Efficacy of Prolonged- and Immediate-release Tacrolimus in Kidney Transplantation: A Pooled Analysis of Two Large, Randomized, Controlled Trials

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ABSTRACT

Background. Two large, prospective studies (12-03; OSAKA) compared the efficacy and tolerability of prolonged-release versus immediate-release tacrolimus in kidney transplant patients also receiving mycophenolate mofetil and low-dose corticosteroids (without induction therapy).

Methods. Data were combined into one database to compare results over 24 weeks using 3 alternative endpoints: biopsy-confirmed acute rejection (BCAR); the Food and Drug Administration composite endpoint (graft loss, BCAR, and loss to follow-up), and the European Medicines Agency composite endpoint (graft loss, BCAR, and graft dysfunction). The 95% confidence intervals were calculated (10% noninferiority margin).

Results. Overall, 633 patients received prolonged-release tacrolimus (12-03, n = 331; OSAKA, n = 302) and 645 received immediate-release tacrolimus (n = 336; n = 309). Baseline characteristics were comparable. Proportionately more patients receiving prolonged-release tacrolimus had trough levels of 5–15 ng/mL on day 1 (60.8%) and 2 (56.6%) versus immediate-release tacrolimus (42.5% and 43.9%, respectively, both $P < .001$). Efficacy of prolonged-release and immediate-release tacrolimus were similar as assessed by BCAR (13.9% vs 14.1%, respectively), European Medicines Agency composite endpoint (40.3% vs 38.3%) and US Food and Drug Administration composite endpoint (21.5% vs 19.8%).

Bernhard K. Krämer, Laetitia Albano, and Bernhard Banas contributed equally to this work.

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Conclusions. Novel efficacy endpoints as required by the European Medicines Agency and US Food and Drug Administration demonstrate noninferiority of prolonged-release versus immediate-release tacrolimus. Significantly more patients treated with prolonged-release tacrolimus versus immediate-release tacrolimus achieved trough levels of 5 to 15 ng/mL early after transplantation. ClinicalTrials.gov NCT00189839; NCT00717470.

DESPITE improvements in short-term graft survival after kidney transplantation, long-term graft and patient outcomes have not shown similar improvements [1,2]. Improving long-term outcomes therefore remains a major challenge facing clinicians today [3].

Ensuring appropriate exposure to immunosuppressive therapy posttransplantation plays a crucial role in improving long-term outcomes, particularly in the immediate posttransplant period, as increased intrapatient variability in exposure is associated with poorer outcomes [4–10]. The once-daily, prolonged-release formulation of tacrolimus was developed to provide more consistent exposure, reduce intrapatient variability, and improve adherence [11–13]. Data for this formulation have demonstrated comparable steady-state exposure to the twice-daily, immediate-release formulation in de novo kidney transplant recipients [14,15], and showed significantly lower intrapatient variability in tacrolimus trough concentrations in stable kidney transplant recipients converted from immediate-release tacrolimus [11,12,16]. However, variability in exposure for prolonged-release versus immediate-release tacrolimus has not previously been compared in de novo kidney transplant recipients. Although achieving potential long-term benefits is the ultimate goal for prolonged-release tacrolimus, it is first necessary to demonstrate that the short-term efficacy of the prolonged-release formulation is comparable with that of the immediate-release tacrolimus formulation.

Two large prospective studies comparing prolonged-release tacrolimus with immediate-release tacrolimus have been performed in de novo kidney transplantation. The first (Study 12-03) was a randomized, double-blind, placebo-controlled study over 24 weeks followed by an open-label extension of 12 months [17]; the second trial, OSAKA (Optimising immunoSuppression After Kidney transplantation with Advagraf), was a 24-week, open-label, parallel-arm study [18]. Both studies assessed the noninferiority of prolonged-release tacrolimus and immediate-release tacrolimus when used in combination with mycophenolate mofetil (MMF) and low-dose corticosteroids. The primary endpoints differed between the 2 trials. In Study 12-03, the primary endpoint was the incidence of biopsy-confirmed acute rejection (BCAR) based on local diagnosis over 24 weeks of treatment [17]. The OSAKA study used a composite endpoint of graft loss, BCAR, and graft dysfunction, estimated using glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease-4 formula of <40 mL/min/1.73 m^2 at the end-of-study visit, based on the European Medicines Agency (EMA) guidelines [18,19]. Using a measure of graft function, as recommended by the EMA, provides a comprehensive assessment of treatment efficacy [20], but this endpoint has not been used routinely in clinical trials to date. It also differs from the advice provided by the US Food and Drug Administration (FDA), which recommends a composite endpoint comprising graft loss, BCAR, and loss to follow-up.

In this analysis, we used 24-week follow-up data from the 2 tacrolimus studies (12-03 and OSAKA) combined into a single database to create a large patient population to evaluate the effects of prolonged-release tacrolimus and immediate-release tacrolimus formulations using different efficacy parameters (including the EMA and FDA composite endpoints). This study is the first to compare variability in exposure with prolonged-release versus immediate-release tacrolimus in de novo kidney transplant recipients. Early tacrolimus exposure, outcomes by donor type, and tolerability were also evaluated for the 2 tacrolimus formulations.

MATERIALS AND METHODS

This analysis used data from the 12-03 (NCT00189839) and OSAKA studies (NCT00717470), combined into a single database, to compare outcomes with prolonged-release tacrolimus (Advagraf, Astellas Pharma Europe BV, Leiden, the Netherlands, hereafter termed prolonged-release tacrolimus) and immediate-release tacrolimus (Prograf, Astellas Pharma Ltd, Chertsey, UK, hereafter termed immediate-release tacrolimus) in de novo kidney transplantation.

Both studies enrolled adult patients with end-stage renal disease receiving a kidney transplant from deceased or living donors with compatible ABO blood types. Study 12-03 compared prolonged-release tacrolimus and immediate-release tacrolimus at an initial postoperative dose of 0.2 mg/kg per day, in combination with low-dose MMF and corticosteroids, in a randomized, double-blind, placebo-controlled trial [17]. OSAKA compared 4 tacrolimus-based arms in a randomized, open-label study; only the patients who received immediate-release tacrolimus or prolonged-release tacrolimus at an initial dose of 0.2 mg/kg per day, in combination with low-dose MMF and corticosteroids (arms 1 and 2), were included in this analysis [18]. Patients in the other arms of the OSAKA study were excluded because they received prolonged-release tacrolimus either at a higher starting dose (0.3 mg/kg per day) or in combination with basiliximab in a steroid-avoidance regimen.

Both studies were conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and the International Conference on Harmonisation guidelines [21–23]. Both studies were approved by the Independent Ethics Committee or Institutional Review Board at each study site. Written informed consent was obtained from all patients before enrollment.

Procedures

In both studies, patients received a preoperative oral tacrolimus dose of 0.1 mg/kg, administered as prolonged-release tacrolimus or immediate-release tacrolimus. After transplantation (day 0), tacrolimus was initiated at 0.2 mg/kg per day for both formulations; doses were then adjusted to maintain recommended tacrolimus whole blood trough levels: 10 to 15 ng/mL (days 1–28) and 5 to 15 ng/mL (days 29–168) for Study 12-03; and 10 to 15 ng/mL (days 1–14), 5 to 12 ng/mL (days 15–42), and 5 to 10 ng/mL (days 43–168) for OSAKA. Immediate-release tacrolimus was taken in the morning and evening, whereas prolonged-release tacrolimus was taken in the morning only. Patients in Study 12-03 also received matching placebo for prolonged-release tacrolimus or immediate-release tacrolimus, as appropriate, to maintain study blinding.

MMF was administered preoperatively (1 g), then at 1 g twice-daily for days 1-14, and at 500 mg twice-daily thereafter in both studies. No induction therapy was administered. Methylprednisolone (or the equivalent) was administered as an intravenous bolus dose of up to 1000 mg (Study 12-03) or up to 500 mg (OSAKA) perioperatively, and of 125 mg on day 1 (both studies). Oral prednisolone (or equivalent) was started at 20 mg/d on days 2 to 14 and tapered as follows in both studies: 15 mg/d (days 15–28), 10 mg/d (days 29–42), 5 mg/d (days 43–84), and 0–5 mg/d (thereafter).

Assessments

In both Study 12-03 and OSAKA, BCAR (based on local pathology following Banff 97 criteria) [24], renal function [25], graft and patient survival were evaluated at the end-of-study follow-up or last visit [17,18]. In Study 12-03, the primary endpoint was incidence of BCAR within 24 weeks after transplantation; renal function was determined using creatinine clearance (Cockcroft–Gault) and the eGFR was calculated using the Modification of Diet in Renal Disease-4 formula as a post hoc analysis [17]. In OSAKA, the primary efficacy variable was the incidence of efficacy failure (based on the EMA composite endpoint) [18], defined as incidence and time to first occurrence of graft loss (retransplantation, nephrectomy, death, or dialysis at study end or at time of discontinuation, unless superseded by follow-up information that indicated graft survival), BCAR, or graft dysfunction (defined as eGFR [Modification of Diet in Renal Disease-4] of <40 mL/min/1.73m^2) at day 168.

In this combined analysis, data collected up to the formal end-of-study visit or the follow-up visit were used to evaluate 3 different efficacy endpoints. These were (a) the single endpoint of BCAR, (b) the FDA composite endpoint of graft loss, BCAR, or loss to follow-up, and (c) the EMA composite endpoint. In addition, the mean tacrolimus dose and mean tacrolimus whole blood levels were assessed over the first 7 days posttransplantation and throughout the study at predefined time points. The intrapatient variability of tacrolimus exposure of both formulations was assessed over the 24-week study period. The incidence of delayed graft function was defined as dialysis for >1 day within the first 7 days post-transplantation. Tolerability profiles for both tacrolimus formulations were also assessed.

Statistical Analysis

Data from the full-analysis set (FAS) for each study (all randomized patients who had a transplant and received ≥ 1 dose of tacrolimus) were combined into a single database. The analyses for this study were performed using the FAS population to provide the most conservative analysis of the data. Noninferiority was demonstrated if the lower limit of the 95% confidence interval for the difference in efficacy failure rate was above -10% for the combined prolonged-release tacrolimus arm versus the immediate-release tacrolimus arm. Although this pooled analysis was retrospective, a noninferiority margin of 10% was deemed appropriate, because this margin was the narrower (and most difficult to meet) of the two noninferiority margins for the two studies. In OSAKA, the predefined noninferiority margin was 12.5%, whereas in Study 12-03 the margin was 10%. Tacrolimus dose and exposure were calculated using the FAS and compared using a t test. The intrapatient variability of tacrolimus exposure was expressed as the coefficient of variation for study completers (completer analysis). In addition, probabilities for event-free survival for the EMA and FDA composite endpoints (Kaplan–Meier method) were calculated and the homogeneity of both arms was assessed by the log-rank test. $P < .05$ was considered statistically significant. Laboratory parameters were compared using an unpaired t test.

RESULTS

Patient and Donor Characteristics

A total of 1278 patients, who received a starting dose of 0.2 mg/kg per day of tacrolimus, were included in the combined analysis database (FAS). Of these, 633 patients received prolonged-release tacrolimus (12-03, n = 331; OSAKA, n = 302) and 645 received immediate-release tacrolimus (12-03, n = 336; OSAKA, n = 309). In total, 1061 patients were study completers; 508 patients (80.3%) in the prolonged-release tacrolimus arm and 553 (85.7%) in the immediate-release tacrolimus arm. The reasons for study discontinuation are reported in Fig 1.

Demographics and baseline characteristics were generally well balanced between the treatment arms (Table 1). The majority of organs were from deceased donors (80.0% overall) and donors <60 years old (77.7%); more than one-half of donors were male (56.7%).

Tacrolimus Dosing and Exposure

The mean daily doses of tacrolimus were similar on day 1 but significantly higher throughout the study in the arm receiving prolonged-release tacrolimus versus immediate-release tacrolimus (Table 2). However, the mean $\pm$ standard deviation tacrolimus trough levels were generally significantly lower with prolonged-release tacrolimus versus immediate-release tacrolimus throughout the study (Table 2). The proportion of patients with tacrolimus trough levels of 5 to 15 ng/mL was higher with prolonged-release tacrolimus compared with immediate-release tacrolimus in the first 2 days post-transplantation ($P < .001$); however, this was comparable between arms by day 3 (Fig 2). The proportion of patients with tacrolimus blood trough levels of >20 ng/mL was significantly lower in patients treated with prolonged-release tacrolimus compared with immediate-release tacrolimus in the first 2 days post-transplantation (Fig 2). In the completer analysis, prolonged-release tacrolimus demonstrated significantly less intrapatient variability of exposure compared with immediate-release tacrolimus by day 168 (coefficient of variation, 0.372 vs

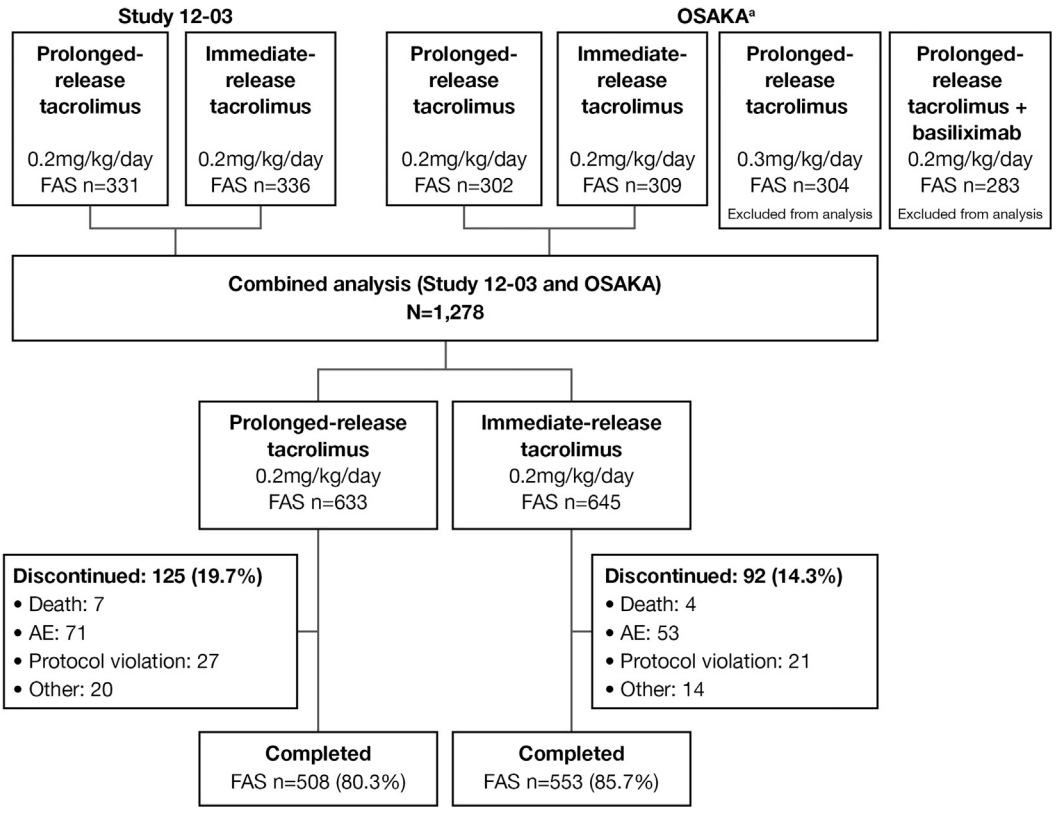

Fig 1. Patient disposition and reasons for discontinuation in the combined analysis. [a]Patients in the OSAKA study were randomized to four treatment arms. Only the prolonged-release tacrolimus and immediate-release tacrolimus arms with an initial dose of 0.2 mg/kg per day were included in the combined analysis. All analyses in this manuscript were performed on the FAS. AE, adverse event; FAS, full-analysis set; OSAKA, Optimising immunoSuppression After Kidney transplantation with Advagraf.

0.398; $P = .015$). When the data were dose-normalized by milligram, a similar pattern was observed (0.380 vs 0.411; $P = .016$); however, no difference was observed when data were dose-normalized by milligrams per day (0.384 vs 0.397; $P = .286$).

Concomitant Medication

As per the study design, no antibody induction therapy was administered in either treatment arm and all patients received low-dose MMF and corticosteroids throughout the study. The median doses of MMF and corticosteroids at day 168 were 1 g and 5 mg, respectively, in both arms. More than 90% of patients received maintenance steroids throughout the study.

Efficacy Endpoints

For all 3 endpoints, the difference in response with prolonged-release tacrolimus and immediate-release tacrolimus ranged from −0.2% to +2.0%, and 95% confidence intervals were between −4.0% and +7.4%. These data are within the 10% margin, which demonstrates noninferiority of prolonged-release tacrolimus versus immediate-release tacrolimus (Table 3).

The incidence of BCAR was similar with prolonged-release tacrolimus (13.9%) and immediate-release tacrolimus (14.1%). The FDA composite endpoint was reached by 21.5% versus 19.8% of patients, respectively (Fig 3A); with both treatments, BCAR was the main reason for efficacy failure, with very few patients lost to follow-up (Table 3). The EMA composite endpoint was reached by 40.3% of patients treated with prolonged-release tacrolimus and 38.3% of those receiving immediate-release tacrolimus (Fig 3B); with both treatments, graft dysfunction was the dominant reason for efficacy failure (Table 3). Renal function was similar for both treatment arms at day 168 (prolonged-release tacrolimus: 47.3 mL/min per 1.73 m^2; immediate-release tacrolimus: 49.5 mL/min per 1.73 m^2).

Stratification of the patients according to deceased or living organ donors showed no significant differences in efficacy between the 2 treatments. For patients receiving organs from deceased donors, the incidence of BCAR was 12.0% (61/510) for prolonged-release tacrolimus and 12.5% (64/512) for immediate-release tacrolimus, and the incidence of patients who achieved the EMA and FDA composite endpoints was 40.3% (255/633) and 21.5% (136/633), respectively, for prolonged-release tacrolimus and 38.3% (247/645) and 19.8% (128/645) for immediate-release

Table 1. Patient and Donor Demographics and Transplantation Information in the Combined Analysis (FAS)

	Prolonged-release Tacrolimus (n = 633)	Immediate-release Tacrolimus (n = 645)
Recipient		
Gender		
Male	410 (64.8)	426 (66.0)
Female	223 (35.2)	219 (34.0)
Mean age in years (SD)	47.6 (12.8)	48.1 (12.9)
<60	510 (80.6)	528 (81.9)
≥60	123 (19.4)	117 (18.1)
Race		
Caucasian	561 (88.6)	569 (88.2)
Black	28 (4.4)	26 (4.0)
Asian	9 (1.4)	9 (1.4)
Other	35 (5.5)	41 (6.4)
Transplant history		
First transplant	605 (95.6)	612 (94.9)
Retransplant	28 (4.4)	33 (5.1)
Donor		
Gender		
Male	354 (55.9)	370 (57.4)
Female	279 (44.1)	275 (42.6)
Mean age in years (SD)*	48.1 (14.7)	48.0 (14.7)
<60	488 (77.1)	505 (78.3)
≥60	138 (21.8)	132 (20.5)
Type		
Living	123 (19.4)	143 (20.6)
Deceased	510 (80.6)	512 (79.4)
HLA type mismatch, mean		
A	1.0	1.0
B	1.2	1.2
DR	0.9	0.8
PRA grade		
<50	624 (98.6)	640 (99.2)
50–100	6 (0.9)	3 (0.5)
Number of patients with missing data	3 (0.5)	2 (0.3)
Mean cold ischemia time† in minutes (SD)	960 (370)	937 (345)

Data are n (%) unless stated otherwise.
Abbreviations: FAS, full-analysis set; HLA, human leukocyte antigen; PRA, panel-reactive antibody; SD, standard deviation.
*The number of patients excluded because of missing data was 8 in the prolonged-release tacrolimus cohort and 7 in the immediate-release tacrolimus cohort.
†Data are for deceased donors only.

tacrolimus. For living donor transplants, the incidence of BCAR was 22.0% (27/123) and 18.9% (27/143) with prolonged-release tacrolimus and immediate-release tacrolimus, respectively. For the composite efficacy endpoints, the incidence was 35.8% (44/123; EMA) and 25.2% (31/123; FDA) of patients with prolonged-release tacrolimus, and 28.7% (41/143; EMA) and 21.0% (30/143; FDA) with immediate-release tacrolimus. The incidence of delayed graft function was similar for patients who received prolonged-release tacrolimus versus immediate-release tacrolimus (15.5% [98/633] vs 16.0% [103/645], respectively).

Tolerability Profile

Prolonged-release and immediate-release tacrolimus had similar adverse event profiles over the study period. The most common adverse events are presented in Table 4. The incidence of new-onset diabetes mellitus (World Health Organization/American Diabetes Association criteria) was low throughout the study (13.4% of patients with prolonged-release tacrolimus compared with 16.4% with immediate-release tacrolimus; $P = .157$). Ongoing antidiabetic medication and ongoing insulin medication were required by 11.9% and 6.9%, respectively, of patients treated with prolonged-release tacrolimus, and 13.1% and 7.9%, respectively, of those treated with immediate-release tacrolimus ($P = .587$ and $P = .570$, respectively). The mean ± standard deviation serum total cholesterol levels showed slight and similar increases over the study period with prolonged-release tacrolimus and immediate-release tacrolimus. The mean ± standard deviation triglyceride levels decreased over the 24-week period in both arms; the low-density lipoprotein/high-density lipoprotein cholesterol ratio was similar with both treatments.

DISCUSSION

This combined analysis showed that prolonged-release tacrolimus was noninferior to immediate-release tacrolimus at 24 weeks of follow-up in patients undergoing de novo kidney transplantation, regardless of the efficacy endpoint used. To our knowledge, this is the first study to compare the EMA- and the FDA-recommended composite efficacy endpoints in kidney transplantation on such a large scale. By including graft function within the EMA composite endpoint, these results can be considered a comprehensive evaluation of treatment efficacy. Results from this large population of patients demonstrated that the prolonged-release formulation provided a narrower range of tacrolimus exposure versus the immediate-release formulation over the initial 2 days after transplantation, with reduced variability maintained over the follow-up period. This study was the first to compare the variability in exposure for prolonged-release versus immediate-release tacrolimus in de novo kidney transplant recipients.

Tacrolimus is known to have a narrow therapeutic index, with both overexposure and underexposure having potentially important effects on clinical outcomes [26]. In this study, a higher proportion of patients achieved tacrolimus trough levels of 5 to 15 ng/mL with prolonged-release tacrolimus versus immediate-release tacrolimus during the first 2 days posttransplantation. A lower initial tacrolimus exposure reported with prolonged-release tacrolimus compared with the immediate-release formulation has also been reported previously [15,27,28]. After the same initial dose, adjustments to obtain target levels resulted in significantly lower mean doses of immediate-release versus prolonged-release tacrolimus (~ 17% from days 84-168). Significantly fewer patients receiving prolonged-release tacrolimus experienced potentially toxic overexposure

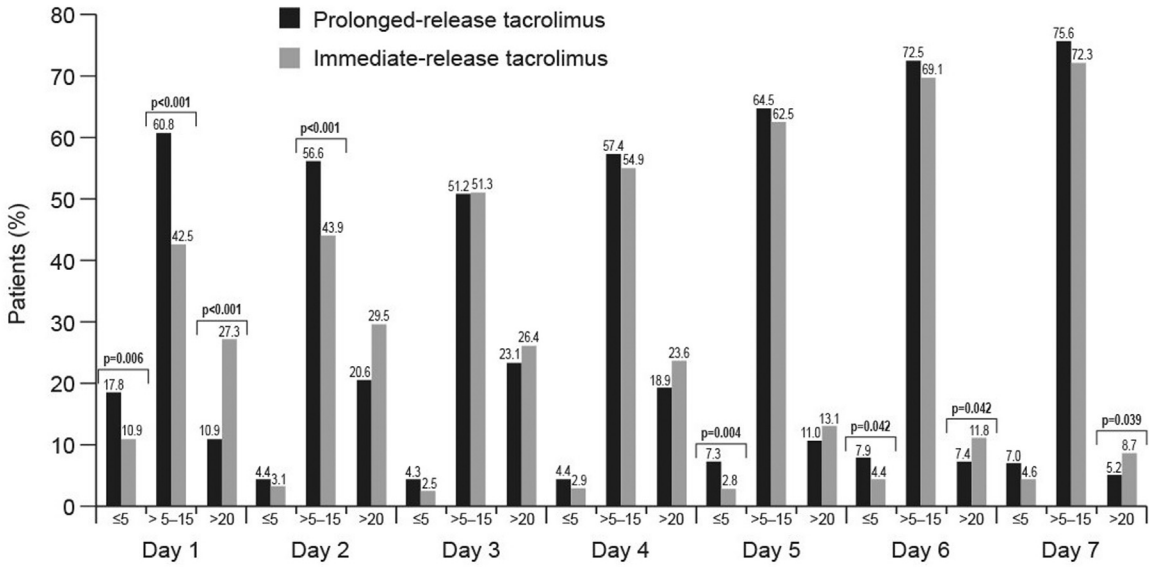

Fig 2. The proportion of patients achieving various tacrolimus trough level ranges in the early posttransplant period (days 1–7). Only significant *P* values are shown on the graph.

(trough levels of >20 ng/mL) in the early days after transplantation compared with those receiving immediate-release tacrolimus. It is important to note, however, that the initial tacrolimus dose (0.2 mg/kg per day) used in the studies included in this analysis was higher than the initial tacrolimus dose generally used in clinical practice today. A lower initial dose of prolonged-release tacrolimus may result in fewer patients reaching trough levels of >20 ng/mL.

Low variability of tacrolimus exposure may be important to prevent patients' trough levels falling outside the therapeutic range, because it is becoming increasingly well-documented that high intrapatient variability in tacrolimus exposure is associated with poorer outcomes after transplantation [5–8,29–31]. In a single-center study of 297 kidney transplant recipients, high intrapatient variability in tacrolimus clearance was a significant predictor of long-term graft failure [7]. Similarly, a study of more than 300 adult

Table 2. Mean Dose and Trough Levels of Prolonged-release Tacrolimus and Immediate-release Tacrolimus

	Prolonged-release Tacrolimus		Immediate-release Tacrolimus		
Day	n	(n = 633)	n	(n = 645)	*P**
Mean tacrolimus dose (mg/kg/day)					
1	630	0.148 (0.06)	643	0.147 (0.05)	.872
2	622	0.189 (0.04)	635	0.184 (0.05)	.013
3	613	0.183 (0.05)	630	0.171 (0.05)	<.001
4	606	0.174 (0.06)	627	0.163 (0.06)	.002
5	605	0.170 (0.07)	625	0.159 (0.07)	.009
6	605	0.169 (0.07)	622	0.159 (0.07)	.015
7	599	0.173 (0.08)	616	0.160 (0.07)	.007
84	489	0.137 (0.09)	560	0.114 (0.07)	<.001
168	506	0.116 (0.08)	535	0.096 (0.07)	<.001
Mean tacrolimus trough levels (ng/mL)					
1	393	10.9 (7.5)	395	15.2 (8.8)	<.001
2	431	14.9 (8.6)	458	16.8 (8.1)	<.001
3	445	15.5 (7.9)	478	16.0 (8.3)	.322
4	413	14.2 (6.9)	415	15.5 (7.8)	.014
5	400	12.8 (6.5)	435	13.9 (7.1)	.018
6	407	11.7 (5.9)	408	13.0 (6.4)	.005
7	459	11.5 (5.7)	458	12.6 (5.6)	.002
84	462	10.1 (3.5)	528	10.3 (3.6)	.610
168	478	9.1 (3.5)	495	8.8 (3.2)	.104

Data are mean (standard deviation).
**P* values were calculated using a *t* test.

Table 3. Efficacy Failure Rates Using Alternative Endpoints

	Prolonged-release Tacrolimus (n = 633)	Immediate-release Tacrolimus (n = 645)	Treatment Difference* % (95% CI)
EMA composite endpoint	255 (40.3)	247 (38.3)	2.0 (−3.4 to 7.4)
FDA composite endpoint	136 (21.5)	128 (19.8)	1.7 (−2.7 to 6.1)
BCAR	88 (13.9)	91 (14.1)	−0.2 (−4.0 to 3.6)
Graft dysfunction†	199 (31.4)	198 (30.7)	0.7 (−4.4 to 5.8)
Death‡	12 (1.9)	10 (1.6)	0.3 (−1.1 to 1.7)
Graft loss§	51 (8.1)	36 (5.6)	2.5 (−0.3 to 5.3)
Loss to follow-up	7 (1.1)	7 (1.1)	0.0 (−1.1 to 1.1)

Data are n (%) unless otherwise stated.
Abbreviations: BCAR, biopsy-confirmed acute rejection; CI, confidence interval; EMA, European Medicines Agency; FDA, Food and Drug Administration.
*Difference = prolonged-release tacrolimus − immediate-release tacrolimus.
†Graft dysfunction was defined as estimated glomerular filtration rate (Modification of Diet in Renal Disease-4 equation) <40 mL/min/1.73 m^2.
‡Includes all deaths throughout the study and up to 6 months of follow-up.
§Graft loss was defined as retransplantation, nephrectomy, death, or dialysis at end or at time of discontinuation, unless superseded by follow-up information that indicated graft survival.

kidney transplant recipients demonstrated that patients with high variability in tacrolimus trough levels had increased 1-year acute rejection and lower graft survival than those with lower variability [32]. Intrapatient variability in tacrolimus trough levels has also been found to predict graft loss and donor-specific antibody development in patients after kidney transplantation [8,31]. Interestingly, stable kidney transplant recipients who converted from immediate-release tacrolimus to prolonged-release tacrolimus showed significantly lower intrapatient variability in tacrolimus trough concentrations [11,12,16]. Data from our analysis demonstrated that intrapatient variability was significantly lower in the patients receiving prolonged-release tacrolimus versus immediate-release tacrolimus over 168 days post-transplantation. However, no difference was observed when the data were dose normalized by milligrams per day. It is also important to note that the difference in variability between the 2 tacrolimus formulations was only observed for the completer analysis and that variability in tacrolimus exposure in the early posttransplant period remains difficult to measure accurately owing to changes in tacrolimus dose.

Prolonged-release tacrolimus was noninferior to immediate-release tacrolimus for all 3 measures of efficacy used in this analysis, though the level of efficacy reported varied with the definition. In our analysis, efficacy failure rate was highest for the EMA versus FDA composite endpoint (the proportion of patients reaching the EMA composite endpoint was approximately double that of the FDA endpoint at day 168). Graft dysfunction was the main driver of failure for the EMA composite endpoint; however, the proportion of patients experiencing graft dysfunction was comparable between treatments (31.4% prolonged-release tacrolimus; 30.7% immediate-release tacrolimus),

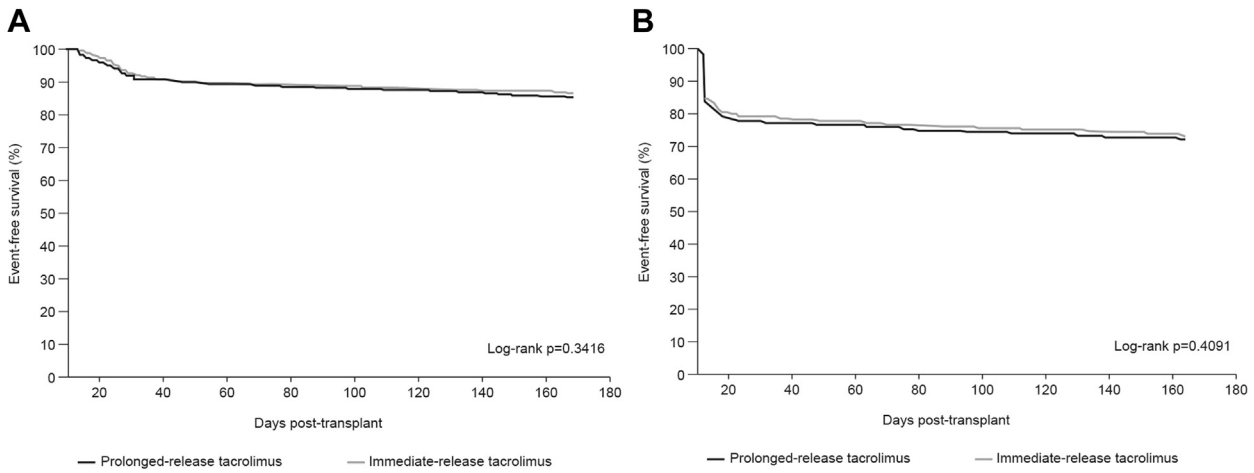

Fig 3. Kaplan–Meier estimates of time to efficacy failure for the **(A)** FDA and **(B)** EMA composite efficacy endpoints. For the EMA composite endpoint, graft dysfunction was defined as the estimated glomerular filtration rate (Modification of Diet in Renal Disease-4 equation) of <40 mL/min/1.73 m^2 (from the first day of reaching graft dysfunction until the end of the study). The EMA composite endpoint is graft loss, BCAR, and graft dysfunction. The FDA composite endpoint is graft loss, BCAR, and loss to follow-up. BCAR, biopsy-confirmed acute rejection; EMA, European Medicines Agency; FDA, Food and Drug Administration.

Table 4. Most Common Adverse Events and Laboratory Parameters

	Prolonged-release Tacrolimus (n = 633)	Immediate-release Tacrolimus (n = 645)	*P* value*
Most common adverse events			
Anemia	202 (31.9)	185 (28.7)	
Urinary tract infection	158 (25.0)	169 (26.2)	
Diarrhea	151 (23.9)	160 (24.8)	
Hyperglycemia	101 (16.0)	99 (15.3)	
Constipation	90 (14.2)	98 (15.2)	
New-onset diabetes mellitus†	74 (13.4)	95 (16.4)	
Hyperkalemia	84 (13.3)	100 (15.5)	
Peripheral edema	89 (14.1)	93 (14.4)	
Tremor	93 (14.7)	89 (13.8)	
Laboratory parameters			
Serum total cholesterol levels (mg/dL)			
Baseline	187.0 ± 49.9	182.7 ± 47.3	.174
Day 168	197.3 ± 45.3	193.9 ± 44.3	.276
Triglyceride levels (mg/dL)			
Baseline	193.6 ± 145.3	190.2 ± 130.0	.635
Day 168	178.8 ± 126.8	167.4 ± 94.1	.111
LDL/HDL cholesterol ratio			
Baseline	2.4 ± 1.0	2.3 ± 1.1	.138
Day 168	2.5 ± 1.0	2.5 ± 1.9	.831

Data are n (%) or mean ± standard deviation.
Abbreviation: LDL/HDL, low-density/high-density lipoprotein cholesterol.
**P* values were calculated using an unpaired *t* test.
†Excludes patients with diabetes at baseline.

and mean eGFR at day 168 was similar with both formulations. In a previous study in de novo kidney transplant patients, renal function parameters were also similar with prolonged-release tacrolimus versus immediate-release tacrolimus over 12 months of follow-up [33]. In a single-center observational study by Tinti et al [27], a significant improvement in eGFR over 6 months was reported after conversion from immediate-release tacrolimus to prolonged-release tacrolimus, whereas van Hooff et al [34] and Guirado et al [28] demonstrated stable renal function for up to 4 years in kidney transplant patients who had received de novo prolonged-release tacrolimus, and also in those who had been converted from the immediate-release to the prolonged-release formulation.

A previous randomized, controlled study in de novo kidney transplant recipients used the FDA composite endpoint and showed a similar efficacy failure rate with prolonged-release tacrolimus and immediate-release tacrolimus (14.0% vs 15.1%, respectively) at 1 year post-transplantation [33]. The lower rates compared with the current analysis probably reflect differences in the organ-donor population; approximately 50% of organs were from deceased donors compared with 80% in the current analysis. However, perhaps the most important factor was the use of antibody induction by Silva et al [33] versus no antibody induction in the current analysis.

Comparable tolerability profiles were observed with prolonged-release tacrolimus and immediate-release tacrolimus, consistent with findings from previous studies in kidney and liver transplant settings [33,35–37]. The incidence of new-onset diabetes mellitus was slightly, but not significantly, lower with prolonged-release versus immediate-release tacrolimus, with correspondingly lower antidiabetic medication and insulin use in the prolonged-release tacrolimus arm, although again this difference was not significant.

The characteristics of the populations involved in the 2 studies were largely similar, hence their suitability for combining into a single database. There were only minor differences in treatment regimens between the 0.2 mg/kg per day arms in Study 12-03 and OSAKA. Although the target whole blood trough ranges were narrower in OSAKA than Study 12-03, the same target trough range over the first 14 days post-transplantation (10–15 ng/mL) allowed early exposure to be compared between the 2 formulations in this combined analysis. However, there are limitations to this study, including those reported for the individual studies [17,18]. In Study 12-03, both treatment arms showed equally well-maintained renal function at 12 months; however, only 24-week data have been published for the OSAKA study. More patients in the immediate-release tacrolimus arm of the OSAKA study experienced BCAR than did those in the prolonged-release tacrolimus arm, whereas it was the opposite in Study 12-03. It is possible that these differences could be due to the optimization of the overall immunosuppressive regimen with prolonged-release tacrolimus over

the time between the two studies, because Study 12-03 was concluded a year and a half before enrollment into the OSAKA study.

CONCLUSIONS

This analysis from a combined database of two large, randomized trials enabled comparison of the treatments using three different efficacy measures (BCAR, and EMA and FDA composite endpoints) in kidney transplantation. Regardless of the measure used, prolonged-release tacrolimus was noninferior to immediate-release tacrolimus treatment in de novo kidney transplantation. The proportion of patients who achieved trough levels of 5 to 15 ng/mL was higher with prolonged-release tacrolimus compared with immediate-release tacrolimus early after transplantation, and tolerability profiles were comparable between the 2 formulations.

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