Received: 22 February 2019 | Revised: 6 August 2019 | Accepted: 19 August 2019

DOI: 10.1111/ctr.13698

ORIGINAL ARTICLE

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
WILEY

Efficacy and safety of tacrolimus in de novo pediatric transplant recipients randomized to receive immediate- or prolonged-release tacrolimus

Karel Vondrak[1] | Francesco Parisi[2] | Anil Dhawan[3] | Ryszard Grenda[4] | Nicholas J. A. Webb[5] | Stephen D. Marks[6] | Dominique Debray[7] | Richard C. L. Holt[8] | Alain Lachaux[9] | Deirdre Kelly[10] | Gbenga Kazeem[11,12] | Nasrullah Undre[11]

[1]University Hospital Motol, Prague, Czech Republic

[2]Ospedale Pediatrico Bambino Gesù, Rome, Italy

[3]King's College Hospital, London, UK

[4]The Children's Memorial Health Institute, Warsaw, Poland

[5]Manchester University Foundation Trust, Manchester, UK

[6]Great Ormond Street Hospital for Children, NHS Foundation Trust, London, UK

[7]APHP-Hôpital Universitaire Necker, Paris, France

[8]Alder Hey Children's Hospital, Liverpool, UK

[9]Université Lyon 1 et Hospices Civils de Lyon, Lyon, France

[10]Birmingham Women's & Children's Hospital, Birmingham, UK

[11]Astellas Pharma Europe Ltd, Chertsey, UK

[12]BENKAZ Consulting Ltd, Cambridge, UK

Correspondence
Nasrullah Undre, Astellas Pharma Global Development, 2000 Hillswood Drive, Chertsey, Surrey KT16 0RS, UK.
Email: Nas.Undre@astellas.com

Funding information
Astellas Pharma Europe; Astellas Pharma, Inc.

Abstract

Background and aims: This multicenter trial compared immediate-release tacrolimus (IR-T) vs prolonged-release tacrolimus (PR-T) in de novo kidney, liver, and heart transplant recipients aged <16 years. Each formulation had similar pharmacokinetic (PK) profiles. Follow-up efficacy and safety results are reported herein.

Materials and methods: Patients, randomized 1:1, received once-daily, PR-T or twice-daily, IR-T within 4 days of surgery. After a 4-week PK assessment, patients continued randomized treatment for 48 additional weeks. At Year 1, efficacy assessments included the number of clinical acute rejections, biopsy-confirmed acute rejection (BCAR) episodes (including severity), patient and graft survival, and efficacy failure (composite of death, graft loss, BCAR, or unknown outcome). Adverse events were assessed throughout.

Results: The study included 44 children. At Year 1, mean ± standard deviation tacrolimus trough levels were 6.6 ± 2.2 and 5.4 ± 1.6 ng/mL, and there were 2 and 7 acute rejection episodes in the PR-T and IR-T groups, respectively. No cases of graft loss or death were reported during the study. The overall efficacy failure rate was 18.2% (PR-T n = 1; IR-T n = 7).

Conclusions: In pediatric de novo solid organ recipients, the low incidence of BCAR and low efficacy failure rate suggest that PR-T-based immunosuppression is effective and well tolerated to 1-year post-transplantation.

KEYWORDS

calcineurin inhibitor: tacrolimus, heart (allograft) function/dysfunction, immunosuppressant, kidney transplantation: living donor, liver transplantation: living donor

1 | INTRODUCTION

Appropriate immunosuppressive therapy is crucial to avoid both acute and long-term organ rejection following transplantation in adult and pediatric patients, and must be able to target both the early post-transplant period and longer-term maintenance therapy.[1] Improvements in transplant procedures, including post-transplant immunosuppressive regimens, mean that 10-year graft and patient survival have increased to approximately 75% and 77%, respectively, in children following liver transplantation.[2]

Discipline: (maximum 3 from submission site): immunosuppression/immune modulation; organ transplantation in general; pediatrics.

Tacrolimus is an important component of immunosuppressive regimens after solid organ transplantation.[3] In an annual transplant registry report in 2012, 96% of pediatric liver transplant recipients received tacrolimus as part of their initial immunosuppressive regimen, while 89%, 47%, and 1% received steroids, mycophenolate, and mammalian target of rapamycin inhibitors, respectively.[4] Currently available tacrolimus formulations include once-daily, prolonged-release and twice-daily, immediate-release tacrolimus capsules,[5,6] as well as immediate-release tacrolimus granules for oral suspension.[7] Although the prolonged- and immediate-release tacrolimus capsule formulations have shown similar efficacy and safety profiles,[8-10] the prolonged-release formulation has been associated with reduced intra-patient variability (IPV) in tacrolimus exposure and improved adherence to treatment in adults,[11,12] which can improve long-term transplant outcomes.[13]

High IPV in tacrolimus trough levels has been linked to adverse transplant outcomes,[14] and is a significant risk factor for poor long-term graft survival in pediatric solid organ transplant patients.[15] A study of more than 6600 kidney transplant patients with a functioning graft at least 3 years post-transplantation also showed that graft survival was significantly reduced with higher IPV.[16] Impact of IPV on graft survival was particularly strong in adolescents 12-17 years of age. Covariates that may influence variability in tacrolimus exposure in pediatric patients include cytochrome P450-related genetic polymorphisms, bodyweight, and hematocrit level.[17,18] In addition, behavioral factors, such as nonadherence to treatment, particularly during adolescence when patients transition into adult care,[2] is also associated with poor graft and survival outcomes.[19] Indeed, nonadherence to immunosuppressive treatment was reported in 17%-53% of adolescents following liver transplantation.[20] A meta-analysis including 12 studies of adolescent kidney, liver, heart, and lung transplant recipients reported that 7.1% of patients did not adhere to medication compared with a meta-analysis of four studies in younger children which reported a nonadherence rate of only 2.4%.[21] As such, it has been suggested that a focus on reducing nonadherence could minimize risk during the transition process to adulthood.[1,22]

Immediate-release tacrolimus is approved for use in pediatric kidney, liver, and heart allograft recipients, and several small studies have demonstrated good efficacy and tolerability of immediate-release tacrolimus in pediatric kidney[23] and liver transplant recipients.[24-26] However, prolonged-release tacrolimus is not widely approved in pediatric recipients and clinical experience in de novo pediatric transplantation is limited. We have previously reported the results of a pharmacokinetic analysis from a multicenter, randomized, open-label, Phase 2, 4-week trial conducted in a large cohort of de novo pediatric kidney, liver, and heart transplant recipients.[27] A similar linear relationship between tacrolimus exposure and trough levels was observed with both immediate-release and prolonged-release formulations.[27] In the present paper, we report the results of a 1-year follow-up study in the same cohort of patients, undertaken to evaluate the efficacy and safety of immediate- vs prolonged-release tacrolimus.

2 | MATERIAL AND METHODS

2.1 | Study design and patients

This was a Phase 2, randomized, parallel-group, open-label study conducted at eight centers in five European countries (UK, France, Czech Republic, Italy, and Poland) between 9 February 2012 and 23 June 2016. (ClinicalTrials.gov NCT01614665). The study was approved by the Ethics Committee at each participating center, and conducted in accordance with good clinical practice, the International Council for Harmonization guidelines, and the Declaration of Helsinki. Written informed consent was provided by all patients or their guardians.

Patients were eligible for inclusion if they were aged <16 years, were undergoing primary kidney, liver, or heart allograft transplantation, and were capable of swallowing intact immediate- or prolonged-release tacrolimus capsules. An additional inclusion criterion for heart transplant patients was the resumption of gastric motility and adequate renal function on Day 1 post-transplant. Patients were excluded if they had received multiple or a previous organ transplantation, or had any malignancies or history of malignancy within 5 years (except basalioma or squamous cell carcinoma of the skin).

2.2 | Treatment

Patients were randomized (1:1) to receive either prolonged-release tacrolimus (Advagraf®, Astellas Pharma Europe BV) or immediate-release tacrolimus (Prograf®, Astellas Pharma Ltd). Heart transplant recipients received tacrolimus within 4 days of skin closure at an initial daily dose of 0.075 mg/kg; liver transplant recipients received an initial daily dose of 0.3 mg/kg within 2 days of skin closure; and kidney transplant recipients received an initial daily dose of 0.3 mg/kg within 24 hours of reperfusion. Prolonged-release and immediate-release tacrolimus were administered at the same initial daily dose; prolonged-release tacrolimus was given once-daily whilst immediate-release tacrolimus was given in two equal doses in the morning and evening. Dose adjustments were made to maintain tacrolimus trough levels of 10-20 ng/mL on Days 1-21 and 5-15 ng/mL from Day 22 onwards. The day of the first tacrolimus administration was designated as Day 1.

The first part of the study was a 4-week PK assessment which has been previously reported.[27] In the second part of the study (the focus of the present paper), patients continued to receive their randomized treatment for 48 additional weeks (Figure 1). Concomitant basiliximab, thymoglobulin, mycophenolate mofetil, and/or steroids were prescribed according to routine clinical practice at each study center. Methylprednisolone or equivalent was given as a 300-600 mg/m^2 intravenous bolus pre, intra-, or postoperatively and at a dose of 60 mg/m^2 on the following day. Prednisolone or equivalent was administered at a daily dose of 40, 30, and 20 mg/m^2 on Days 2, 3, and 4, respectively, in kidney transplant patients; on Days 1, 2, and 3, respectively, in liver transplant patients; and on Days 2-7, 8-14, and 15-28, respectively, in heart transplant patients. Concomitant medications known to interact with tacrolimus were prohibited during the

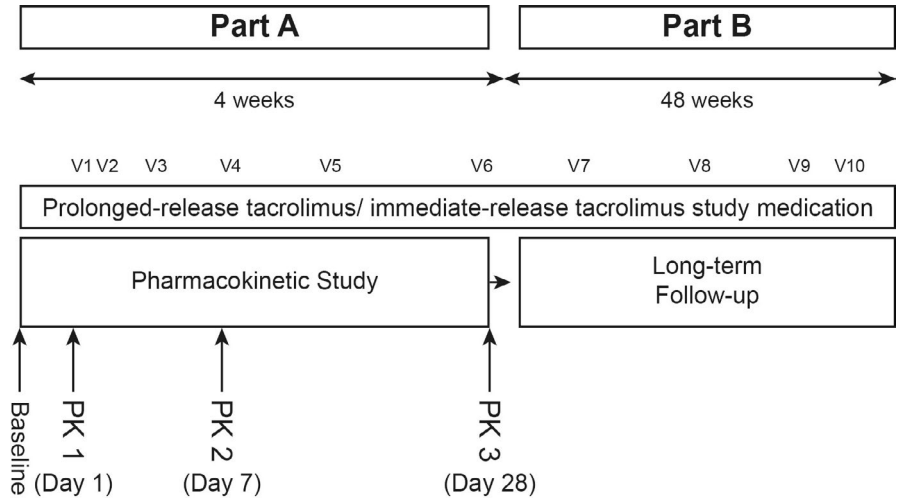

FIGURE 1 Study design. Initial doses of prolonged-release tacrolimus and immediate-release tacrolimus administered on Day 1 were: 0.075 mg/kg, 0.3 mg/kg and 0.3 mg/kg for heart, liver, and kidney transplant recipients, respectively; subsequent doses were adjusted on the basis of clinical evidence of efficacy, AEs and target whole blood trough levels. Patients received basiliximab, thymoglobulin, MMF, and/or steroids according to routine clinical practice at each study center. During the PK study, pharmacokinetic profiles were taken on Days 1, 7, and 28 (data reported previously). During the efficacy study, follow-up of patients occurred on Days 60, 90, 180, and 365 (data presented here). AE, adverse event; MMF, mycophenolate mofetil; PK, pharmacokinetics, V, visit

PK period but were permitted during the follow-up period; however, no data on their effect on tacrolimus blood levels were collected.

2.3 | Assessments

Safety, efficacy, and tacrolimus trough level data were obtained during follow-up visits on Day 60, 90, 180, and 365. Biopsy-confirmed acute rejection (BCAR) episodes were confirmed by histopathology performed by individual study centers following their usual protocol; a non-BCAR episode was defined as any acute rejection episode not confirmed by biopsy. Rejection episodes were managed according to usual practice in the study center. Acute rejection episodes were classified as: (a) spontaneously resolving acute rejection: an episode not treated with new or increased corticosteroid medication, antibodies, or any other medication, and that resolved irrespective of any tacrolimus dose changes; (b) corticosteroid-sensitive acute rejection: a rejection episode that was treated with new or increased corticosteroid medication only and that resolved irrespective of any tacrolimus dose changes; (c) corticosteroid-resistant acute rejection: a rejection episode that did not resolve following treatment with corticosteroids. Graft loss was defined as retransplantation, death, nephrectomy, or dialysis. Safety variables including adverse events (AEs), serious AEs (SAEs), treatment-emergent AEs (TEAEs; including causality), vital signs, and clinical laboratory variables were also recorded throughout the follow-up.

2.4 | Endpoints

The efficacy endpoints at Year 1 included the number of clinical acute rejections, BCAR episodes (including severity), patient and graft survival, and efficacy failure (a composite endpoint of death, graft loss, BCAR, or unknown outcome).

2.5 | Statistical analysis

A total of 64 patients were to be enrolled to achieve 48 evaluable patients: 24 patients with three complete evaluable PK profiles in each treatment arm (immediate-release tacrolimus or prolonged-release tacrolimus). Approximately eight patients per indication of liver, kidney, or heart transplantation per treatment were required, totaling 16 patients per indication in the study. Although no power calculations were performed, it was anticipated that a study with 24 evaluable patients per treatment would be sufficient for the previously reported PK evaluation in this patient population.[27] Evaluable patients were assessed for efficacy and safety during the follow-up period. All assessments were performed on the full analysis set (FAS), which included all patients who received at least one dose of study drug post randomization.

Efficacy variables (rejection episodes, patient survival, graft survival, and efficacy failure) were summarized by treatment arm and overall, and further stratified by type of organ transplant when necessary. The study was not powered for formal statistical analysis, and the data were analyzed descriptively. All data processing, summarization, and analyzes were performed using SAS® Version 9.3 or higher.

3 | RESULTS

3.1 | Study population

Of the 47 screened patients, 44 were enrolled and included in the FAS, of whom 24 and 20 patients were randomized to receive immediate- and prolonged-release tacrolimus, respectively (Figure 2). Three patients prematurely discontinued the study in

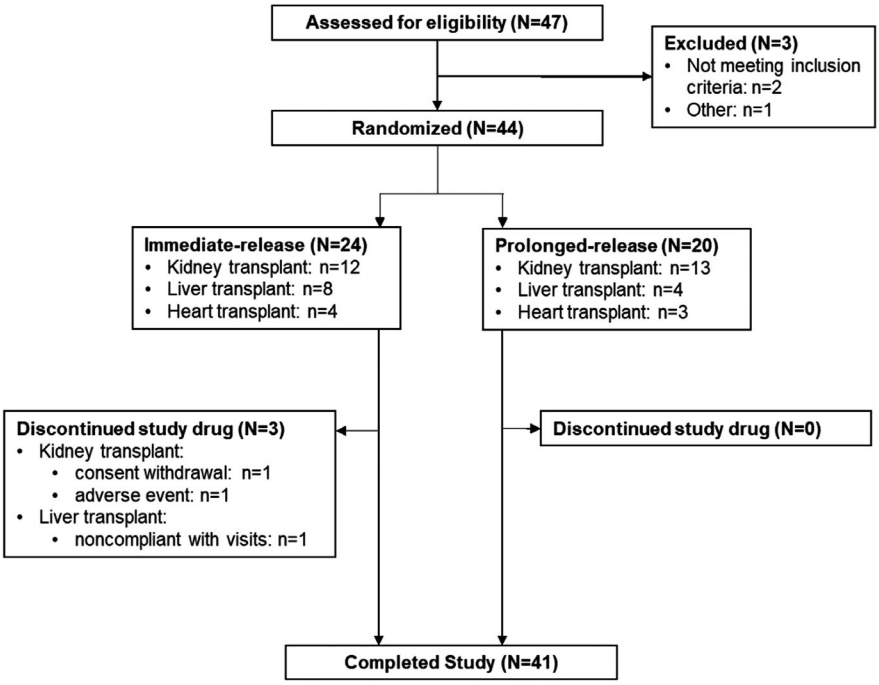

FIGURE 2 Patient distribution

the immediate-release tacrolimus group due to consent withdrawal (n = 1), SAE (n = 1) and noncompliance (n = 1).

The majority of patients were Caucasian (95%) and male (75%). The mean ± standard deviation (SD) age was 10.6 ± 3.1 years (range, 4-15 years); 54.5% of patients were children, and 45.5% were adolescents (Table 1). The most common type of transplantation was kidney (n = 25 [56.8%]), liver (n = 12 [27.3%]), and heart (n = 7 [15.9%]). Baseline demographics and type of organ transplanted were similar in both tacrolimus groups (Table 1). Overall, 31/44 patients (70.5%) were prescribed basiliximab and 4/44 (9.1%) were prescribed thymoglobulin.

3.2 | Tacrolimus dose and whole blood trough levels

In the overall group, the mean ± SD duration of tacrolimus treatment was shorter in patients receiving immediate- vs prolonged-release tacrolimus (328.5 ± 100.2 vs 362.6 ± 11.8 days). The mean duration of treatment was also shorter with the immediate-release formulation in kidney and liver transplant recipients (kidney, 314.2 vs 361.8 days; liver, 326.1 vs 354.8 days), but similar in heart transplant recipients (376.5 vs 376.3 days). Overall, the mean ± SD daily dose of immediate- and prolonged-release tacrolimus was 0.20 ± 0.13 mg/kg and 0.21 ± 0.11 mg/kg, respectively (Figure 3A). Mean tacrolimus trough levels were comparable between the two formulations and decreased over 12 months (Figure 3B), with tacrolimus trough levels typically within or below the target range in both formulation groups. At Year 1, mean ± SD tacrolimus trough levels were 6.6 ± 2.2 and 5.4 ± 1.6 ng/mL, in the prolonged- and immediate-release tacrolimus groups, respectively.

The mean ± SD daily dose of immediate-release vs prolonged-release tacrolimus in kidney transplant recipients was 0.226 ± 0.173 vs 0.192 ± 0.089 mg/kg, compared with 0.185 ± 0.049 vs 0.322 ± 0.126 mg/kg in liver transplant recipients, and 0.150 ± 0.058 vs 0.115 ± 0.032 mg/kg in heart transplant recipients (Figure 4A). Tacrolimus trough levels were comparable across organ types (Figure 4B).

3.3 | Rejection episodes, graft and patient survival

Seven patients receiving immediate-release tacrolimus experienced an acute rejection episode: two kidney, four liver, and one heart recipient (Table 2). All episodes in the liver transplant patients were classified as BCAR, whilst all episodes in the kidney and heart transplant recipients were classified as non-BCAR (Table 2). Of the nine patients who experienced acute rejection, three were adolescents (13-15 years of age) and six were children (8-12 years of age). All but one event was classified as corticosteroid-sensitive. Of patients receiving prolonged-release tacrolimus, one liver transplant recipient experienced corticosteroid-sensitive BCAR and one heart transplant recipient experienced corticosteroid-sensitive non-BCAR (Table 2). All of the acute rejection episodes resolved typically within a few weeks. There were no cases of graft loss or death reported during the study.

3.4 | Efficacy failure

Composite efficacy failure occurred in eight (18.2%) patients, seven in the immediate-release and one in the prolonged-release tacrolimus group (Table 3). Five efficacy failures were due to BCAR episodes in liver transplant recipients. In three patients in the immediate-release tacrolimus group, the reason for efficacy failure was unknown outcome resulting from early discontinuation from the

TABLE 1 Patient baseline demographics and characteristics for the overall population, and stratified by tacrolimus treatment group (FAS)

Parameter	Immediate-release tacrolimus (n = 24)	Prolonged-release tacrolimus (n = 20)	Total (n = 44)
Age, y			
Mean ± SD	10.3 ± 3.2	11.1 ± 3.0	10.6 ± 3.1
Median	11.0	11.0	11.0
Minimum, maximum	4, 15	4, 15	4, 15
Age category, n (%)			
≤23 mo (infants and toddlers)	0	0	0
≥2 to ≤11 y (children)	13 (54.2)	11 (55.0)	24 (54.5)
≥12 to ≤17 y (adolescents)	11 (45.8)	9 (45.0)	20 (45.5)
Sex, n (%)			
Male	17 (70.8)	16 (80.0)	33 (75.0)
Race, n (%)			
White	18 (90.0)	18 (100)	36 (94.7)
Black	0	0	0
Asian	2 (10.0)	0	2 (5.3)
Missing	4	2	6
Organ transplant, n (%)			
Kidney	12 (50.0)	13 (65.0)	25 (56.8)
Liver	8 (33.3)	4 (20.0)	12 (27.3)
Heart	4 (16.7)	3 (15.0)	7 (15.9)
Weight, kg			
Mean ± SD	34.2 ± 17.9	39.2 ± 13.0	36.5 ± 15.9
Median	28.5	36.0	32.3
Minimum, maximum	16, 97	16, 59	16, 97
Height, cm			
Mean ± SD	135.1 ± 18.5	143.8 ± 19.1	139.1 ± 19.1
Median	134.0	140.5	137.0
Minimum, maximum	107, 171	101, 188	101, 188

Abbreviations: FAS, full analysis set; SD, standard deviation.

study. One kidney transplant recipient withdrew consent on Day 4, one kidney transplant recipient withdrew due to an AE on Day 135 and one liver transplant recipient was noncompliant with scheduled visits and discontinued the study on Day 88.

3.5 | Safety and tolerability

There were no new safety signals reported for either tacrolimus formulation during the course of this study. Overall, 42 (95.5%) patients reported TEAEs, which were mild or moderate in most patients (31/42 [73.8%] patients; Table 4). The most common events were diarrhea (22/44 [50.0%] patients) and hypertension (15/44 [34.1%] patients). A total of 29 (65.9%) patients experienced drug-related TEAEs, of whom 19 (43.2%) patients had drug-related serious TEAEs (Table 4).

The most common drug-related TEAEs were increased blood creatinine (7/44 [15.9%] patients), diarrhea (6/44 [13.6%] patients), and upper respiratory tract infection (5/44 [11.4%] patients; Table 5). Serious drug-related TEAEs were reported in 19 (43.2%) patients overall (9/24 [37.5%] and 10/20 [50.0%] patients in the immediate- and prolonged-release tacrolimus groups, respectively). Increased blood creatinine, cytomegalovirus infection, pneumonia, pyrexia, sapovirus gastroenteritis, and renal impairment were the only drug-related SAEs experienced by more than one patient. One drug-related SAE led to study discontinuation: a kidney transplant recipient receiving immediate-release tacrolimus developed sapovirus gastroenteritis on Day 55 and discontinued the study on Day 163. BK virus was not reported in any patient.

3.6 | Laboratory parameters

There were no remarkable laboratory test results or vital signs observed during the study; laboratory evaluations and vital signs were similar in the immediate- and prolonged-release tacrolimus groups.

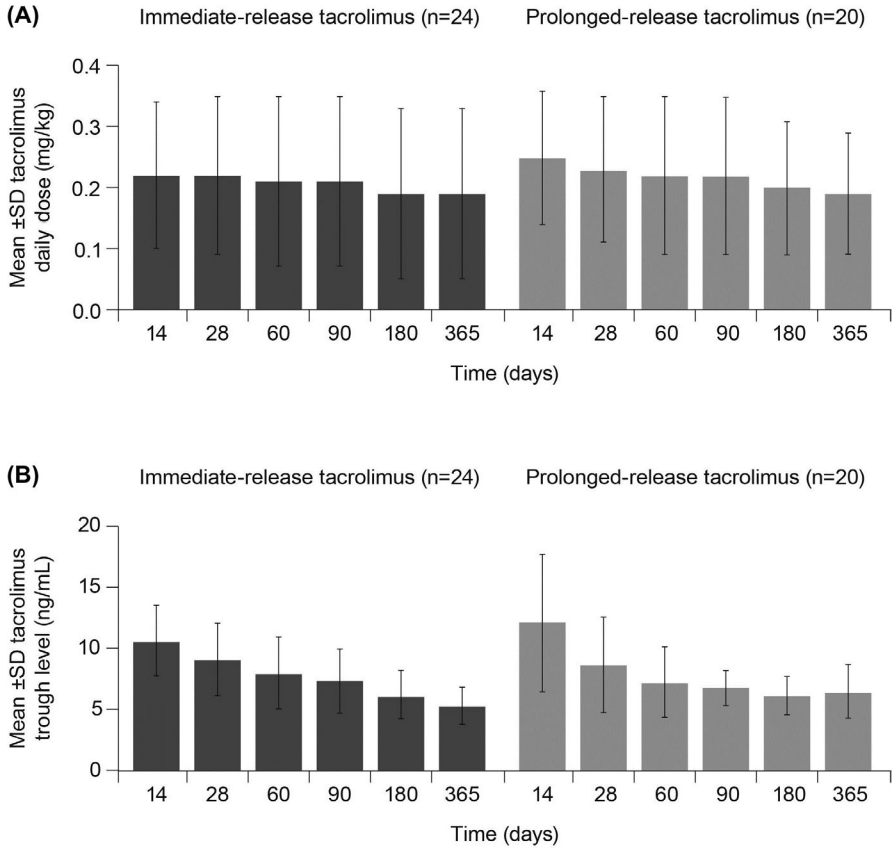

FIGURE 3 Mean ± SD tacrolimus (A) weight-adjusted daily dose and (B) blood trough levels stratified by tacrolimus treatment group (FAS). FAS, full analysis set; SD, standard deviation

Overall, nine patients had clinically significant hematology test results: seven kidney transplant recipients (immediate-release: n = 3; prolonged-release: n = 4), one liver and one heart transplant recipient (both receiving immediate-release tacrolimus); these were often related to the patient's underlying condition, elevated leukocytes, or low hemoglobin levels. A total of 10 patients had clinically significant abnormal biochemistry test results: nine kidney transplant recipients (immediate-release, n = 3; prolonged-release, n = 6) and one liver transplant patient receiving immediate-release tacrolimus. Elevated serum creatinine, alanine aminotransferase, and aspartate transaminase levels were the most commonly reported anomalies.

4 | DISCUSSION

In this Phase 2, open-label, 1-year study, comparing immediate- and prolonged-release tacrolimus in pediatric de novo kidney, liver, and heart allograft recipients, there was a low incidence of acute rejection and BCAR (which were predominantly mild/moderate in severity) with no deaths or graft losses. Safety profiles were comparable between treatment groups and, importantly, no new safety signals were identified for either formulation in this pediatric population.

Mean tacrolimus trough levels were comparable between the two formulations and decreased over the treatment period. At 12 months, mean tacrolimus trough levels were typically within or below the target range for both formulations, although levels were slightly higher in the prolonged- vs the immediate-release tacrolimus group (6.6 ± 2.2 vs 5.4 ± 1.6 ng/mL, respectively). The tacrolimus trough levels observed in this study were consistent with those previously reported for immediate-release tacrolimus in pediatric liver transplant recipients (7.3 ± 2.8 ng/mL from Month 10-12),[28] and similar to 6-month and 1-year data in pediatric kidney transplant recipients.[29,30] The median age of the patients in our study was 11.0 (range: 4-15) years. Although tacrolimus clearance is known to be higher in patients aged <5 years,[31] patients nearly aged 5 years who were able to swallow intact capsules were included if they were considered old enough for tacrolimus clearance not to affect results.

In our de novo study population, seven (29.2%) patients receiving immediate-release tacrolimus experienced acute rejection, compared with two (10.0%) patients receiving prolonged-release tacrolimus. The number of acute rejections was too small to draw meaningful conclusions, and the study was not powered to examine results by organ class. Nevertheless, the low incidence of acute rejection in patients receiving prolonged-release tacrolimus is in line with previous 1-year post-transplant data in pediatric kidney transplant recipients, with acute rejection occurring in five (9.3%) and two (8.5%) patients receiving immediate-release tacrolimus and assigned to corticosteroid withdrawal and corticosteroid maintained treatment regimens, respectively.[32] In addition, in liver transplanted children, the incidence of acute rejections (about 40%) was in line with a 1-year study of pediatric liver transplant recipients which reported that BCAR occurred in 38 (41.6%) patients post-transplant.[28] Composite efficacy failure occurred in eight (18.2%) patients, the majority (seven) of whom received immediate-release tacrolimus.

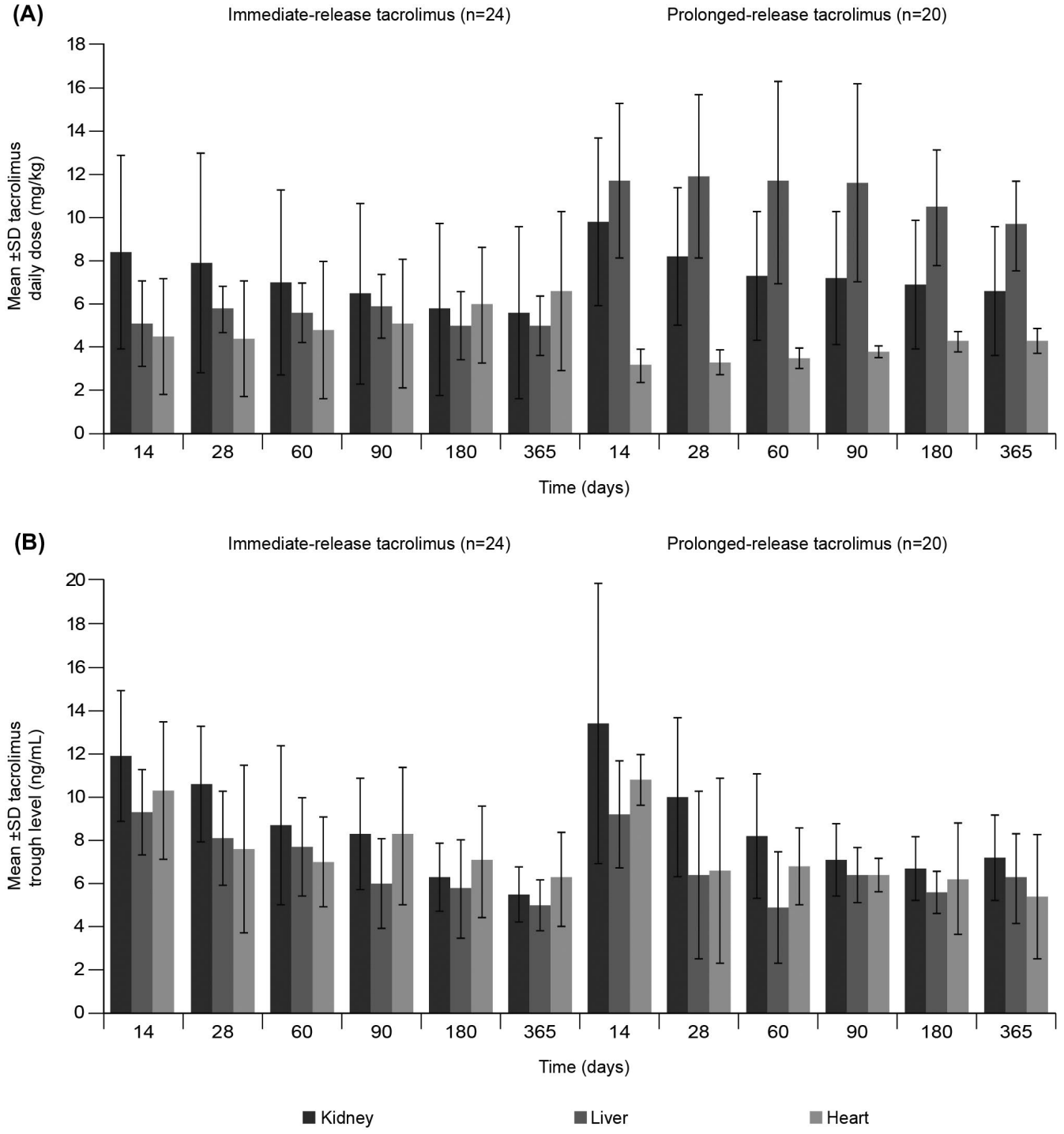

FIGURE 4 Mean ± SD tacrolimus (A) weight-adjusted daily dose and (B) blood trough levels in immediate- and prolonged-release tacrolimus according to organ type (FAS). FAS, full analysis set; SD, standard deviation

These findings, together with our acute rejection data, suggest that prolonged-release tacrolimus is associated with good transplant outcomes over 1 year in pediatric solid organ transplant recipients.

Both tacrolimus formulations were generally well tolerated during our study and no new safety signals were identified. Approximately two-thirds of patients experienced drug-related TEAEs, although most were mild in severity, and all resolved. Several analyzes of data from pediatric liver transplant recipients have suggested that tacrolimus could be associated with an increased risk for lymphoproliferative disease related to the Epstein-Barr virus.[25] In our study, three (6.8%) patients recorded drug-related TEAEs related to Epstein-Barr virus, all of whom received the immediate-release tacrolimus formulation. In a previous study of pediatric liver transplant recipients, five (6%) patients receiving immediate-release tacrolimus had experienced symptoms of post-transplant lymphoproliferative disease by 1-year post-transplant.[28]

TABLE 2 Acute rejection and biopsy-confirmed acute rejection over 1 y of treatment, stratified by tacrolimus treatment group and organ type (FAS)

	Immediate-release tacrolimus n (%)			Prolonged-release tacrolimus n (%)		
	Kidney transplant (n = 12)	Liver transplant (n = 8)	Heart transplant (n = 4)	Kidney transplant (n = 13)	Liver transplant (n = 4)	Heart transplant (n = 3)
All acute rejections	2 (16.7)	4 (50.0)	1 (25.0)	0	1 (25.0)	1 (33.3)
BCAR	0	4 (50.0)	0	0	1 (25.0)	0
Non-BCAR	2 (16.7)	0	1 (25.0)	0	0	1 (33.3)
Classification of acute rejection						
Spontaneously resolved	0	1 (12.5)	0	0	0	0
Corticosteroid-sensitive	2 (16.7)	3 (37.5)	1 (25.0)	0	1 (25.0)	1 (33.3)
Corticosteroid-resistant	0	0	0	0	0	0
Classification of BCAR						
Spontaneously resolved	0	1 (12.5)	0	0	0	0
Corticosteroid-sensitive	0	3 (37.5)	0	0	1 (25.0)	0
Corticosteroid-resistant	0	0	0	0	0	0

Abbreviations: BCAR, biopsy-confirmed acute rejection; FAS, full analysis set.

TABLE 3 Efficacy failure outcomes for the overall population and stratified by tacrolimus treatment group (FAS)

N (%)	Immediate-release tacrolimus (n = 24)	Prolonged-release tacrolimus (n = 20)	Total (n = 44)
Efficacy failure	7 (29.2)	1 (5.0)	8 (18.2)
Graft loss	0	0	0
BCAR	4 (16.7)	1 (5.0)	5 (11.4)
Death	0	0	0
Unknown	3 (12.5)[a]	0	3 (6.8)[a]

Abbreviations: BCAR, biopsy-confirmed acute rejection; FAS, full analysis set.
[a]Efficacy failure unknown due to these patients discontinuing early from the study.

TABLE 4 Overview of treatment-emergent adverse events for the overall population and stratified by tacrolimus treatment group (FAS)

N (%)	Immediate-release tacrolimus (n = 24)	Prolonged-release tacrolimus (n = 20)	Total (n = 44)
Overall AEs	23 (95.8)	19 (95.0)	42 (95.5)
Drug-related AEs	15 (62.5)	14 (70.0)	29 (65.9)
SAEs	15 (62.5)	13 (65.0)	28 (63.6)
Drug-related SAEs	9 (37.5)	10 (50.0)	19 (43.2)
AEs leading to permanent discontinuation of study drug	1 (4.2)	0	1 (2.3)

Abbreviations: AE, adverse event; FAS, full analysis set; SAE, serious adverse event.

Immediate-release tacrolimus has been associated with comparable renal function to ciclosporin in pediatric liver transplant recipients[28]; however, a significant improvement in renal function has been reported in pediatric kidney transplant recipients receiving immediate-release tacrolimus vs ciclosporin at 1-year post-transplant (estimated glomerular filtration rate 62.5 vs 56.4 mL/min

TABLE 5 Drug-related treatment-emergent adverse events in the overall population and stratified by tacrolimus treatment group (FAS)

N (%)	Immediate-release tacrolimus (n = 24)	Prolonged-release tacrolimus (n = 20)	Total (n = 44)
Overall	15 (62.5)	14 (70.0)	29 (65.9)
Drug-related TEAEs reported in ≥5% patients			
Blood creatinine increased	2 (8.3)	5 (25.0)	7 (15.9)
Diarrhea	4 (16.7)	2 (10.0)	6 (13.6)
Upper respiratory tract infection	4 (16.7)	1 (5.0)	5 (11.4)
Hypertension	3 (12.5)	1 (5.0)	4 (9.1)
Abdominal pain	2 (8.3)	1 (5.0)	3 (6.8)
Anemia	1 (4.2)	2 (10.0)	3 (6.8)
Blood urea increased	2 (8.3)	1 (5.0)	3 (6.8)
Cytomegalovirus viremia	1 (4.2)	2 (10.0)	3 (6.8)
Epstein-Barr viremia	3 (12.5)	0	3 (6.8)
Immunosuppressant drug level increased	1 (4.2)	2 (10.0)	3 (6.8)
Oral candidiasis	1 (4.2)	2 (10.0)	3 (6.8)
Pyrexia	3 (12.5)	0	3 (6.8)
Vomiting	2 (8.3)	1 (5.0)	3 (6.8)
Incidence of BK virus			
BK virus	0	0	0

Note: A TEAE was defined as an adverse event occurring within 7 d after taking the last dose of study drug. A drug-related TEAE was defined as an event with a possible/probable relationship to study drug.

Abbreviations: FAS, full analysis set; TEAE, treatment-emergent adverse event.

per 1.73 m^2; $P = .03$).[29] In our study, an increase in blood creatinine as a drug-related TEAE was reported in 25% of patients receiving prolonged-release tacrolimus, all of whom were kidney transplant recipients. A similar incidence of increased creatinine (23.3%) has previously been reported 6 months after transplantation in pediatric kidney transplant recipients.[29] The patient numbers were too small to allow meaningful interpretation of the data; however, the fact that no liver transplant recipients in our study experienced increased blood creatinine is a promising result, considering that impaired renal function has been reported in pediatric patients postliver transplant,[33] and is a major cause of post-transplant morbidity.[4] These results suggest that neither formulation of tacrolimus was associated with renal insufficiency over the 1-year treatment period.

All the results presented here must be considered within the context of the limitations of the study. The study was not powered for formal statistical analysis and all analyzes presented are descriptive. The once-daily tacrolimus formulation is not considered appropriate for younger children with faster clearance; therefore, the study preferentially targeted older children. In addition, only 20 (45.5%) of our patients were adolescent, and given that IPV, adherence to treatment, and subsequent outcomes, are a concern in this age group,[2] it would be of interest to investigate this patient population in further detail and to collect data on medication adherence. It would also be valuable in a future study to include patients from different racial groups (most children in the present study were White) and to perform genetic testing for the cytochrome-P450 enzymes CYP3A4 and CYP3A5 to determine whether participants are slow or fast metabolizers of tacrolimus. A further limitation is that biopsies were read locally rather than centrally, and treatment was given according to local results, which might have influenced biopsy outcomes. However, pathomorphologic evaluation according to revised Banff criteria was standardized across study centers in an attempt to mitigate potential variability between centers.

In conclusion, this is the first study to compare immediate- vs prolonged-release tacrolimus in pediatric de novo kidney, liver, and heart allograft recipients. There was a low incidence of acute rejections and BCAR, the majority of which were mild/moderate in severity, and no deaths or graft losses occurred over the 1-year study period. Safety profiles were comparable between treatment groups and, importantly, no new safety signals were identified for either formulation in this pediatric population. The comparable PK profile of the tacrolimus formulations as well as the current data shows that over 1-year post-transplant, prolonged-release tacrolimus-based immunosuppression is effective and well tolerated in de novo pediatric solid organ transplant recipients.

ACKNOWLEDGEMENTS

This study was supported by the NIHR Manchester Clinical Research Facility and was sponsored by Astellas Pharma Europe Ltd. Anna

Thompson, PhD and Amy MacLucas, PhD, from Cello Health MedErgy assisted in drafting and revising the manuscript under the direction of the authors throughout the publication process. Editorial support was funded by Astellas Pharma, Inc.

CONFLICT OF INTEREST

KV, FP, AD, NJAW, and AL report other and nonfinancial support from Astellas during the conduct of the study. RG reports other and nonfinancial support from Astellas during the conduct of the study, and other from Novartis outside the submitted work. SDM reports other and nonfinancial support from Astellas, during the conduct of the study, and grants from Novartis outside the submitted work. DD reports other and nonfinancial support from Astellas, during the conduct of the study, and other from Astellas outside the submitted work. RCH reports other and nonfinancial support from Astellas during the conduct of the study, and personal fees from Alexion outside the submitted work. DK reports nonfinancial support from Astellas during the conduct of the study. GK reports other and nonfinancial support from Astellas, during the conduct of the study, and is a consulting Statistician working on behalf of Astellas. NU reports other and nonfinancial support from Astellas, during the conduct of the study, and is an employee of Astellas. NJAW is an employee of Novartis.

DATA AVAILABILITY STATEMENT

Access to anonymized individual participant level data will not be provided for this trial as it meets one or more of the exceptions described on www.clinicalstudydatarequest.com under "Sponsor Specific Details for Astellas."

ORCID

Ryszard Grenda https://orcid.org/0000-0002-6814-6589
Stephen D. Marks https://orcid.org/0000-0001-9850-8352
Dominique Debray https://orcid.org/0000-0002-0345-963X
Richard C. L. Holt https://orcid.org/0000-0003-1619-325X
Nasrullah Undre https://orcid.org/0000-0001-7294-7883

REFERENCES

1. Hackl C, Schlitt HJ, Melter M, Knoppke B, Loss M. Current developments in pediatric liver transplantation. *World J Hepatol*. 2015;7:1509-1520.
2. Kim JJ, Marks SD. Long-term outcomes of children after solid organ transplantation. *Clinics (Sao Paulo)*. 2014;69(suppl 1):28-38.
3. La Manna G, Todeschini P, Capelli I, et al. Advagraf vs. Prograf immunosuppressive therapy in de novo kidney transplant: a single center experience. *J Transplant Technol Res*. 2014;4:6-10.
4. Kim WR, Smith JM, Skeans MA, et al. OPTN/SRTR 2012 annual data report: liver. *Am J Transplant*. 2014;14(suppl 1):69-96.
5. Astellas Pharma Europe Ltd. Advagraf 0.5mg, 1mg, 3mg and 5mg prolonged-release hard capsules summary of product characteristics. https://www.medicines.org.uk/emc/product/345. Accessed May 9, 2019.
6. Astellas Pharma Europe Ltd. Prograf 0.5mg, 1mg, 5mg hard capsules summary of product characteristics. https://www.medicines.org.uk/emc/product/6720. 2019, Accessed April 17, 2019.
7. Astellas Pharma Ltd. Modigraf 0.2mg granules for oral suspension summary of product characteristics. https://www.medicines.org.uk/emc/product/461. Accessed May 9, 2019.
8. Trunečka P, Boillot O, Seehofer D, et al. Once-daily prolonged-release tacrolimus (ADVAGRAF) versus twice-daily tacrolimus (PROGRAF) in liver transplantation. *Am J Transplant*. 2010;10:2313-2323.
9. Urbanowicz T, Baszyńska-Wachowiak H, Ligowski M, Straburzyńska-Migaj E, Misterski M, Jemielity M. Comparison of conventional tacrolimus versus prolong release formula as initial therapy in heart transplantation. *Ann Transplant*. 2014;19:295-299.
10. Albano L, Banas B, Klempnauer JL, Glyda M, Viklicky O, Kamar N. OSAKA trial: a randomized, controlled trial comparing tacrolimus QD and BD in kidney transplantation. *Transplantation*. 2013;96:897-903.
11. Stifft F, Stolk L, Undre N, van Hooff JP, Christiaans MH. Lower variability in 24-hour exposure during once-daily compared to twice-daily tacrolimus formulation in kidney transplantation. *Transplantation*. 2014;97:775-780.
12. Kuypers D, 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.
13. Adam R, Karam V, Delvart V, et al. Improved survival in liver transplant recipients receiving prolonged-release tacrolimus in the European Liver Transplant Registry. *Am J Transplant*. 2015;15:1267-1282.
14. Shuker N, Shuker L, van Rosmalen J, et al. A high intrapatient variability in tacrolimus exposure is associated with poor long-term outcome of kidney transplantation. *Transpl Int*. 2016;29:1158-1167.
15. Pollock-BarZiv SM, Finkelstein Y, Manlhiot C, et al. Variability in tacrolimus blood levels increases the risk of late rejection and graft loss after solid organ transplantation in older children. *Pediatr Transplant*. 2010;14:968-975.
16. Süsal C, Döhler B. Late intra-patient tacrolimus trough level variability as a major problem in kidney transplantation - a Collaborative Transplant Study Report. *Am J Transplant*. 2019. https://doi.org/10.1111/ajt.15346 [Epub ahead of print]
17. Zhao W, Elie V, Roussey G, et al. Population pharmacokinetics and pharmacogenetics of tacrolimus in de novo pediatric kidney transplant recipients. *Clin Pharmacol Ther*. 2009;6:609-618.
18. Abdel Jalil MH, Hawwa AF, McKiernan PJ, Shields MD, McElnay JC. Population pharmacokinetic and pharmacogenetic analysis of tacrolimus in paediatric liver transplant patients. *Br J Clin Pharmacol*. 2014;77:130-140.
19. Shellmer DA, Dabbs AD, Dew MA. Medical adherence in pediatric organ transplantation: what are the next steps? *Curr Opin Organ Transplant*. 2011;16:509-514.
20. Dobbels F, Damme-Lombaert RV, Vanhaecke J, Geest SD. Growing pains: Non-adherence with the immunosuppressive regimen in adolescent transplant recipients. *Pediatr Transplant*. 2005;9:381-390.
21. Dew MA, Dabbs AD, Myaskovsky L, et al. Meta-analysis of medical regimen adherence outcomes in pediatric solid organ transplantation. *Transplantation*. 2009;88:736-746.
22. Fredericks EM. Nonadherence and the transition to adulthood. *Liver Transplant*. 2009;15(suppl 2):S63-S69.
23. Latin American Pediatric Nephrology Association, Latin American Pediatric Renal Transplant Cooperative Study. Latin American Registry of Pediatric Renal Transplantation 2004-2008. *Pediatr Transplant*. 2010;14:701-708.

24. Cao S, Cox KL, Berquist W, et al. Long-term outcomes in pediatric liver recipients: comparison between cyclosporin A and tacrolimus. *Pediatr Transplant*. 1999;3:22-26.
25. McDiarmid SV, Busuttil RW, Ascher NL, et al. FK506 (tacrolimus) compared with cyclosporine for primary immunosuppression after pediatric liver transplantation. *Transplantation*. 1995;59:530-536.
26. Reding R. Tacrolimus in pediatric liver transplantation. *Pediatr Transplant*. 2002;6:447-451.
27. Vondrak K, Dhawan A, Parisi F, et al. Comparative pharmacokinetics of tacrolimus in de novo pediatric transplant recipients randomized to receive immediate- or prolonged-release tacrolimus. *Pediatr Transplant*. 2018;22:e13289.
28. Kelly D, Jara P, Rodeck B, et al. Tacrolimus and steroids versus ciclosporin microemulsion, steroids, and azathioprine in children undergoing liver transplantation: randomised European multicentre trial. *Lancet*. 2004;364:1054-1061.
29. Trompeter R, Filler G, Webb N, et al. Randomized trial of tacrolimus versus cyclosporin microemulsion in renal transplantation. *Pediatr Nephrol*. 2002;17:141-149.
30. Grenda R, Watson A, Trompeter R, et al. A randomized trial to assess the impact of early steroid withdrawal on growth in pediatric renal transplantation: the TWIST study. *Am J Transplant*. 2010;10:828-836.
31. 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.
32. Webb N, Douglas SE, Rajai A, et al. Corticosteroid-free kidney transplantation improves growth: 2-year follow-up of the TWIST randomized controlled trial. *Transplantation*. 2015;99:1178-1185.
33. Kivelä JM, Räisänen-Sokolowski A, Pakarinen MP, et al. Long-term renal function in children after liver transplantation. *Transplantation*. 2011;91:115-120.

How to cite this article: Vondrak K, Parisi F, Dhawan A, et al. Efficacy and safety of tacrolimus in de novo pediatric transplant recipients randomized to receive immediate- or prolonged-release tacrolimus. *Clin Transplant*. 2019;33:e13698. https://doi.org/10.1111/ctr.13698