Accepted Article

Received Date : 05-Sep-2016

Revised Date : 24-Feb-2017

Accepted Date : 06-Mar-2017

Article type : Original Article

Pharmacokinetics of prolonged-release tacrolimus versus immediate-release tacrolimus in *de novo* liver transplantation: a randomized phase III sub-study

Bo-Göran Ericzon[a], Evaristo Varo[b], Pavel Trunečka[c], Lutz Fischer[d], Michele Colledan[e], Bruno Gridelli[f], Andrés Valdivieso[g], John O'Grady[h], James Dickinson[i], Nasrullah Undre[j]

[a]Division of Transplantation Surgery, Karolinska University Hospital Huddinge, Stockholm, Sweden; [b]Liver Transplant Unit, University Hospital Santiago de Compostela, Santiago de Compostela, Spain; [c]Transplantcentre, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; [d]Department of Hepatobiliary and Transplant Surgery, University Medical Center, Hamburg-Eppendorf, Germany; [e]Department of Surgery, Ospedale Giovanni XXIII, Bergamo, Italy; [f]Division of Abdominal and Transplantation Surgery, ISMETT, Palermo, Italy; [g]Liver Transplant Unit, Cruces University Hospital, Baracaldo-Bilbao, Spain; [h]Liver Transplant Unit, King's College Hospital, London, UK; [i]Clinical Services, NUVISAN GmbH, Neu-Ulm, Germany (former employee of Fujisawa GmbH, Munchen, Germany, now Astellas Pharma Europe Ltd); [j]Medical affairs, Astellas Pharma Europe Ltd, Chertsey, UK

Running title: PKs of prolonged-release tacrolimus in LTx

Corresponding author: Nasrullah Undre, Astellas Pharma Europe Ltd, 2000 Hillswood Drive, Chertsey, Surrey, KT16 0RS, UK. Tel: +44 203 379 8000; fax: +44 203 379 8001 (e-mail: Nas.Undre@astellas.com).

Target journal: *Clinical Transplantation*

Abbreviations

AUC	Area under the curve
AUC_{0-12}	Area under the curve from 0 to 12 hours
AUC_{0-24}	Area under the curve from 0 to 24 hours

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ctr.12958

This article is protected by copyright. All rights reserved.

Accepted Article

C_{12}	Concentration at 12 hours
C_{24}	Concentration at 24 hours
CI	Confidence interval
C_{max}	Maximum observed concentration
FPKS	Full pharmacokinetic set
NA	Not analysed
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
SD	Standard deviation
T_{max}	Time of maximum observed concentration

Ericzon B, Varo E, Trunečka P, Fischer L, Colledan M, Gridelli B, Valdivieso A, O'Grady J, Dickinson J, Undre N

Pharmacokinetics of prolonged-release tacrolimus versus immediate-release tacrolimus in de novo liver transplantation: a randomized phase III sub-study

Journal title: *Clin Transplant*

Abstract

Background: With the same dose of tacrolimus, lower systemic exposure on the first day of dosing has been reported for prolonged-release tacrolimus compared with immediate-release tacrolimus, prompting investigation of differing initial doses.

Methods: This sub-study of a double-blind, randomized, phase III trial in *de novo* liver transplant recipients compared the pharmacokinetics of once-daily prolonged-release tacrolimus (initial dose: 0.2mg/kg/day) versus twice-daily immediate-release tacrolimus (initial dose: 0.1mg/kg/day) during the first 2 weeks post-transplant.

Results: Pharmacokinetic data were analysed from patients receiving prolonged-release tacrolimus (n=13) and immediate-release tacrolimus (n=12). Mean systemic exposure ($AUC_{0–24}$) was higher with prolonged-release versus immediate-release tacrolimus. Dose-normalized $AUC_{0–24}$ (normalized to 0.1mg/kg/day) showed generally lower exposure with prolonged-release tacrolimus versus immediate-release tacrolimus. There was good correlation between $AUC_{0–24}$ and concentration at 24 hours after the morning dose (r=0.96 and r=0.86, respectively), and the slope of the line of best fit was similar for both formulations.

Conclusions: Doubling the initial starting dose of prolonged-release tacrolimus compared with immediate-release tacrolimus overcompensated for lower exposure on Day 1. A 50% higher starting dose of prolonged-release tacrolimus than immediate-release tacrolimus may be required for similar systemic exposure. However, doses of both formulations can be optimized using the same trough-level monitoring system. (ClinicalTrials.gov number: NCT00189826).

This article is protected by copyright. All rights reserved.

Accepted Article

Discipline: liver transplantation/hepatology, immunosuppression/immune modulation

Key words: immunosuppressant, calcineurin inhibitor: tacrolimus; rejection; immunosuppressant; liver transplantation: living donor; pharmacokinetics/pharmacodynamics

Corresponding author: Nasrullah Undre, Astellas Pharma Europe Ltd, 2000 Hillswood Drive, Chertsey, Surrey, KT16 0RS, UK. Tel: +44 203 379 8000; fax: +44 203 379 8001 (e-mail: Nas.Undre@astellas.com).

Introduction

Tacrolimus is well-established as an immunosuppressive agent for the prevention and treatment of allograft rejection in solid organ transplantation. Oral tacrolimus is available as an immediate-release formulation that is usually administered twice daily, as well as a prolonged-release formulation for once-daily (morning) dosing. Interventional studies performed in *de novo* liver or kidney transplant recipients have shown that these two tacrolimus formulations have a similar efficacy and safety profile. (1, 2)

Given that tacrolimus is a medication with a narrow therapeutic window (3, 4) and that systemic exposure is subject to variability between and within patients, (5, 6) tacrolimus therapy is individualized on the basis of systemic exposure in blood by monitoring trough levels as surrogate markers of exposure (area under the curve [AUC]). (5) Previous pharmacokinetic (PK) studies in stable and *de novo* transplant populations have established that the relationship between trough levels and AUC between the two formulations is similar; obtaining the same trough levels with the two formulations indicated that similar exposure to tacrolimus was obtained. (7, 8)

In a phase II study in *de novo* liver transplant recipients, mean systemic exposure to prolonged-release tacrolimus over a 24-hour period (AUC_{0-24}) on Day 1 post-transplantation was approximately 50% lower than that for immediate-release tacrolimus at equivalent doses. Exposure for the two formulations was comparable on Day 14 and at Week 6, although slightly higher doses of prolonged-release tacrolimus were required to achieve parity of exposure. Other than trough levels, there were no PK data for the two formulations between Day 1 and Day 14. (7)

To gain a better understanding of the PKs of the two formulations of tacrolimus during the first 2 weeks post-transplant, a study was performed in a sub-population of patients included in a large, multicenter, phase III, comparative study of the efficacy and safety of immediate-release versus prolonged-release tacrolimus (NCT00189826) in liver transplant recipients. (2) In order to compensate for the lower systemic exposure observed in the phase II study of prolonged-released tacrolimus, (7) the first dose of the prolonged-release formulation in this study was doubled compared with that of immediate-release tacrolimus.

Patients and methods

Study design

This analysis was a 2-week PK sub-study of a multicenter, two-arm, parallel-group, 1:1 randomized, double-blind, double-dummy, phase III, comparative study (NCT00189826) of the efficacy and safety

This article is protected by copyright. All rights reserved.

Accepted Article

of immediate-release tacrolimus (Prograf™, Astellas Pharma Ltd, UK, hereafter termed immediate-release tacrolimus), versus prolonged-release tacrolimus (Advagraf™, Astellas Pharma Europe BV, Netherlands, hereafter termed prolonged-release tacrolimus) in patients undergoing *de novo* liver transplantation. Data from the original 11-03 study have been published previously. (2) This sub-study was conducted in 11 transplant centers from the original clinical study.

The study was conducted in accordance with the Declaration of Helsinki. The Independent Ethics Committee and/or review boards from each study center granted approval for the study prior to implementation. Written informed consent to participate in the PK part of the study was obtained from each patient prior to enrollment into the study.

Patients

The study population for the phase III study has been described in detail elsewhere. (2) Briefly, male and female patients (aged ≥18 years) receiving a primary liver, split liver or whole liver graft, who had received the first dose of tacrolimus within 12 hours (but not later than 24 hours depending on the time of surgery) of skin closure, and who agreed to participate in this PK sub-study were included. The main exclusion criteria for the PK sub-study were: first dose of tacrolimus after transplantation administered in the evening; omeprazole or esomeprazole within 2 days before enrollment and during the PK sub-study; certain concomitant medications within 28 days before enrollment and during the PK sub-study (antifungal agents [ketoconazole, fluconazole, itraconazole, clotrimazole, voriconazole], antibiotics [erythromycin, clarithromycin, josamycin], danazol, ethinyl estradiol, calcium antagonists [except nifedipine and amlodipine], nefazodone, phenobarbital, phenytoin, rifampicin and St John's Wort). Patients were also excluded if they were receiving carbamazepine, or received a multi-visceral transplant and had human immunodeficiency virus/acquired immune deficiency syndrome.

Study treatment

During this PK sub-study, patients were randomized to receive prolonged-release tacrolimus and placebo matching immediate-release tacrolimus in the morning, and immediate-release tacrolimus placebo in the evening, or immediate-release tacrolimus in the morning and evening, and placebo matching prolonged-release tacrolimus in the morning. All treatments were taken with fluid on an empty stomach, or ≥1 hour before or 2–3 hours after food. (2)

The first oral total daily dose of prolonged-release tacrolimus was 0.2mg/kg (once-daily, morning dosing). The initial dose of immediate-release tacrolimus was 0.1mg/kg/day (0.05mg/kg twice daily, morning and evening dosing). Patients unable to swallow a capsule at the time of their first oral dose received their first tacrolimus dose by nasogastric tube. Subsequent doses could be adjusted by the investigator on an individual patient basis according to clinical signs, with whole-blood trough levels (determined at each center), recommended to be maintained within the target whole-blood tacrolimus trough level range of 10–20ng/mL for the first 28 days. (2)

Pharmacokinetics profiles and assay

This article is protected by copyright. All rights reserved.

Accepted Article

Whole-blood samples were collected to provide four blood concentration–time profiles on Days 1, 3, 7 and 14 (±3 days for the Day 14 timepoint only) post-transplantation. The Day 14 profile was collected under steady−state conditions (the tacrolimus dose had not been modified during the previous 3 days and no therapy for acute rejection had been administered). Blood samples were taken prior to the morning dose (time 0) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 12.5, 13, 14, 15, 16, 18, 20, and 24 hours. The 0 and 12 hour samples were no earlier than 5 minutes prior to dosing. At each timepoint, whole-blood samples (2mL aliquots) were drawn into ethylene diamine tetraacetic acid tubes/vacutainers; samples were frozen at –20ºC within 1 hour of collection until shipment.

Tacrolimus concentrations were determined using high-performance liquid chromatography with tandem-mass spectrometric detection in compliance with the principles of good laboratory practice. Assays were performed by Farmovs Parexel (proprietary) Ltd, South Africa, using validated high-performance liquid chromatography tandem-mass spectroscopy assay methods (lower limit of quantification 0.1ng/mL).

Endpoints

The primary endpoint was the comparison of AUC from 0 to 24 hours ($AUC_{0–24}$) of tacrolimus. Systemic exposure was also evaluated by using dose-normalized $AUC_{0–24}$ (dose-normalized to 0.1mg/kg). Secondary endpoints were the determination of maximum observed concentration (C_{max}), time of C_{max} (T_{max}) and concentration at 24 hours (C_{24}) after the morning tacrolimus dose. Concentration at 12 hours (C_{12}) after the morning dose of immediate-release tacrolimus and AUC from 0 to 12 hours ($AUC_{0–12}$) was also evaluated. No separate analysis of safety or efficacy was performed for the PK sub-set.

Statistical analyses and sample size calculation

Patients in the PK sub-study were classified into two sets. The full PK set (FPKS) consisted of all patients enrolled into the PK sub-study who signed a PK informed consent form and for whom there were at least some PK assessments. The PK analysis set (PKAS) consisted of all patients from the FPKS for whom all four PK profiles were complete with no missing samples, and for whom there was no major PK-related protocol violation. Only patients in the PKAS were included in the analysis of PK parameters. A minimum of 12 patients from each treatment group was considered sufficient for the PKAS to characterize the PK parameters.

The PK parameters for prolonged-release and immediate-release tacrolimus ($AUC_{0–24}$, C_{max} and C_{24}) were compared over the complete 24 hour concentration–time profiles, using standard non-compartmental analysis with the computer program WinNonlin®-Professional version 4.0.1 (Pharsight Corporation, California, USA); a two-sided 90% confidence interval (CI) for the ratio of means was estimated, with an acceptance interval for presumption of similarity being 80%–125%. AUC was calculated using the linear trapezoidal rule. C_{max}, T_{max}, C_{12} and C_{24} were obtained directly from the concentration–time profiles. In case of duplicated C_{max} values, T_{max} was assigned to the first occurrence of C_{max}. The correlation between C_{24} and $AUC_{0–24}$ was assessed for both formulations. Descriptive statistics (mean, standard deviation (SD), median, minimum and maximum) were calculated for continuous variables; frequency distribution and percentages were summarized for categorical variables.

This article is protected by copyright. All rights reserved.

Accepted Article

Results

Study population

A total of 35 patients from the phase III study were included in the FPKS; 10 of these patients were excluded from the PKAS for the following reasons: receiving prohibited medication (n=7), questionable dosing (n=2), and pharmacologically implausible blood levels (n=1). Of the 25 patients included in the PKAS, 13 received prolonged-release tacrolimus (mean age 53.4 years) and 12 received immediate-release tacrolimus (mean age 55.7 years). Patient baseline demographics were similar between treatment arms (**Table 1**). The majority of patients were male, and more men received prolonged-release tacrolimus (11, 84.6%) compared with the immediate-release formulation (8, 66.7%). All patients in the PKAS were of Caucasian ethnicity.

Dosage

The first dose of tacrolimus was administered via the nasogastric route in 10 patients in both the prolonged-release tacrolimus and immediate-release tacrolimus arms (76.9% and 83.3% of patients, respectively). As per the protocol, the mean daily doses on Day 1 for prolonged-release tacrolimus and immediate-release tacrolimus were 0.191mg/kg and 0.094mg/kg, respectively. Following dose adjustment in both arms, the corresponding doses were 0.164mg/kg and 0.087mg/kg (Day 3); 0.158mg/kg and 0.150mg/kg (Day 7); and 0.223mg/kg and 0.176mg/kg (Day 14), respectively.

Pharmacokinetic parameters

Reflecting the characteristics of the formulation, median T_{max} for prolonged-release tacrolimus (3–4 hours) occurred later than for immediate-release tacrolimus (1–2 hours) (**Figure 1**). Mean whole-blood tacrolimus trough levels (C_{24}) for prolonged-release tacrolimus were higher than for immediate-release tacrolimus (**Table 2**). Mean AUC_{0-24} was higher with prolonged-release tacrolimus versus the immediate-release formulation. The AUC_{0-24} ratio of means for prolonged-release tacrolimus versus immediate-release tacrolimus (90% CI) on Days 1, 3, 7 and 14 was 147.9% (96.2–199.6), 142.2% (95.6–188.8), 143.9% (109.5–178.4), and 124.8% (100.19–149.40), respectively. In the dose-normalized analysis, exposure per unit dose was lower with prolonged-release tacrolimus compared with immediate-release tacrolimus on Days 1, 3 and 14, but similar on Day 7 (**Figure 2**). The correlation between AUC_{0-24} and C_{24} is shown in **Figure 3**. There was good correlation for both prolonged-release and immediate-release tacrolimus (r=0.96 and r=0.86, respectively), and the slope of the line of best fit was similar for both formulations.

Discussion

It has previously been shown in liver transplant recipients that systemic exposure to tacrolimus was approximately 50% lower with prolonged-release tacrolimus compared with immediate-release tacrolimus when administered at equivalent doses. (7) Hence, the present PK study was conducted

This article is protected by copyright. All rights reserved.

Accepted Article

to assess whether using a higher starting dose for prolonged-release tacrolimus (0.2mg/kg/day versus 0.1mg/kg/day of immediate-release tacrolimus) would compensate for the lower exposure seen with the prolonged-release formulation on Day 1. We also aimed to explore the PKs of tacrolimus during the first 2 weeks post-transplant.

Data from the original 11-03 study showed that initiating therapy at 0.2mg/kg/day for prolonged-release tacrolimus compared with 0.1mg/kg/day for immediate-release tacrolimus overcompensated for the lower exposure seen on Day 1 post-transplant in an earlier study (mean (SD) tacrolimus trough levels on Day 7 were 12.0 (5.9) ng/ml versus 9.5 (4.5) ng/mL, respectively). (2) In this PK study, analysis of systemic exposure using $AUC_{0–24}$ dose-normalized to 0.1mg/kg on Day 1 showed lower exposure with prolonged-release tacrolimus compared with immediate-release tacrolimus. Therefore, initiating prolonged-release tacrolimus therapy at 0.1mg/kg/day or 0.2mg/kg/day on Day 1 could result in underexposure and overexposure, respectively. These data suggest that a starting dose of approximately 0.15mg/kg/day could be appropriate for prolonged-release tacrolimus in the *de novo* liver transplant population, although additional research is required to confirm this. Interestingly, the DIAMOND study assessed whether immunosuppression regimens with delayed introduction of prolonged-release tacrolimus until Day 5, or a reduced dose of 0.15–0.175mg/kg/day prolonged-release tacrolimus given immediately post-transplant improved renal function in liver transplant patients versus 0.2mg/kg/day prolonged-release tacrolimus given immediately post-transplant. (9) Initial dosing with prolonged-release tacrolimus 0.15–0.175mg/kg/day enabled patients to readily achieve target trough levels of 5–15ng/mL, which were lower than those achieved with the initial 0.2mg/kg/day dose. (9) However, it is important to consider that the number of patients in this pharmacokinetics study were far fewer than those in the Phase II study. (7) It is not yet understood why there are differences in the extent of absorption between the two tacrolimus formulations during the immediate post-transplant period, and further research to evaluate initial doses in the range of 0.15 to 0.2mg/kg/day for prolonged-release tacrolimus is clearly warranted.

The present study supports earlier findings in patients with liver transplants that the relationship between C_{24} and $AUC_{0–24}$ is similar and highly correlated for the two formulations of tacrolimus. (7, 10) Hence, the same whole-blood trough level monitoring concept can be used for both the immediate-release and prolonged-release formulations.

There were a number of limitations to this sub-study. Although a total of 12 patients per treatment arm was deemed sufficient for this analysis, the study population was smaller than previous studies of the PKs of tacrolimus. It has previously been shown that tacrolimus bioavailability was significantly higher after partial liver transplant compared with full transplants, and the volume of the split liver should be used to calculate the more appropriate dose of tacrolimus. (11) However, this study did not examine the effects of split liver grafts on the PKs of tacrolimus. Furthermore, most patients received their first dose of tacrolimus via the nasogastric route rather than as an oral intact capsule, which may impact tacrolimus absorption and, therefore, the pharmacokinetic profile of tacrolimus on Day 1.

In conclusion, although a higher starting dose of prolonged-release tacrolimus is required to achieve similar systemic exposure to immediate-release tacrolimus, the data from this study suggest an increment in the range of 50−100% is adequate to achieve comparable exposure but this requires

This article is protected by copyright. All rights reserved.

Accepted Article

further evaluation in a clinical study. This study confirmed that the same therapeutic drug monitoring system that has been established for immediate-release tacrolimus can be used for prolonged-release tacrolimus.

Acknowledgments

The authors would like to thank Nina Kennard and James Wallis from iS LifeScience for their editorial support throughout the development and finalisation of this manuscript. ACUMED supported the authors with early draft preparation of the manuscript, with medical writing services provided by Paul Barlass (previously of ACUMED) and Tamsin Williamson (freelance medical writer). Editorial support and medical writing services were funded by Astellas Pharma, Inc.

Funding sources: This study was funded by Astellas Pharma, Inc.

Disclosures: The authors of this manuscript have the following disclosures: Bo-Göran Ericzon has received honoraria and consultancy fees from Astellas, Pfizer and Novartis, and participated in clinical trials sponsored by Novartis and Astellas; Pavel Trunečka has received honoraria and consultancy fees from Astellas and Pfizer, received payment for development of educational presentations for advisory boards from Astellas, and received payment for participating in clinical trials sponsored by Astellas and Novartis; Lutz Fischer has received grants for study support from Astellas and Novartis; Michele Colledan has received honoraria from Novartis; Andrés Valdivieso has received consultancy fees from Astellas, and participated in clinical trials sponsored by Astellas and Novartis; John O'Grady has received speaker honoraria from Astellas and Novartis; Nasrullah Undre is employed by Astellas; Evaristo Varo, Bruno Gridelli and James Dickinson have no disclosures in regards to this manuscript.

Author contribution: Bo-Göran Ericzon was involved in performing the study, data collection and data analysis; Evaristo Varo was involved in performing the study; Pavel Trunečka was involved in performing the study and data collection; Lutz Fischer was involved in performing the study, data collection and data interpretation; Michele Colledan was involved in data collection; Bruno Gridelli was involved in performing the study; Andrés Valdivieso was involved in performing the study and data collection; John O'Grady was involved in patient recruitment; James Dickinson was involved in data collection and data analysis; Nasrullah Undre was involved in study design, data collection, data analysis, data interpretation and oversaw study performance. All authors were involved in critically revising the manuscript for important intellectual content and final approval of the version to be published.

References

1. Krämer BK, Charpentier B, Backman L, et al. Tacrolimus once daily (ADVAGRAF) versus twice daily (PROGRAF) in *de novo* renal transplantation: a randomized phase III study. Am J Transplant 2010;10:2632-2643.

2. Trunečka P, Boillot O, Seehofer D, et al. Once-daily prolonged-release tacrolimus (ADVAGRAF)

This article is protected by copyright. All rights reserved.

Accepted Article

versus twice-daily tacrolimus (PROGRAF) in liver transplantation. Am J Transplant 2010;10:2313-2323.

3. Scott LJ, McKeage K, Keam SJ, et al. Tacrolimus: a further update of its use in the management of organ transplantation. Drugs 2003;63:1247-1297.

4. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. Clin Pharmacokinet 2004;43:623-653.

5. Wallemacq P, Armstrong VW, Brunet M, et al. Opportunities to optimize tacrolimus therapy in solid organ transplantation: report of the European consensus conference. Ther Drug Monit 2009;31:139-152.

6. Provenzani A, Santeusanio A, Mathis E, et al. Pharmacogenetic considerations for optimizing tacrolimus dosing in liver and kidney transplant patients. World J Gastroenterol 2013;19:9156-9173.

7. Fischer L, Trunecka P, Gridelli B, et al. Pharmacokinetics for once- versus twice-daily tacrolimus formulations in de novo liver transplantation: a randomized, open-label trial. Liver Transpl 2011;17:167-177.

8. Wlodarczyk Z, Squifflet JP, Ostrowski M, et al. Pharmacokinetics for once- versus twice-daily tacrolimus formulations in *de novo* kidney transplantation: a randomized, open-label trial. Am J Transplant 2009;9:2505-2513.

9. Trunečka P, Klempnauer J, Bechstein WO, et al. Renal function in *de novo* liver transplant recipients receiving different prolonged-release tacrolimus regimens–the DIAMOND study. Am J Transplant 2015;15:1843-1854.

10. 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.

11. Wilberg J, Küpper B, Thrum K, et al. Oral tacrolimus bioavailability is increased after right split liver transplantation. Transplant Proc 2007;39:3237-3238.

FIGURE LEGENDS

Figure 1: Median T_{max} of prolonged-release and immediate-release tacrolimus.

T_{max}, time of maximum observed concentration; T_{max} is presented as median (range).

This article is protected by copyright. All rights reserved.

Accepted Article

Figure 2: Mean AUC_{0-24} of prolonged-release and immediate-release tacrolimus, normalized to a dose of 0.1mg/kg/day.

AUC_{0-24}, area under the curve from 0 to 24 hours; CI, confidence interval; data presented for ratio of dose-normalized mean AUC_{0-24} (90% CI) for prolonged-release tacrolimus versus immediate-release tacrolimus post-transplantation.

Figure 3: Correlation between AUC_{0-24} and C_{24} for prolonged-release and immediate-release tacrolimus.

Line of best fit: prolonged-release tacrolimus: y=27.053x + 63.002; immediate-release tacrolimus: y=22.811x + 61.931; AUC_{0-24}, area under the curve from 0 to 24 hours; C_{24}, concentration at 24 hours.

Table 1: Patient baseline demographics.

Parameter	**Prolonged-release tacrolimus (N=13)**	**Immediate-release tacrolimus (N=12)**
Mean (SD) age, years	53.4 (9.0)	55.7 (7.1)
Gender, n (%)		
Male	11 (84.6)	8 (66.7)
Female	2 (15.4)	4 (33.3)
Caucasian ethnicity, n (%)	13 (100.0)	12 (100.0)
Mean (SD) height, cm	173.4 (10.9)	170.7 (10.5)
Mean (SD) weight, kg	81.4 (12.8)	74.6 (12.7)

SD, standard deviation

This article is protected by copyright. All rights reserved.

Accepted Article

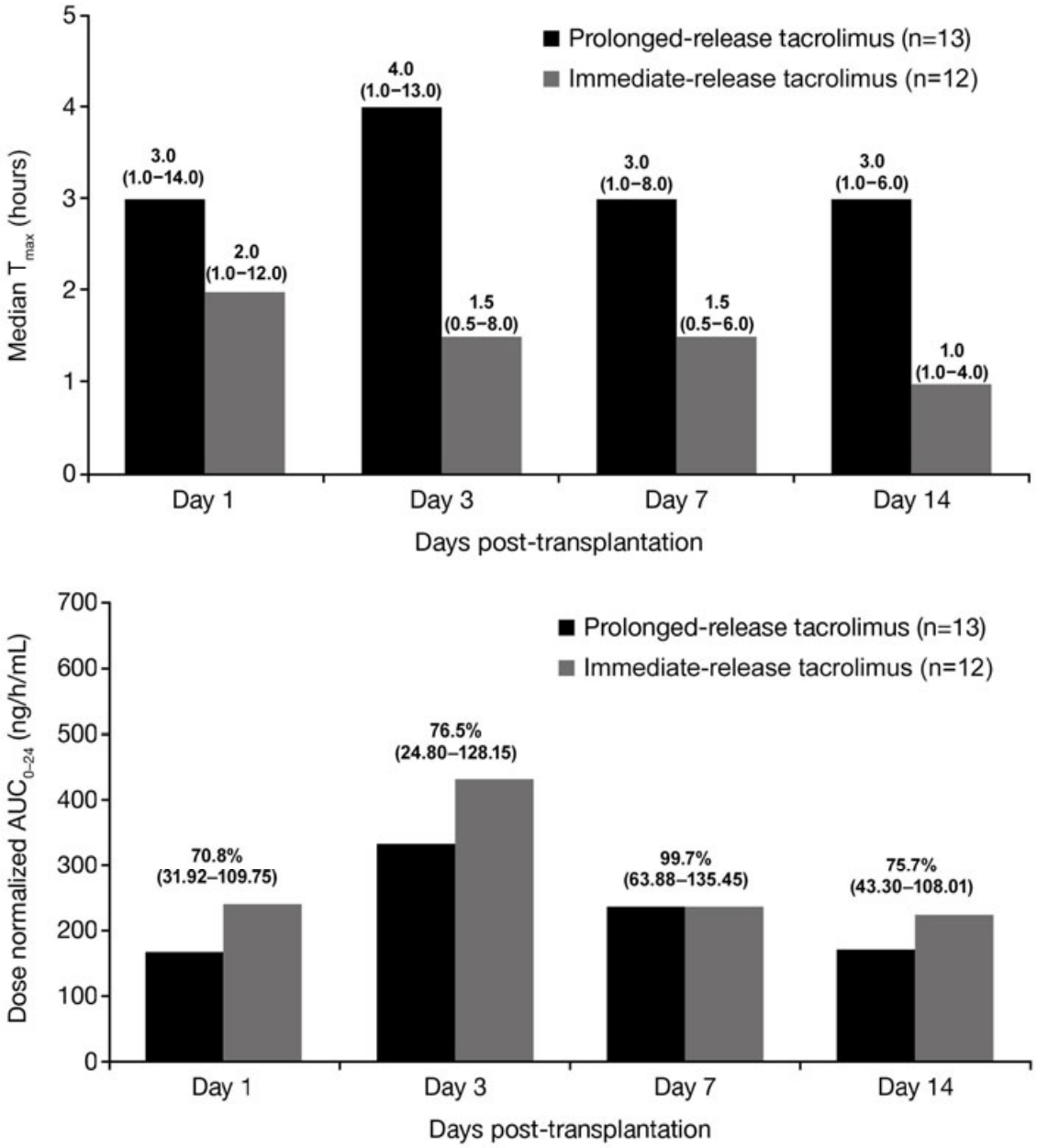
Table 2: Summary of pharmacokinetic parameters.

PK parameters	Mean (SD)		Ratio (%) prolonged-release : immediate-release (90% CI)
	Prolonged-release tacrolimus (N=13)	Immediate-release tacrolimus (N=12)	
Day 1			
C_{max} (ng/mL)	21.29 (10.53)	12.21 (8.70)	174.3 (119.82 to 228.76)
C_{12} (ng/mL)	NA	4.87 (4.91)	NA
C_{24} (ng/mL)	9.97 (6.70)	9.18 (7.26)	108.6 (56.52 to 160.71)
$AUC_{0–12}$ (ng/h/mL)	NA	82.87 (62.63)	NA
$AUC_{0–24}$ (ng/h/mL)	320.44 (186.93)	216.63 (132.51)	147.9 (96.24 to 199.60)
Day 3			
C_{max} (ng/mL)	27.82 (11.72)	19.47 (11.69)	142.9 (101.68 to 184.21)
C_{12} (ng/mL)	NA	10.06 (7.69)	NA
C_{24} (ng/mL)	14.06 (7.11)	10.41 (7.61)	135.1 (86.57 to 183.59)
$AUC_{0–12}$ (ng/h/mL)	NA	161.14 (109.77)	NA
$AUC_{0–24}$ (ng/h/mL)	452.06 (213.19)	317.90 (218.63)	142.2 (95.63 to 188.78)
Day 7			
C_{max} (ng/mL)	23.20 (9.83)	19.94 (12.18)	116.3 (78.43 to 154.25)
C_{12} (ng/mL)	NA	7.33 (3.21)	NA
C_{24} (ng/mL)	11.06 (5.63)	7.43 (2.63)	148.9 (107.73 to 190.01)
$AUC_{0–12}$ (ng/h/mL)	NA	134.95 (60.28)	NA
$AUC_{0–24}$ (ng/h/mL)	358.60 (146.62)	249.12 (96.40)	143.9 (109.48 to 178.41)
Day 14			
C_{max} (ng/mL)	24.85 (7.24)	29.34 (22.36)	84.7 (46.35 to 123.04)
C_{12} (ng/mL)	NA	9.02 (3.16)	NA
C_{24} (ng/mL)	10.47 (4.14)	8.89 (2.24)	117.8 (91.77 to 143.75)
$AUC_{0–12}$ (ng/h/mL)	NA	155.54 (60.20)	NA
$AUC_{0–24}$ (ng/h/mL)	353.42 (109.42)	283.19 (92.21)	124.8 (100.19 to 149.40)

$AUC_{0–12}$, area under the curve from 0 to 12 hours; $AUC_{0–24}$, area under the curve from 0 to 24 hours; C_{12}, concentration at 12 hours; C_{24}, concentration at 24 hours; CI, confidence interval; C_{max}, maximum observed concentration; NA, not analysed; SD, standard deviation.

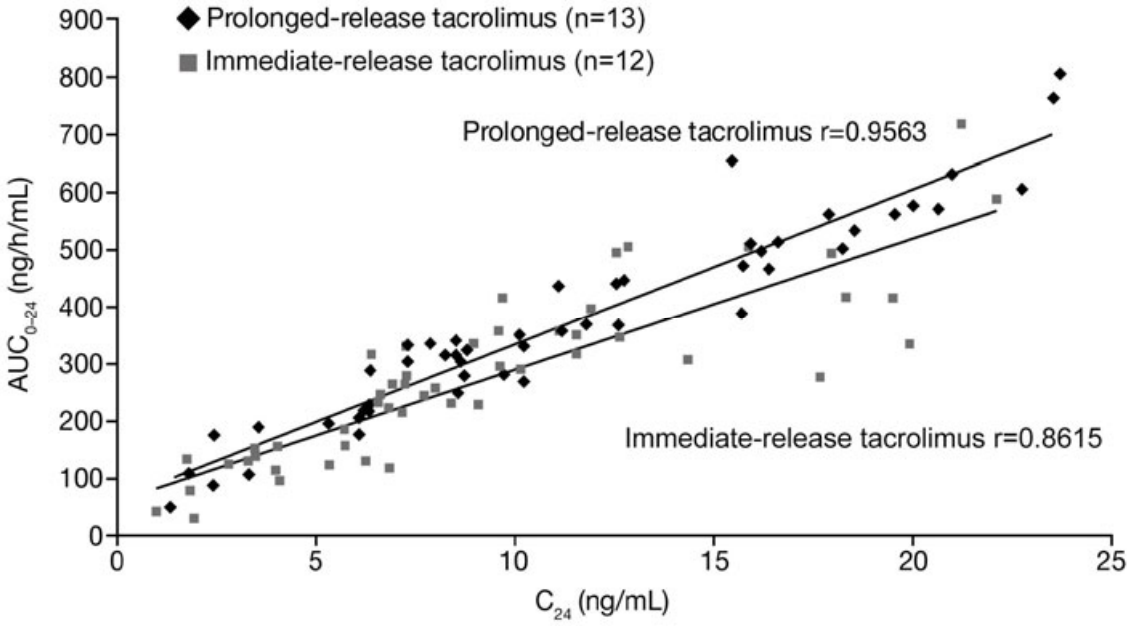
This article is protected by copyright. All rights reserved.

Accepted Article



This article is protected by copyright. All rights reserved.

Accepted Article



This article is protected by copyright. All rights reserved.