 109	29, 66	–	17, 109
Height, cm				
Mean ± SD[a]	138.1 ± 18.1	153.8 ± 12.3	164.5	144.4 ± 17.8
Median	137.4	155.2	–	146.0
Minimum, maximum	103, 181	130, 174	–	103, 181

Note. due to rounding errors, percentages may not add up to 100%.
[a]SD and median are not reported for heart transplant, as n = 1. PKAS, pharmacokinetics analysis set; SD, standard deviation.

presented for the overall PKAS in Figure 3. As the immediate-release formulation is administered twice daily, the concentration–time profile was biphasic, with a second concentration peak at approximately 14 hours, which was about 2 hours after the second dose.

3.4 | Pharmacokinetic parameters

Overall, the tacrolimus AUC_{24} was comparable for prolonged- and immediate-release formulations (169.5 and 175.4 ng·h/mL, respectively). The geometric LSM ratio for prolonged-release:immediate-release tacrolimus was 96.7%, and the 90% CI (92.3%, 101.2%) was within the predefined similarity interval (Table 2). As expected based on clinical practice, the mean exposure was higher in kidney than in liver transplant patients (p = 0.026). Nevertheless, tacrolimus systemic exposure was similar between formulations in both kidney and liver recipients (geometric LSM ratios (90% CI): 91.8% (86.6%, 97.2%) and 104.1% (96.8%, 111.9%), respectively). As only one heart recipient was included in the PKAS, statistical assessment regarding the similarity of tacrolimus formulations was precluded for this organ type.

The 90% CIs of the geometric LSM ratio for C_{24} were within the similarity interval for the overall PKAS, and when stratified by the organ transplanted (kidney or liver). Geometric LSM ratios for prolonged-release:immediate-release tacrolimus (90% CI) were 90.4% (85.0%, 96.1%), 90.5% (83.5%, 98.0%), and 89.9% (81.2%, 99.4%), respectively (Table 2). No interaction was observed between treatment and transplanted organ for tacrolimus C_{24} (p = 0.929).

With both the prolonged-release and immediate-release formulations, the linear relationships between tacrolimus AUC_{24} and C_{24} were similar, with a strong positive correlation (Figure 4), irrespective of organ type. For the overall population, the Pearson correlation coefficients were comparable with prolonged- and immediate-release tacrolimus (0.89 and 0.84, respectively). This was also true for kidney (0.89 and 0.90, respectively) and liver recipients (0.83 and 0.77).

In the overall population, the geometric LSM for C_{max} was approximately 11 ng/mL with both formulations. The prolonged-release:immediate-release tacrolimus geometric LSM ratio (90% CI) was 94% (87.1%, 100.8%), and the 90% CI was within the predefined similarity interval (Table 2). When stratified by organ transplant, the C_{max} geometric LSM ratio 90% CI was within the predefined similarity interval for liver recipients, but the lower limit fell outside the range for

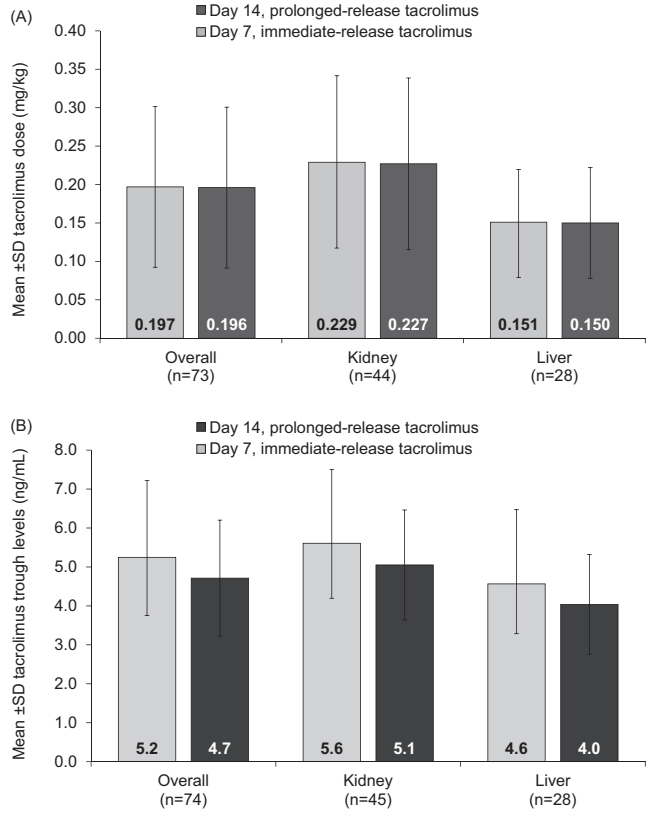

FIGURE 2 Mean tacrolimus (A) daily dose and (B) trough levels at Day 7 (immediate-release formulation) and Day 14 (prolonged-release formulation) for the overall population, and split by organ type (PKAS). Tacrolimus dose was adjusted for the body weight at the time of dosing; weight-adjusted dosing data are missing for one kidney transplant patient. The single heart transplant patient is included in the overall population. PKAS, pharmacokinetics analysis set; SD, standard deviation

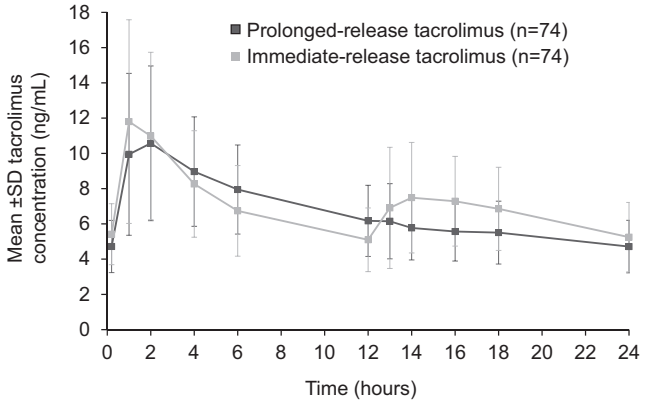

FIGURE 3 Mean whole-blood concentration of tacrolimus for the overall PKAS (linear plot). n = 73 at 13, 14, and 18 h after prolonged-release tacrolimus administration, and at 1 and 13 h after immediate-release tacrolimus administration as the sample was not taken. The missing sample was not considered to affect the estimation of PK data. PK, pharmacokinetics; PKAS, pharmacokinetics analysis set; SD, standard deviation

kidney transplant patients (Table 2). There was a significant interaction between treatment and organ transplanted, indicating that C_{max} differed between recipients of different organs ($p = 0.003$).

Overall, mean T_{max} was numerically longer with prolonged- vs immediate-release tacrolimus (mean ± SD 2.9 ± 3.6 vs 1.7 ± 1.1 hours, respectively). A similar pattern was observed in kidney and liver allograft recipients (Table 3).

4 | DISCUSSION

While PK studies of stable pediatric patients converted from immediate- to prolonged-release tacrolimus have been published,[16-18] to our knowledge, this is the largest and most robust study to date. The study was designed to have a power of 97% to assess similarity of tacrolimus exposure between the formulations, based on a two-sided 90% CI for the ratio of geometric LSM and a similarity interval of 80%-125%. We report that, in a population of stable pediatric kidney, liver, and heart transplant patients converted from immediate- to prolonged-release tacrolimus (1 mg:1 mg), the mean systemic exposure to tacrolimus (AUC_{24}) for prolonged-release tacrolimus is similar, under steady-state conditions (after 7 days on unchanged dose), to that for immediate-release tacrolimus. There is also a strong correlation between AUC_{24} and C_{24} for both formulations during steady state.

In this study, the linear relationship between tacrolimus trough concentration (C_{24}) and systemic exposure (AUC_{24}) was comparable for prolonged- and immediate-release tacrolimus (rho 0.89 and 0.84, respectively). Furthermore, the relationship was strong, irrespective of organ type. These findings are consistent with previous PK studies of adult and pediatric patients,[12-14,16,17] for example, a strong and similar, positive correlation between C_{24} and AUC_{24} with prolonged- and immediate-release tacrolimus (rho 0.90 and 0.94, respectively) in pediatric liver transplant patients.[16] Targeting the same trough levels with both formulations should, therefore, provide comparable steady-state exposure to tacrolimus in stable pediatric transplant patients, converted from immediate- to prolonged-release tacrolimus on a 1 mg:1 mg total daily dose basis. Importantly, these data also suggest that the same therapeutic drug monitoring approach can be used with both formulations.

The observed mean C_{max} was similar with both tacrolimus formulations in the overall PKAS and in the liver recipients in this study. For AUC_{24} and C_{max}, we observed a significant interaction between treatment and transplanted organ type. The significance of these interactions is uncertain. Many factors may contribute to a difference in exposure between immediate- and prolonged-release tacrolimus, including age, concomitant medications, and genotype (e.g, cytochrome P450 3A5 polymorphisms).[20,21] However, as described above, the relationship between C_{24} and AUC_{24} is similar for both formulations; therefore, the same trough levels can be targeted.

We also observed that the mean T_{max} was longer in patients receiving prolonged-release tacrolimus than in those receiving the immediate-release formulation (3 hours vs 2 hours, respectively), irrespective of transplanted organ type. This was expected, as the

TABLE 2 Statistical comparison of PK parameters between prolonged- and immediate-release tacrolimus for the overall population and stratified by organ type (PKAS)

Organ type	Parameter	Geometric LSM for prolonged-release tacrolimus	Geometric LSM for immediate-release tacrolimus	LSM ratio	90% CI of ratio
Overall (n = 74)	AUC_{24} (ng·h/mL)	169.52	175.37	96.66	92.31, 101.22
	C_{max} (ng/mL)	11.18	11.94	93.69	87.07, 100.81
	C_{24} (ng/mL)	5.18	5.74	90.39	85.00, 96.13
Kidney (n = 45)	AUC_{24} (ng·h/mL)	169.00	184.19	91.75	86.64, 97.16
	C_{max} (ng/mL)	11.79	14.05	83.89	77.02, 91.36
	C_{24} (ng/mL)	4.93	5.44	90.48	83.53, 98.01
Liver (n = 28)	AUC_{24} (ng·h/mL)	129.70	124.63	104.07	96.78, 111.91
	C_{max} (ng/mL)	9.74	9.01	108.09	97.01, 120.44
	C_{24} (ng/mL)	3.76	4.18	89.86	81.20, 99.44

Note. AUC_{24}, concentration–time curve over 24 h; C_{24}, concentration at 24 h; CI, confidence interval; C_{max}, maximum concentration; LSM, least squares mean; PK, pharmacokinetics; PKAS, pharmacokinetics analysis set.

prolonged-release formulation has an extended oral absorption profile for tacrolimus, throughout the gastrointestinal tract, compared with the immediate-release formulation of tacrolimus.[22,23]

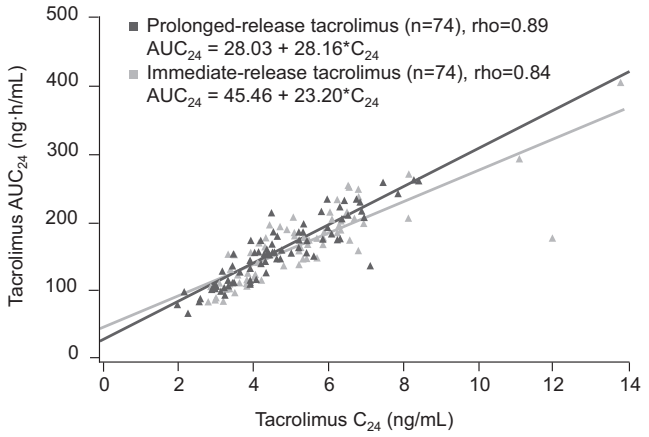

FIGURE 4 Linear scatter plot of tacrolimus AUC_{24} vs C_{24} for the overall PKAS, after administration of the immediate-release and prolonged-release formulation. AUC_{24}, area under the concentration–time curve over 24 h; C_{24}, concentration at 24 h; PKAS, pharmacokinetics analysis set

Consistent with the study design, the mean daily dose (mg/kg) of tacrolimus was similar pre- and post-conversion from immediate- to prolonged-release tacrolimus. Systemic exposure to tacrolimus was numerically higher in kidney recipients than in liver recipients. This is not surprising as, in clinical practice, liver transplant patients tend to be maintained with lower exposure than kidney transplant recipients. In the overall PKAS, exposure to tacrolimus was slightly lower following prolonged-release tacrolimus administration (as indicated by prolonged-release:immediate-release tacrolimus geometric LSM ratios of 90.39% for AUC_{24} and 96.66% for C_{24}); this has been observed in previous studies in adult transplant patients. Across five studies of stable adult patients converted from immediate- to prolonged-release tacrolimus, the mean systemic exposure to tacrolimus (AUC_{24}) for the prolonged-release formulation was approximately 10% lower (mean from 3% to 13%) than that for immediate-release tacrolimus.[8,12-15] A recent head-to-head PK study found that a conversion factor of +8% was required to obtain similar tacrolimus exposure, when converting stable kidney transplant patients from immediate- to prolonged-release tacrolimus.[24] Despite these findings, encouragingly, others have demonstrated the clinical efficacy and safety of the prolonged-release formulation following conversion from immediate-release formulation in pediatric transplant recipients. For example, in several studies of stable pediatric liver

TABLE 3 T_{max} with prolonged- and immediate-release tacrolimus for the overall population and stratified by organ type (PKAS)

	T_{max}, h			
	Prolonged-release tacrolimus		Immediate-release tacrolimus	
Population	Mean ±SD[a]	Median (minimum, maximum)	Mean ± SD	Median (minimum, maximum)
Overall (n = 74)	2.92 ± 3.58	1.98 (0.92, 24.0)	1.71 ± 1.11	1.06 (0.90, 6.00)
Kidney (n = 45)	2.60 ± 2.73	1.97 (0.92, 13.0)	1.64 ± 1.24	1.00 (0.95, 6.00)
Liver (n = 28)	3.39 ± 4.69	2.00 (0.98, 24.0)	1.75 ± 0.79	1.96 (0.90, 4.00)

Note. SD and median are not reported for heart transplant, as n = 1.
PKAS, pharmacokinetics analysis set; SD, standard deviation; T_{max}, time to maximum concentration.

and kidney recipients, no cases of biopsy-confirmed acute rejection, graft losses, or patient deaths were reported up to 1 year after conversion from immediate- to prolonged-release tacrolimus.[16,25,26]

In this study, only pediatric patients aged ≥5 years were included, as participants needed to be capable of swallowing intact capsules. Given that tacrolimus clearance is reportedly higher in children aged <5 years,[27] a once-daily formulation would not be appropriate in pediatric patients <5 years old. The results of this study are, therefore, not applicable to younger patients.

In conclusion, we report data from the largest PK study of pediatric solid organ recipients converted from immediate- to prolonged-release tacrolimus. Compared with other PK trials to date in this patient population, our study has the greatest statistical power to assess similarity of tacrolimus exposure between immediate- and prolonged-release formulations. In this study, AUC_{24} and C_{24} were within the predefined similarity intervals for these formulations, and the C_{24}:AUC_{24} relationship was similar between prolonged-and immediate-release tacrolimus. This indicates that targeting the same trough levels should provide comparable steady-state tacrolimus exposure, in pediatric solid organ recipients converted from twice-daily, immediate-release to once-daily, prolonged-release tacrolimus on a 1 mg:1 mg total daily dose basis. The same therapeutic drug monitoring approach may be used with both formulations.

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CONFLICTS OF INTEREST

JR, KV, ASL, DK, PC, LD and CR report non-financial support from Astellas, during the conduct of the study. DD and FI report non-financial support and other from Astellas, during the conduct of the study, and other from Astellas, outside the submitted work. NJAW and SR report non-financial support and other from Astellas, during the conduct of the study. SDM reports grants, other, and non-financial support from Astellas, during the conduct of the study, and grants from Novartis, outside the submitted work. BT reports non-financial support and other from Astellas, during the conduct of the study; grants and other from Astellas and Novartis, outside the submitted work; and other from Bristol-Myers Squibb and Roche, outside the submitted work. GK reports non-financial support and other from Astellas, during the conduct of the study, and GK is a consulting statistician working on behalf of Astellas. NU reports non-financial support and other from Astellas, during the conduct of the study, and NU is an employee of Astellas. Medical writing support in the development of this manuscript was provided by Cello Health MedErgy, funded by Astellas Pharma, Inc.

AUTHOR CONTRIBUTIONS

Jacek Rubik: Contributed to data collection, analyzed and interpreted the data, and critically revised the manuscript for important intellectual content. Dominique Debray: Contributed to data collection, analyzed and interpreted the data, and critically revised the manuscript for important intellectual content. Franck Iserin: Contributed to data collection, analyzed and interpreted the data, and critically revised the manuscript for important intellectual content. Karel Vondrak: Contributed to data collection, analyzed and interpreted the data, and critically revised the manuscript for important intellectual content. Anne-Laure Sellier-Leclerc: Contributed to data collection, analyzed and interpreted the data, and critically revised the manuscript for important intellectual content. Deirdre Kelly: Contributed to data collection, analyzed and interpreted the data, and critically revised the manuscript for important intellectual content. Piotr Czubkowski: Contributed to data collection, analyzed and interpreted the data, and critically revised the manuscript for important intellectual content. Nicholas JA Webb: Contributed to data collection, analyzed and interpreted the data, and critically revised the manuscript for important intellectual content. Silvia Riva: Contributed to data collection, analyzed and interpreted the data, and critically revised the manuscript for important intellectual content. Lorenzo D'Antiga: Contributed to data collection, analyzed and interpreted the data, and critically revised the manuscript for important intellectual content. Stephen D Marks: Contributed to data collection, analyzed and interpreted the data, and critically revised the manuscript for important intellectual content. Christine Rivet: Contributed to data collection, analyzed and interpreted the data, and critically revised the manuscript for important intellectual content. Burkhard Tönshoff: Contributed to data collection, analyzed and interpreted the data, and critically revised the manuscript for important intellectual content. Gbenga Kazeem: Performed the statistical analyses, analyzed and interpreted the data, and critically revised the manuscript for important intellectual content. Nasrullah Undre: Designed the study, collected, analyzed, and interpreted the data, and critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

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REFERENCES

1. OPTN/SRTR United States Organ Transplantation. 2012 Annual Data Report; 2014. http://srtr.transplant.hrsa.gov/annual_reports/2012/pdf/2012_SRTR_ADR_updated_full_intro.pdf.
2. Kuypers DRJ, Claes K, Evenepoel P, Maes B, Vanrenterghem Y. Clinical efficacy and toxicity profile of tacrolimus and mycophenolic acid in relation to combined long-term pharmacokinetics in de novo renal allograft recipients. *Clin Pharmacol Ther*. 2004;75:434-447.
3. Sellarés J, de Freitas DG, Mengel M, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. *Am J Transplant*. 2012;12:388-399.
4. Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Rates and determinants of progression to graft failure in kidney allograft recipients with de novo donor-specific antibody. *Am J Transplant*. 2015;15:2921-2930.
5. Pashaee N, Bouamar R, Hesselink DA, et al. CYP3A5 genotype is not related to the intrapatient variability of tacrolimus clearance. *Ther Drug Monit*. 2011;33:369-371.
6. Undre N, Van Hooff J, Christiaans M, et al. Low systemic exposure to tacrolimus correlates with acute rejection. *Transplant Proc*. 1999;31:296-298.
7. Astellas Pharma Europe Ltd. Prograf 0.5 mg, 1 mg, 5 mg hard capsules. Summary of product characteristics. 2019. https://www.medicines.org.uk/emc/product/6720/smpc. Accessed March 27, 2019.
8. Stifft F, Stolk LML, Undre N, van Hooff JP, Christiaans MHL. Lower variability in 24-hour exposure during once-daily compared to twice-daily tacrolimus formulation in kidney transplantation. *Transplantation*. 2014;97:775-780.
9. Wu M-J, Cheng C-HC-Y, Chen C-H, et al. Lower variability of tacrolimus trough concentration after conversion from Prograf to Advagraf in stable kidney transplant recipients. *Transplantation*. 2011;92:648-652.
10. Kuypers DRJ, Peeters PC, Sennesael JJ, et al. Improved adherence to tacrolimus once-daily formulation in renal recipients: a randomized controlled trial using electronic monitoring. *Transplantation*. 2013;95:333-340.
11. Sapir-Pichhadze R, Wang Y, Famure O, Li Y, Kim SJ. Time-dependent variability in tacrolimus trough blood levels is a risk factor for late kidney transplant failure. *Kidney Int*. 2014;85:1404-1411.
12. Van Hooff J, Van der Walt I, Kallmeyer J, et al. Pharmacokinetics in stable kidney transplant recipients after conversion from twice-daily to once-daily tacrolimus formulations. *Ther Drug Monit*. 2012;34:46-52.
13. Alloway R, Steinberg S, Khalil K, et al. Conversion of stable kidney transplant recipients from a twice daily Prograf-based regimen to a once daily modified release tacrolimus-based regimen. *Transplant Proc*. 2005;37:867-870.
14. Florman S, Alloway R, Kalayoglu M, et al. Conversion of stable liver transplant recipients from a twice-daily Prograf-based regimen to a once-daily modified release tacrolimus-based regimen. *Transplant Proc*. 2005;37:1211-1213.
15. Alloway R, Vanhaecke J, Yonan N, et al. Pharmacokinetics in stable heart transplant recipients after conversion from twice-daily to once-daily tacrolimus formulations. *J Heart Lung Transplant*. 2011;30:1003-1010.
16. Heffron TG, Pescovitz MD, Florman S, et al. Once-daily tacrolimus extended-release formulation: 1-year post-conversion in stable pediatric liver transplant recipients. *Am J Transplant*. 2007;7:1609-1615.
17. Min SKI, Ha J, Kang HG, et al. Conversion of twice-daily tacrolimus to once-daily tacrolimus formulation in stable pediatric kidney transplant recipients: pharmacokinetics and efficacy. *Am J Transplant*. 2013;13:2191-2197.
18. Lapeyraque A-L, Kassir N, Théorêt Y, et al. Conversion from twice- to once-daily tacrolimus in pediatric kidney recipients: a pharmacokinetic and bioequivalence study. *Pediatr Nephrol*. 2014;29:1081-1088.
19. Alak AM, Moy S, Cook M, et al. An HPLC/MS/MS assay for tacrolimus in patient blood samples. Correlation with results of an ELISA assay. *J Pharm Biomed Anal*. 1997;16:7-13.
20. Stratta P, Quaglia M, Cena T, et al. The interactions of age, sex, body mass index, genetics, and steroid weight-based doses on tacrolimus dosing requirement after adult kidney transplantation. *Eur J Clin Pharmacol*. 2012;68:671-680.
21. Pulk RA, Schladt DS, Oetting WS, et al. Multigene predictors of tacrolimus exposure in kidney transplant recipients. *Pharmacogenomics*. 2015;16:841-854.
22. Tsunashima D, Kawamura A, Murakami M, et al. Assessment of tacrolimus absorption from the human intestinal tract: open-label, randomized, 4-way crossover study. *Clin Ther*. 2014;36:748-759.
23. Tsunashima D, Yamashita K, Ogawara K-I, Sako K, Higaki K. Preparation of extended release solid dispersion formulations of tacrolimus using ethylcellulose and hydroxypropylmethylcellulose by solvent evaporation method. *J Pharm Pharmacol*. 2016;68:316-323.
24. Tremblay S, Nigro V, Weinberg J, Woodle ES, Alloway RR. A steady-state head-to-head pharmacokinetic comparison of all FK-506 (tacrolimus) formulations (ASTCOFF): an open-label, prospective, randomized, two-arm, three-period crossover study. *Am J Transplant*. 2017;17:432-442.
25. Carcas-Sansuán AJ, Hierro L, Almeida-Paulo GN, et al. Conversion from Prograf to Advagraf in adolescents with stable liver transplants: comparative pharmacokinetics and 1-year follow-up. *Liver Transpl*. 2013;19:1151-1158.
26. Carcas-Sansuán AJ, Espinosa-Román L, Almeida-Paulo GN, et al. Conversion from Prograf to Advagraf in stable paediatric renal transplant patients and 1-year follow-up. *Pediatr Nephrol*. 2014;29:117-123.
27. Kim JS, Aviles DH, Silverstein DM, Leblanc PL, Matti Vehaskari V. Effect of age, ethnicity, and glucocorticoid use on tacrolimus pharmacokinetics in pediatric renal transplant patients. *Pediatr Transplant*. 2005;9:162-169.

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