

ORIGINAL ARTICLE

Efficacy and safety of prolonged-release tacrolimus in stable pediatric allograft recipients converted from immediate-release tacrolimus – a Phase 2, open-label, single-arm, one-way crossover study

Jacek Rubik¹, Dominique Debray² , Deirdre Kelly³, Franck Iserin⁴, Nicholas J. A. Webb⁵, Piotr Czubkowski⁶, Karel Vondrak⁷, Anne-Laure Sellier-Leclerc⁸, Christine Rivet⁹, Silvia Riva¹⁰, Burkhard Tönshoff¹¹, Lorenzo D'Antiga¹² , Stephen D. Marks¹³ , Raymond Reding¹⁴, Gbenga Kazeem^{15,16} & Nasrullah Undre¹⁶ 

1 Department of Nephrology, Kidney Transplantation and Hypertension, The Children's Memorial Health Institute, Warsaw, Poland

2 Pediatric Hepatology Unit, APHP-Hôpital Universitaire Necker, Paris, France

3 The Liver Unit, Birmingham Women's & Children's Hospital, Birmingham, UK

4 Pediatric Cardiology Unit, APHP-Hôpital Universitaire Necker, Paris, France

5 Department of Pediatric Nephrology, NIHR/Wellcome Trust Manchester Clinical Research Facility, Manchester Academic Health Science Centre, Royal Manchester Children's Hospital, University of Manchester, Manchester, UK

6 Department of Gastroenterology, Hepatology, Nutritional Disturbances and Pediatrics, The Children's Memorial Health Institute, Warsaw, Poland

7 Department of Pediatrics, Second School of Medicine, University Hospital Motol, Charles University, Prague, Czech Republic

8 Department of Nephrology, Rheumatology, and Dermatology, Center for Rare Diseases, Civil Hospice of Lyon, 'Woman-Mother-Child' Hospital, Bron Cedex, France

9 Pediatric Hepatology, Gastroenterology and Transplantation, Civil Hospice of Lyon, Lyon, France

SUMMARY

There are limited clinical data regarding prolonged-release tacrolimus (PR-T) use in pediatric transplant recipients. This Phase 2 study assessed the efficacy and safety of PR-T in stable pediatric kidney, liver, and heart transplant recipients (aged ≥ 5 to ≤ 16 years) over 1 year following conversion from immediate-release tacrolimus (IR-T), on a 1:1 mg total-daily-dose basis. Endpoints included the incidence of acute rejection (AR), a composite endpoint of efficacy failure (death, graft loss, biopsy-confirmed AR, and unknown outcome), and safety. Tacrolimus dose and whole-blood trough levels (target 3.5–15 ng/ml) were also evaluated. Overall, 79 patients (kidney, $n = 48$; liver, $n = 29$; heart, $n = 2$) were assessed. Following conversion, tacrolimus dose and trough levels remained stable; however, 7.6–17.7% of patients across follow-up visits had trough levels below the target range. Two (2.5%) patients had AR, and 3 (3.8%) had efficacy failure. No graft loss or deaths were reported. No new safety signals were identified. Drug-related treatment-emergent adverse events occurred in 28 patients (35.4%); most were mild, and all resolved. This study suggests that IR-T to PR-T conversion is effective and well tolerated over 1 year in pediatric transplant recipients and highlights the importance of therapeutic drug monitoring to maintain target tacrolimus trough levels.

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Key words

calcineurin inhibitor: tacrolimus, clinical trial, heart (allograft) function/dysfunction, immunosuppressant, kidney (allograft) function/dysfunction, liver (allograft) function/dysfunction

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Correspondence

Dr. Nasrullah Undre, Astellas Pharma Global Development, 2000 Hillswood Drive, Chertsey, Surrey KT16 0RS, UK.

Tel.: +44 203 379 8000;

fax: +44 203 379 8315;

e-mail: nas.undre@astellas.com

10 Department of Pediatrics ISMETT–IRCCS Palermo Italy

11 Department of Pediatrics I University Children's Hospital Heidelberg Heidelberg Germany

12 Pediatric Hepatology, Gastroenterology and Transplantation Hospital Papa Giovanni XXIII Bergamo Italy

13 Department of Pediatric Nephrology Great Ormond Street Hospital for Children NHS Foundation Trust London UK

14 Unité de Chirurgie et Transplantation Pédiatrique Cliniques Universitaires Saint-Luc Université Catholique de Louvain Brussels Belgium

15 BENKAZ Consulting Ltd Cambridge UK

16 Astellas Pharma Europe Ltd Chertsey UK

Introduction

Tacrolimus is the most frequently used immunosuppressive therapy following organ transplantation, with over 95% of pediatric kidney and liver transplant recipients in North America receiving tacrolimus-based regimens following transplantation in 2016 [1,2]. Tacrolimus is available as an immediate-release formulation (capsules and granules), administered twice-daily, and as a prolonged-release formulation (capsules), administered once daily. Immediate-release tacrolimus is licensed to prevent allograft rejection in both adult and pediatric kidney, liver, and heart transplant recipients [3]. The prolonged-release formulation is currently licensed for use in adult and pediatric kidney transplant recipients in the United States [4], and in adult kidney and liver transplant recipients in Europe [5].

High inpatient variability in tacrolimus exposure and poor adherence to immunosuppressive therapy have been associated with an increased risk of graft loss and rejection post-transplantation [6–9]. However, some studies in stable adult transplant recipients have shown that conversion from twice-daily, immediate-release to once-daily, prolonged-release tacrolimus may reduce inpatient variability in tacrolimus exposure and increase medication adherence, thereby, potentially improving transplant outcomes [10–13].

Evidence from clinical studies suggests that prolonged-release tacrolimus is effective and well tolerated in adult transplant recipients converted from the immediate-release formulation [10,14,15]. From the small number of published studies, efficacy and safety outcomes in pediatric kidney and liver transplant recipients converted from immediate- to prolonged-release tacrolimus were generally comparable to those in adult transplant patients [16–21]. Indeed, Heffron *et al.* [16] found no episodes of acute rejection (AR), graft loss, or death in an open-label study of 18 stable pediatric liver transplant recipients over a 1-year period after conversion from immediate- to prolonged-release tacrolimus. Furthermore, there were no severe drug-related adverse

events (AEs) and no significant changes in renal function reported in a 1-year follow-up open-label study of 21 pediatric kidney transplant recipients following conversion from immediate- to prolonged-release tacrolimus [21].

Clinical experience with prolonged-release tacrolimus is limited in pediatric solid organ transplant recipients and reported data are generally from small patient numbers [16–21]. Therefore, we undertook this study to assess the pharmacokinetics, efficacy, and safety of prolonged-release tacrolimus over a 1-year period in a large cohort of pediatric kidney, liver, and heart transplant recipients following conversion from immediate-release tacrolimus. Results from the pharmacokinetics evaluation are reported elsewhere [22].

Patients and methods

Study design and patients

This was a Phase 2, open-label, single-arm, one-way crossover study in stable pediatric transplant recipients converted from immediate-release tacrolimus (Prograf[®]; Astellas Pharma Ltd, Chertsey, UK) to prolonged-release tacrolimus (Advagraf[®]; Astellas Pharma Europe BV, Leiden, the Netherlands; ClinicalTrials.gov NCT01294020). The study was conducted at 14 centers in seven European countries between June 2011 and October 2015. Ethics Committee approval was obtained for each participating center, and the study was carried out in accordance with Good Clinical Practice, the International Council for Harmonisation guidelines, and the Declaration of Helsinki. All patients or their guardians provided written informed consent.

Patients were eligible for inclusion in the study if they were aged ≥ 5 and ≤ 16 years, had received a kidney, liver, or heart transplant ≥ 6 months prior to the study, were maintained on an immediate-release tacrolimus-based regimen for ≥ 3 months before the study, and were able to swallow intact tacrolimus capsules. Patients were required to have whole-blood tacrolimus trough

levels in the range 3.5–15.0 ng/ml on two or more occasions ≥ 6 days apart, and within 30 days prior to Day 1 of the study (the first day of study drug treatment). Key exclusion criteria were a multi-organ transplant, a rejection episode within 3 months, or within 6 months if anti-lymphocyte antibody therapy was required, or two or more rejection episodes within 12 months prior to the study. Patients were excluded if they were receiving rapamycin, everolimus, or mycophenolic acid (Myfortic; Novartis Pharmaceuticals UK Ltd, Camberley, Surrey, UK). Use of substances known to interfere with tacrolimus metabolism was not permitted during the 28 days pre-transplantation or the 28 days post-transplantation.

All eligible patients entered a 30-day screening period (Day –30 to Day –1) during which they continued to receive their routine, twice-daily, immediate-release tacrolimus-based regimen. On Days 1–7, patients received twice-daily, immediate-release tacrolimus orally, at the same dose as during the screening period. On Day 8, all patients were converted on a 1:1 mg total-daily-dose basis from twice-daily immediate-release tacrolimus to once-daily, prolonged-release tacrolimus, and continued to receive prolonged-release tacrolimus to Week 54. Dose adjustments for clinical reasons were permitted at any time during the study, and adjustments to maintain target whole-blood tacrolimus trough levels within the range 3.5–15 ng/ml [5] were permitted after Day 15 based on the clinical practice protocol at each center. Patients could maintain their pre-enrollment treatment with steroids, azathioprine, or mycophenolate mofetil (CellCept; Roche Pharma AG, Grenzach-Wyhlen, Germany) throughout the study period, but dose adjustment was not permitted until after Day 15. Concomitant medications included prescribed

and over-the-counter drugs, taken from the start of the 30-day screening period to the end-of-study visit.

The initial pharmacokinetic assessment was undertaken from Day –30 to Day –15 (part A) [22], and the efficacy, safety, tacrolimus daily dose, and blood trough levels were assessed from Week 2 to Week 54 (part B; assessments at Weeks 2, 6, 10, 14, 28, 42, and 54; Fig. 1).

Endpoints and variables

Efficacy endpoints included the number of AR and biopsy-confirmed AR (BCAR) episodes, patient and graft survival, and efficacy failure (a composite of death, graft loss, BCAR, and unknown outcome). Graft loss was defined as retransplantation, death, graft nephrectomy, or dialysis ongoing at the end of the study or at study discontinuation (in kidney transplant recipients). For the composite endpoint, a patient was considered to have an unknown outcome if they did not have the event of interest (death, graft loss or BCAR), did not have a study assessment within 30 days prior to the target day of analysis, and had no further assessments thereafter. Other endpoints included tacrolimus total daily dose and number of dose adjustments, tacrolimus whole-blood trough levels (monitored using local assay methods, e.g., IMX[®], EMIT[®] or high-performance liquid chromatography/tandem mass spectrometry), and the proportion of patients within the recommended target trough level range (3.5–15 ng/ml). Renal function was assessed using the estimated glomerular filtration rate (eGFR), calculated with the Schwartz equation [23].

Treatment-emergent AEs (TEAEs), vital signs, and clinical laboratory variables were also recorded. A

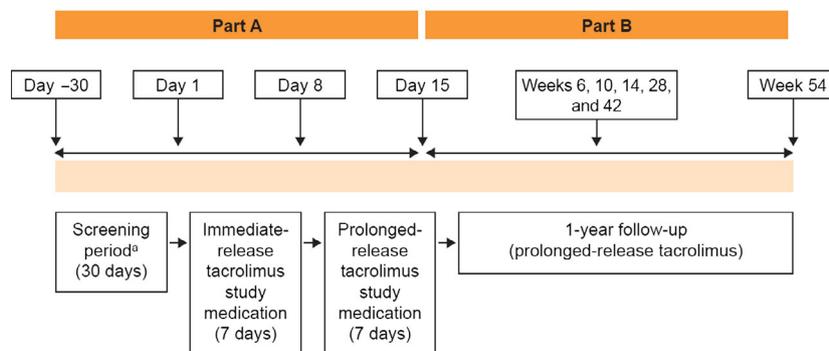


Figure 1 Study design. ^aDuring the screening period, patients received their routine twice-daily, immediate-release tacrolimus-based immunosuppressive regimen. After the initial pharmacokinetic assessment (Day –30 to Day 15; part A), patients were administered a prolonged-release tacrolimus-based immunosuppressive regimen for 52 additional weeks (part B). Part B follow-up visits occurred at 6, 10, 14, 28, 42, and 54 weeks.

serious TEAE was defined as a TEAE that in the opinion of the investigator resulted in one of the following outcomes: (i) death; (ii) a life-threatening adverse event; (iii) inpatient hospitalization or prolongation of existing hospitalization (for >24 h); (iv) persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; and (v) a congenital anomaly/birth defect. TEAEs were graded mild, moderate, or severe according to the Common Terminology Criteria for Adverse Events [24].

Statistical analysis

The planned study sample size of 72 patients (24 patients for each organ type) provided a power of 97% to assess similarity of tacrolimus exposure in the pharmacokinetic evaluation [22]. A separate power calculation was not undertaken for the efficacy and safety assessments, and the analysis was descriptive. The full-analysis set (FAS) included all patients who received at least one dose of study drug. Efficacy and safety analyses were performed on the modified FAS (mFAS), which included all patients who received at least one dose of prolonged-release tacrolimus. Patients who were lost to follow-up or alive at the end of the study (Week 54) were censored in survival analyses.

Descriptive statistics were reported for continuous variables. All analyses were stratified by organ type; however, no statistical comparisons were made between different organ transplant groups. The last observation on or before the day that prolonged-release tacrolimus treatment was initiated was considered the baseline for prolonged-release tacrolimus efficacy and safety outcomes. SAS[®] version 9.3 or higher was used for data processing, summarization and analyses.

Results

Study population

Of 113 patients who were screened, 81 were enrolled, received immediate-release tacrolimus and were included in the FAS. Two liver transplant recipients did not receive prolonged-release tacrolimus; therefore, the mFAS comprised 79 patients (kidney transplant, $n = 48$; liver transplant, $n = 29$; heart transplant, $n = 2$; Fig. 2). Three patients discontinued prolonged-release tacrolimus treatment: two due to AEs and one patient withdrew consent. Overall, 76 patients completed the 12-month efficacy and safety study.

Patient baseline demographics and characteristics are presented in Table 1. In the mFAS, most patients were Caucasian (93%) and over half were male (57%). Overall, the mean \pm standard deviation (SD) age was 11.6 ± 2.8 years (range, 5–16 years); 41.8% of patients were children (aged 2–11 years) and 58.2% were adolescents (aged 12–16 years). There was wide variation in weight and height due to the age range of the patients; mean \pm SD weight and height were 43.0 ± 16.6 kg and 144.8 ± 17.5 cm, respectively.

Tacrolimus dose and whole-blood trough levels

The mean \pm SD duration of prolonged-release tacrolimus exposure was 361.0 ± 53.3 days in the overall patient population and was similar for the kidney and liver transplant recipients (368.5 ± 14.8 and 360.6 ± 54.0 days, respectively). Overall, 88.6% of patients received prolonged-release tacrolimus for between 253 and 378 days.

Mean tacrolimus total daily dose (Fig. 3a) and blood trough levels (Fig. 3b) remained stable during the 12-

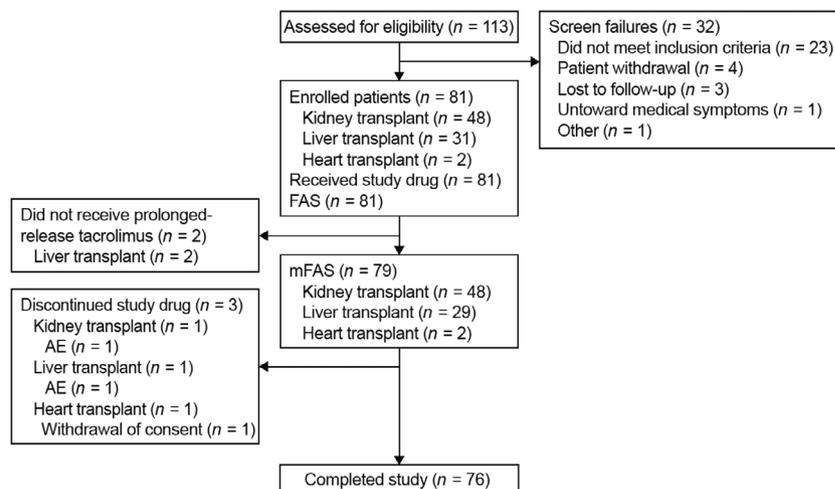


Figure 2 Patient flow through the study. AE, adverse event; FAS, full-analysis set; mFAS, modified full-analysis set.

Table 1. Patient baseline demographics and characteristics for the overall population and stratified by organ type (mFAS)

| Parameter | Kidney transplant (n = 48) | Liver transplant (n = 29) | Heart transplant (n = 2) | Overall (n = 79) |
|--------------------------------------------|----------------------------|---------------------------|--------------------------|------------------|
| Age, years | | | | |
| Mean \pm SD | 11.0 \pm 3.0 | 12.4 \pm 2.3 | 13.5 \pm 0.7 | 11.6 \pm 2.8 |
| Median | 11.5 | 13.0 | 13.5 | 12.0 |
| Minimum, maximum | 5, 16 | 7, 16 | 13, 14 | 5, 16 |
| Age category, n (%) | | | | |
| ≥ 2 to ≤ 11 years (children) | 24 (50.0) | 9 (31.0) | 0 | 33 (41.8) |
| ≥ 12 to ≤ 16 years (adolescents) | 24 (50.0) | 20 (69.0) | 2 (100.0) | 46 (58.2) |
| Sex, n (%) | | | | |
| Male | 29 (60.4) | 15 (51.7) | 1 (50.0) | 45 (57.0) |
| Race, n (%) | | | | |
| Caucasian | 37 (92.5) | 16 (94.1) | 0 | 53 (93.0) |
| Asian | 2 (5.0) | 0 | 0 | 2 (3.5) |
| Other | 1 (2.5) | 1 (5.9) | 0 | 2 (3.5) |
| Missing* | 8 | 12 | 2 | 22* |
| Weight, kg | | | | |
| Mean \pm SD | 40.5 \pm 19.2 | 45.9 \pm 10.3 | 62.0 \pm 0 | 43.0 \pm 16.6 |
| Median | 35.1 | 47.4 | 62.0 | 41.0 |
| Minimum, maximum | 17, 109 | 29, 66 | 62, 62 | 17, 109 |
| Height, cm | | | | |
| Mean \pm SD | 139.2 \pm 18.3 | 153.2 \pm 12.4 | 158.5 \pm 8.6 | 144.8 \pm 17.5 |
| Median | 137.8 | 155.2 | 158.5 | 146.5 |
| Minimum, maximum | 103, 181 | 130, 174 | 152, 165 | 103, 181 |

mFAS, modified full-analysis set; SD, standard deviation.

*Data on race were not collected from French patients as this was not permitted in France.

month period following conversion from immediate- to prolonged-release tacrolimus. The overall mean \pm SD daily dose of prolonged-release tacrolimus was 0.097 ± 0.053 mg/kg at Week 2 and 0.088 ± 0.046 mg/kg at Week 54. The mean \pm SD dose was numerically higher for kidney transplant recipients (Week 2: 0.112 ± 0.057 mg/kg; Week 54: 0.100 ± 0.049 mg/kg) than for liver transplant recipients (Week 2: 0.074 ± 0.036 mg/kg; Week 54: 0.070 ± 0.031 mg/kg) throughout the 12-month follow-up period (Fig. 3a), in line with lower mean tacrolimus trough levels in liver transplant recipients (Fig. 3b).

Throughout the study period, mean tacrolimus trough levels remained within the target range of 3.5–15 ng/ml for both kidney and liver transplant recipients. At Day 14, 14 patients (17.7%) had trough levels below 3.5 ng/ml, and across follow-up visits from Week 6 to Week 54, below target trough levels were observed in 7.6–11.4% of patients. None of the patients had trough levels above 15 ng/ml. At Week 2, the mean \pm SD tacrolimus trough levels were 5.07 ± 1.87 ng/ml for the overall transplant population, 5.57 ± 1.72 ng/ml for the

kidney transplant group, and 4.07 ± 1.40 ng/ml for the liver transplant group. Tacrolimus trough levels were stable during the follow-up period, and levels were similar to Week 2 at Week 54 (overall: 5.16 ± 2.06 ; kidney: 5.56 ± 1.54 ; liver: 4.00 ± 1.52 ng/ml; Fig. 3b).

Tacrolimus dose adjustments were made based on individual centers' clinical practice protocol, and to maintain the patient at the target trough level. Overall, 52/79 (65.8%) patients had a dose adjustment during the study. At Week 6, 12.7% of patients had an increased dose, and 7.6% had a decreased dose (Fig. 4). At Week 54, just 5.1% of patients had a dose adjustment, with similar numbers receiving increased and decreased dosages (2.5% and 3.8%, respectively; Fig. 4). Concomitant mycophenolate mofetil, prednisone, prednisolone, and azathioprine were continued in 49.4%, 38.0%, 17.7%, and 12.7% of patients, respectively.

Rejection episodes, graft and patient survival

Two transplant recipients (2.5%, both kidney) had AR episodes (Table 2), both considered as a serious TEAE

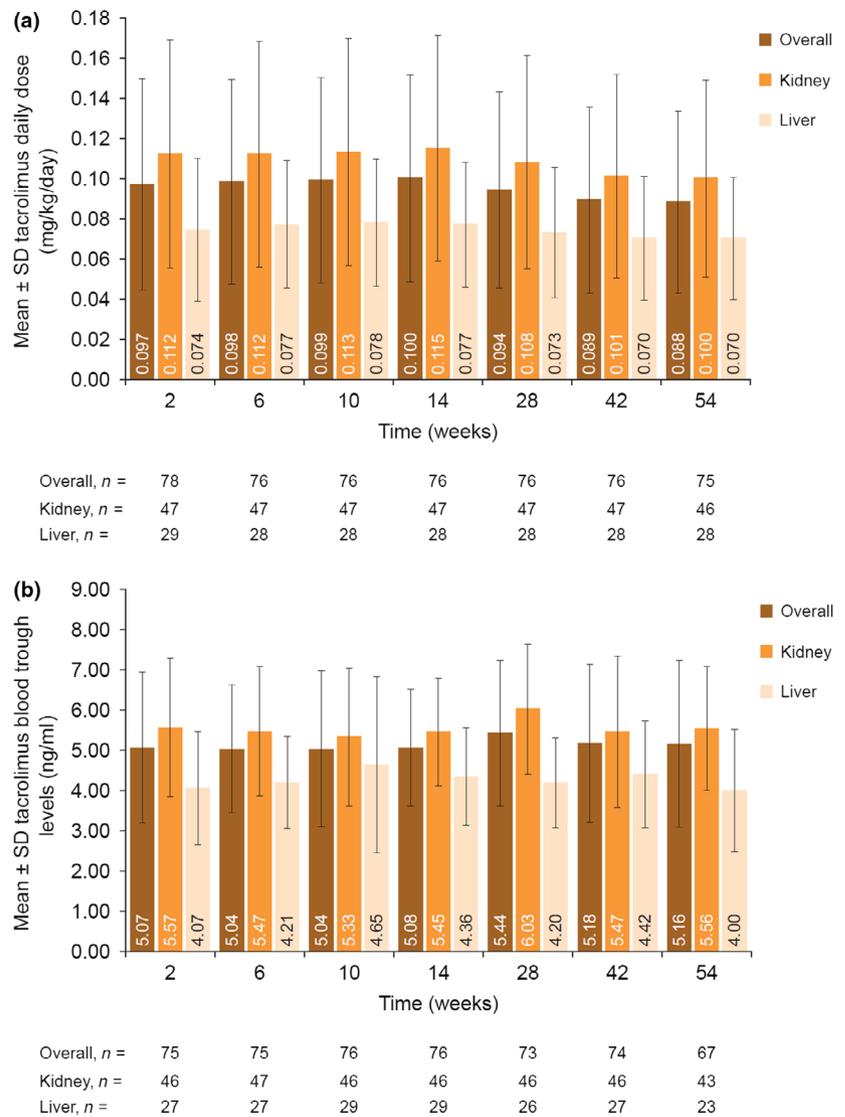


Figure 3 Mean \pm SD tacrolimus (a) weight-adjusted daily dose and (b) blood trough levels following conversion to prolonged-release tacrolimus for the overall pediatric transplant population and stratified by organ type (mFAS). Note: One of two heart transplant patients withdrew at an early stage in the study. The data for the remaining heart transplant recipient are not presented separately, but are included in the overall population. mFAS, modified full-analysis set; SD, standard deviation.

of moderate severity. In one patient, a BCAR episode (an acute T-cell-mediated rejection and acute antibody-mediated rejection) occurred on Day 281 and was resistant to corticosteroid treatment. The patient discontinued prolonged-release tacrolimus and was withdrawn from the study. The rejection episode resolved after further treatment with methylprednisolone, anti-thymocyte immunoglobulin and rituximab. The AR episode in the second patient on Day 145 was not confirmed by biopsy and was treated with corticosteroids and plasmapheresis. Following further treatment with intravenous immunoglobulins, intravenous methylprednisolone, and oral prednisone, the AR episode resolved with sequelae (elevated serum creatinine levels). There were no episodes of graft loss or deaths during the follow-up period (Table 2).

Efficacy failure

Overall, three transplant recipients (3/79, 3.8%) had composite efficacy failure (Table 2). One kidney transplant recipient had a BCAR episode on Day 281 (discussed above); one liver transplant recipient had an AE (diarrhea) on Day 90 that led to study withdrawal. A heart transplant recipient withdrew consent and discontinued the study on Day 14.

Renal function

Renal function, as assessed by mean \pm SD eGFR, was relatively stable during the study period in kidney transplant recipients: 112.1 ± 31.0 ml/min/1.73 m² at Week 2 and 101.8 ± 28.2 ml/min/1.73 m² at Week 54 (Fig. 5).

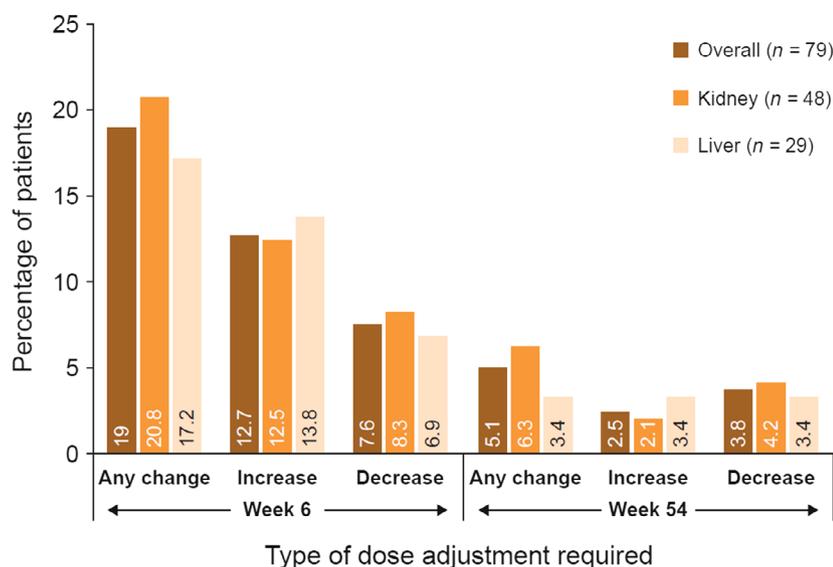


Figure 4 Patients, as a percentage of the study population, requiring dose adjustments at study Week 6 and study Week 54, for the overall pediatric transplant population and kidney and liver transplant patients (mFAS). Note: One of two heart transplant patients withdrew at an early stage in the study. The data for the remaining heart transplant recipient are not presented separately, but are included in the overall population; this patient had no changes in dosage at either Week 6 or Week 54; Week 6 is from Day 19 to 56 and Week 54 (end of study) from Day 337; mFAS, modified full-analysis set.

Safety

No new safety signals for prolonged-release tacrolimus were identified during the course of this study. Overall, 282 TEAEs were reported in 84.8% (67/79) of patients; serious TEAEs occurred in 24.1% (19/79) of patients (Table 3). The most common TEAEs were diarrhea (13.9%), headache (13.9%), and cough (11.4%). TEAEs were mild in 56.7% and severe in 7.6% of patients.

Overall, 28 patients (28/79, 35.4%) had drug-related TEAEs, of whom 10 (10/79, 12.7%) had drug-related serious TEAEs. All drug-related TEAEs subsequently resolved. Overall, infections and infestations were the most common class of drug-related TEAE (18/79, 22.8%) (Table 4). Most drug-related TEAEs were mild in severity.

Laboratory and vital signs

No unusual laboratory test results or vital signs were observed in patients during the course of this study. Results from laboratory evaluations and vital signs were comparable in the liver and kidney transplant recipients. Overall, 12 patients (8/48 kidney and 4/29 liver transplant recipients) had potentially clinically significant increases in hematocrit, hemoglobin levels, leukocyte counts, and platelet counts. Overall, 15 patients (11/48 kidney and 4/29 liver transplant recipients) had potentially clinically significant biochemistry test results. The most common changes from baseline were reductions in total bilirubin and high-density lipoprotein levels.

Discussion

During this prospective, open-label study, mean tacrolimus whole-blood trough levels were stable up to 1 year following conversion from immediate-release to prolonged-release tacrolimus and were in the target range for most patients. There were just two ARs in kidney transplant recipients and no deaths or graft loss during the study. Importantly, no new safety signals were identified for prolonged-release tacrolimus in this pediatric population.

In the companion pharmacokinetics paper based on the same patient cohort, we recently demonstrated that following conversion from immediate- to prolonged-release tacrolimus (1:1 mg), the mean systemic exposure to tacrolimus (AUC_{0-24}) under steady-state conditions (after 7 days on the same dose) and the linear relationship between AUC_{0-24} and C_{24} were similar for the two formulations (ρ , 0.89 and 0.84, respectively) [22]. This indicated that stable pediatric transplant recipients can be converted from immediate-release to prolonged-release tacrolimus on a 1:1 mg total-daily-dose basis, in line with previous reports [14–16,19]. In the present study, mean \pm SD trough levels prior to conversion were 5.80 ± 1.73 ng/ml. Following conversion, tacrolimus exposure remained stable, with observed trough levels at Week 2 of 5.07 ± 1.87 ng/ml and Week 54 of 5.16 ± 2.06 ng/ml. The tacrolimus trough levels observed in our study were comparable with that observed in a study of 11 pediatric kidney transplant recipients (preconversion: 6.2 ± 2.0 ng/ml; 1 year post-conversion: 6.5 ± 0.9 ng/ml) [19], and 18 pediatric

Table 2. Efficacy outcomes for the overall population and stratified by organ type (mFAS)

| Parameter | Patients, <i>n</i> (%) | | | Overall (<i>n</i> = 79) |
|---------------------------------------------|------------------------------------|-----------------------------------|----------------------------------|--------------------------|
| | Kidney transplant (<i>n</i> = 48) | Liver transplant (<i>n</i> = 29) | Heart transplant (<i>n</i> = 2) | |
| All ARs | 2 (4.2) | 0 | 0 | 2 (2.5) |
| BCAR | 1 (2.1) | 0 | 0 | 1 (1.3) |
| Non-BCAR | 1 (2.1) | 0 | 0 | 1 (1.3) |
| Any ARs | 2 (4.2) | 0 | 0 | 2 (2.5) |
| Corticosteroid-sensitive AR | 1 (2.1) | 0 | 0 | 1 (1.3) |
| Corticosteroid-resistant AR | 1 (2.1)* | 0 | 0 | 1 (1.3) |
| Resolved with further treatment | 2 (4.2) | 0 | 0 | 1 (1.3) |
| All BCARs | 1 (2.1) | 0 | 0 | 1 (1.3) |
| Corticosteroid-sensitive AR | 0 | 0 | 0 | 0 |
| Corticosteroid-resistant AR | 1 (2.1) | 0 | 0 | 1 (1.3) |
| Resolved with further treatment | 1 (2.1) | 0 | 0 | 1 (1.3) |
| Efficacy failure [†] | 1 (2.1) | 1 (3.4) | 1 (50.0) | 3 (3.8) |
| Death | 0 | 0 | 0 | 0 |
| Graft loss | 0 | 0 | 0 | 0 |
| BCAR, <i>n</i> (%) | 1 (2.1) [‡] | 0 | 0 | 1 (1.3) |
| Unknown outcome [§] , <i>n</i> (%) | 0 | 1 (3.4) | 1 (50.0) | 2 (2.5) |

AR, acute rejection; BCAR, biopsy-confirmed acute rejection; mFAS, modified full-analysis set; SAE, serious adverse event.

*This patient was withdrawn from the study.

[†]Composite of subcategories shown.

[‡]Moderate SAE (corticosteroid-resistant BCAR in a kidney transplant recipient; the patient discontinued from the study and the event resolved after treatment with methylprednisolone, anti-thymocyte immunoglobulin, and rituximab).

[§]A patient was considered to have an unknown outcome if he/she did not have the event of interest (death, graft loss, BCAR) and did not have a study assessment within 30 days prior to the target day of analysis, and had no further assessments thereafter.

liver transplant recipients: (4.9 ± 2.4 – 5.9 ± 2.7 ng/ml during the first year following conversion) [16].

While mean exposure to tacrolimus was stable in pediatric transplant recipients converted from immediate- to prolonged-release tacrolimus, almost two-thirds of patients (65.8%) had dose adjustments during the study. It is noteworthy that although no patients had tacrolimus trough levels above the target range, six patients (7.6%) at Week 6 and three patients (3.8%) at Week 54 were administered a decreased tacrolimus dose. These dose adjustments were tailored to the specific clinical characteristics of individual patients (including concomitant immunosuppressive medications used, time post-transplantation, growth-related changes in body weight and age-related changes in tacrolimus clearance), according to the clinical practice protocol at each center.

Tacrolimus has a narrow therapeutic index and, therefore, exposure to the drug should be maintained within a tightly defined target range on an individual patient basis,

as underexposure is associated with poor transplant outcomes [25,26], while overexposure can cause drug-related adverse effects and toxicity [27]. During the study, 7.6–17.7% of all transplant recipients across visits had individual tacrolimus trough levels less than 3.5 ng/ml.

In this study, only two (2.5%) kidney transplant recipients experienced AR, and there were no deaths or graft losses. These data are aligned with previous reports of pediatric kidney and liver transplant recipients converted from immediate- to prolonged-release tacrolimus, in whom ARs were very low, or absent, over follow-up periods ranging from 6 months to 5 years [16–21]. For example, in a study of 11 pediatric stable kidney transplant recipients converted from immediate- to prolonged-release tacrolimus, there were two BCAR episodes in one patient during the 1-year follow-up period [19]. Furthermore, a study of 55 Spanish pediatric liver transplant recipients reported no graft losses or patient deaths over a mean postconversion follow-up time of 5.2 ± 2.4 years [17].

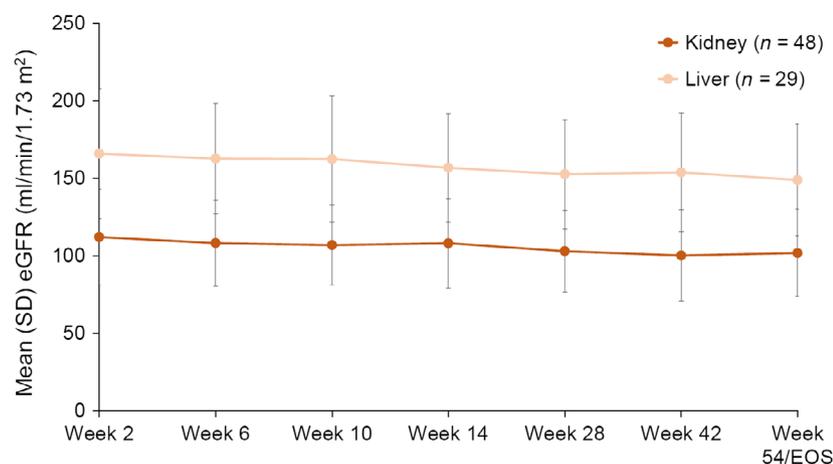


Figure 5 Renal function over time in kidney and liver transplant patients (mFAS). eGFR was calculated using the Schwartz equation. eGFR, estimated glomerular filtration rate; mFAS, modified full-analysis set; SD, standard deviation.

Table 3. Overview of TEAEs for overall population and stratified by organ type (mFAS)

| Parameter | Patients, <i>n</i> (%) | | |
|--------------------------------------------|------------------------------------|-----------------------------------|--------------------------|
| | Kidney transplant (<i>n</i> = 48) | Liver transplant (<i>n</i> = 29) | Overall (<i>n</i> = 79) |
| TEAEs | 39 (81.3) | 27 (93.1) | 67 (84.8) |
| Drug-related TEAEs* | 24 (50.0) | 4 (13.8) | 28 (35.4) |
| Serious TEAEs | 15 (31.3) | 4 (13.8) | 19 (24.1) |
| Drug-related serious TEAEs* | 9 (18.8) | 1 (3.4) | 10 (12.7) |
| TEAEs leading to permanent discontinuation | 0 | 1 (3.4) [†] | 1 (1.3) |

mFAS, modified full-analysis set; TEAE, treatment-emergent adverse event.

Data for the heart transplant recipient (*n* = 1) are not presented separately, but are included in the overall population.

*Possible or probable, as assessed by the investigator, or records where relationship is missing.

[†]Drug-related TEAE (diarrhea).

We found that renal function was stable in both kidney and liver transplant recipients after conversion from immediate- to prolonged-release tacrolimus, in accordance with previous studies [15,17,18,20,21]. Collectively, the efficacy data presented here suggest that conversion from immediate- to prolonged-release tacrolimus is associated with a very low AR rate over 1 year in solid organ transplant recipients.

Prolonged-release tacrolimus was generally well tolerated during our study and no new safety signals were identified in this pediatric population. Although approximately one-third of patients experienced drug-related TEAEs following conversion from immediate- to prolonged-release tacrolimus, most were mild in severity, and all resolved. Similar results have been seen in previous studies of pediatric kidney and liver transplant recipients converted from immediate- to prolonged-release tacrolimus [16–21].

This study had several limitations, including the absence of a control group to act as a comparator. In

addition, since the patient population was predominantly Caucasian (93%), the results of the study may not be applicable to the general population due to differences in the pharmacokinetic profile and metabolism of tacrolimus between races. For example, African Americans exhibit 20–50% lower bioavailability and higher clearance of tacrolimus compared with Caucasians [28,29], and therefore require 1.5- to 2-times higher tacrolimus doses to achieve equivalent target trough concentrations [30–34]. The study was only powered to compare the pharmacokinetics of immediate- and prolonged-release tacrolimus; therefore, it was not possible to assess the statistical significance of differences in efficacy and safety between the different organ transplant groups. Furthermore, as only two heart transplant recipients were enrolled in this study, and one of these patients subsequently withdrew at an early stage, it was not possible to assess the efficacy and safety of conversion from immediate- to prolonged-release tacrolimus in this transplant group. Clearance of prolonged-release tacrolimus has been shown to be

Table 4. Drug-related TEAEs by system organ class and preferred term (mFAS)

| System organ class (≥5% overall) preferred term | Patients, n (%) | | |
|----------------------------------------------------|-------------------------------|------------------------------|---------------------|
| | Kidney transplant (n = 48) | Liver transplant (n = 29) | Overall (n = 79) |
| Overall | 24 (50.0) | 4 (13.8) | 28 (35.4) |
| Gastrointestinal disorders | 4 (8.3) | 1 (3.4) | 5 (6.3) |
| Diarrhea | 2 (4.2) | 1 (3.4) | 3 (3.8) |
| Vomiting | 1 (2.1) | 1 (3.4) | 2 (2.5) |
| Enterocolitis | 1 (2.1) | 0 | 1 (1.3) |
| Nausea | 0 | 1 (3.4) | 1 (1.3) |
| Infections and infestations | 17 (35.4) | 1 (3.4) | 18 (22.8) |
| Acute sinusitis | 2 (4.2) | 0 | 2 (2.5) |
| Cytomegalovirus infection | 1 (2.1) | 0 | 1 (1.3) |
| Escherichia urinary tract infection | 2 (4.2) | 0 | 2 (2.5) |
| Gastroenteritis | 2 (4.2) | 0 | 2 (2.5) |
| Liver abscess | 0 | 1 (3.4) | 1 (1.3) |
| Nasopharyngitis | 0 | 1 (3.4) | 1 (1.3) |
| Oral fungal infection | 1 (2.1) | 0 | 1 (1.3) |
| Oral herpes | 3 (6.3) | 0 | 3 (3.8) |
| Pharyngitis | 2 (4.2) | 0 | 2 (2.5) |
| Pneumonia | 1 (2.1) | 0 | 1 (1.3) |
| Scarlet fever | 1 (2.1) | 0 | 1 (1.3) |
| Superinfection bacterial | 1 (2.1) | 0 | 1 (1.3) |
| Tracheobronchitis mycoplasmal | 1 (2.1) | 0 | 1 (1.3) |
| Upper respiratory tract infection | 2 (4.2) | 0 | 2 (2.5) |
| Urinary tract infection | 1 (2.1) | 0 | 1 (1.3) |
| Viral upper respiratory tract infection | 1 (2.1) | 0 | 1 (1.3) |
| Investigations | 6 (12.5) | 1 (3.4) | 7 (8.9) |
| Aspartate aminotransferase increased | 0 | 1 (3.4) | 1 (1.3) |
| Blood creatinine increased | 2 (4.2) | 0 | 2 (2.5) |
| Blood iron decreased | 1 (2.1) | 0 | 1 (1.3) |
| Blood pressure increased | 1 (2.1) | 0 | 1 (1.3) |
| C-reactive protein increased | 1 (2.1) | 0 | 1 (1.3) |
| Immunosuppressant drug level decreased | 1 (2.1) | 0 | 1 (1.3) |
| Immunosuppressant drug level increased | 1 (2.1) | 0 | 1 (1.3) |

mFAS, modified full-analysis set; TEAE, treatment-emergent adverse event.

Data for the heart transplant recipient (n = 1) are not presented separately, but are included in the overall population.

higher in younger patients aged <5 years (even if they are able to swallow the capsules intact), which can necessitate twice-daily treatment with tacrolimus [35]. Patients enrolled in this study were ≥5 years, and therefore conclusions drawn about efficacy and safety may not be applicable to younger children. Additionally, there is limited information regarding an appropriate dose in these patients. Per-protocol biopsies were not performed in this study, so smoldering (sub-clinical) rejection, an important pathogenesis in chronic antibody-mediated rejection [36], could not be detected. Further limitations are that neither medication adherence nor donor-specific antibodies were evaluated in the present study.

In conclusion, our data suggest that conversion from twice-daily, immediate-release to once-daily, prolonged-release tacrolimus on a 1:1 mg total-daily-dose basis is effective over 1 year postconversion in pediatric transplant recipients. Prolonged-release tacrolimus was generally well tolerated and no new safety signals were identified in this pediatric population. Tacrolimus dose adjustments may be required to maintain stable post-conversion target tacrolimus blood trough levels, thereby highlighting the importance of therapeutic drug monitoring in pediatric transplant recipients following conversion from immediate- to prolonged-release tacrolimus.

Authorship

JR, DD, DK, FI, NJAW, PC, KV, ASL, CR, SR, BT, LD, SDM and RR: performed research and collected data. GK: analyzed the data. NU: designed the study, and all authors reviewed and approved the manuscript.

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Conflict of interest

JR, DK, PC, KV, ASL, CR and LD report nonfinancial support from Astellas, during the conduct of the study. DD and FI report nonfinancial, and other support from Astellas, during the conduct of the study, and other support from Astellas, outside the submitted work. NJAW, SR and RR report nonfinancial, and other support from Astellas, during the conduct of the study. BT reports nonfinancial, and other support from Astellas, during the conduct of the study; grants and other support from Astellas and Novartis, outside the submitted work; and other support from Bristol-Myers Squibb and Roche, outside the submitted work. SDM reports grants, other, and nonfinancial support from Astellas, during the conduct of the study, and grants from Novartis, outside the submitted work. GK reports nonfinancial, and other support from Astellas, during the conduct of the study, and is a consulting statistician working on behalf of Astellas. NU reports nonfinancial, and other support from Astellas, during the conduct of the study, and is an employee of Astellas. Medical

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Data statement

Access to anonymized individual participant level data collected during the trial, in addition to supporting clinical documentation, is planned for trials conducted with approved product indications and formulations, as well as compounds terminated during development. Conditions and exceptions are described under the Sponsor Specific Details for Astellas on www.clinicalstudydatarequest.com. Study-related supporting documentation is redacted and provided if available, such as the protocol and amendments, statistical analysis plan and clinical study report. Access to participant level data is offered to researchers after publication of the primary manuscript (if applicable) and is available as long as Astellas has legal authority to provide the data. Researchers must submit a proposal to conduct a scientifically relevant analysis of the study data. The research proposal is reviewed by an Independent Research Panel. If the proposal is approved, access to the study data is provided in a secure data sharing environment after receipt of a signed Data Sharing Agreement.

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