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Long-term Prolonged-release Tacrolimus-based Immunosuppression in De Novo Kidney Transplant Recipients: 5-Y Prospective Follow-up of Patients in the ADVANCE Study

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Background. Although prolonged-release tacrolimus (PR-T) is widely approved for posttransplantation immunosuppression in kidney recipients, large-scale studies are required to assess long-term outcomes. We present follow-up data from the Advagraf-based Immunosuppression Regimen Examining New Onset Diabetes Mellitus in Kidney Transplant Recipients (ADVANCE) trial, in which kidney transplant patients (KTPs) received corticosteroid minimization with PR-T. **Methods.** ADVANCE was a 24-wk, randomized, open-label, phase-4 study. De novo KTPs received PR-T with basiliximab and mycophenolate mofetil and were randomized to receive an intraoperative corticosteroid bolus plus tapered corticosteroids until day 10 (arm 1) or an intraoperative corticosteroid bolus (arm 2). In this 5-y, noninterventional follow-up, patients received maintenance immunosuppression according to standard practice. The primary endpoint was graft survival (Kaplan-Meier). Secondary endpoints included patient survival, biopsy-confirmed acute rejection-free survival, and estimated glomerular filtration rate (4-variable modification of diet in renal disease). **Results.** Follow-up study included 1125 patients. Overall graft survival at 1 and 5 y posttransplantation was 93.8% and 88.1%, respectively, and was similar between treatment arms. At 1 and 5 y, patient survival was 97.8% and 94.4%, respectively. Five-year graft and patient survival rates in KTPs who remained on PR-T were 91.5% and 98.2%, respectively. Cox proportional hazards analysis demonstrated similar risk of graft loss and death between treatment arms. Five-year biopsy-confirmed acute rejection-free survival was 84.1%. Mean ± standard deviation values of estimated glomerular filtration rate were 52.7 ± 19.5 and 51.1 ± 22.4 mL/min/1.73 m^2 at 1 and 5 y, respectively. Fifty adverse drug reactions were recorded, probably tacrolimus-related in 12 patients (1.5%). **Conclusions.** Graft survival and patient survival (overall and for KTPs who remained on PR-T) were numerically high and similar between treatment arms at 5 y posttransplantation.

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Kidney transplantation remains the treatment of choice for patients with end-stage renal disease, surpassing dialysis in terms of cost-effectiveness, as well as duration and quality of life.[1,2] Following kidney transplantation, recipients require lifelong immunosuppressive therapy to prevent organ rejection.[3] However, although advances in immunosuppressive regimens have improved short-term outcomes, long-term outcomes after transplantation remain a challenge.[4] Indeed, graft survival in kidney transplant recipients at 1 y posttransplantation ranges from 89% to 92% but falls to 34% to 57% at 10 y.[5] Patient survival also shows a decline over time falling from 96% to 98% at 1 y posttransplantation to 87% to 90% at 5 y posttransplantation.[6]

Posttransplantation immunosuppression typically consists of a combination of a calcineurin inhibitor, corticosteroids, and an antiproliferative agent, which is usually mycophenolate mofetil (MMF) or mycophenolic acid (MPA).[3,7] Tacrolimus is the most frequently used calcineurin inhibitor and the mainstay of immunosuppressive regimens, being used in >90% of kidney transplant recipients.[8]

Originally, tacrolimus was only available as a twice-daily, immediate-release formulation; however, in 2007, a once-daily, prolonged-release formulation was widely approved for posttransplantation immunosuppression in kidney recipients.[9] As well as having comparable short-term patient and graft survival, renal function, and adverse event (AE) rates with the twice-daily formulation,[10-13] once-daily tacrolimus has the advantage of reducing intrapatient variability in tacrolimus exposure and increasing patient adherence to medication,[9,14-16] which could improve long-term patient outcomes. Additional large-scale studies are now required to assess long-term outcomes in kidney transplant recipients treated with prolonged-release tacrolimus-based immunosuppression.

The ADVANCE (Advagraf-based Immunosuppression Regimen Examining New Onset Diabetes Mellitus in Kidney Transplant Recipients) study originally assessed the incidence of posttransplantation diabetes (PTD) in de novo kidney transplant patients receiving prolonged-release tacrolimus-based immunosuppression for 24 wk.[17] Here, we present the 5-y follow-up of patients from the ADVANCE study.

MATERIALS AND METHODS

Study Design

Details of the ADVANCE study (NCT01304836) have been described previously.[17] Briefly, ADVANCE was a multicenter, 24-wk, randomized, open-label, parallel-group, phase-4 study that compared the incidence of PTD between 2 corticosteroid-minimization regimens, both of which included prolonged-release tacrolimus (Advagraf, Astellas Pharma Europe BV, the Netherlands) and MPA immunosuppression.[17] Eligible patients were aged ≥18 y and underwent primary renal transplantation or retransplantation.[17]

The present study (NCT02057484) was a multicenter, 5-y, prospective, noninterventional follow-up of patients who had received a kidney transplant and prolonged-release tacrolimus in the ADVANCE study.

The follow-up period consisted of 6 study visits. Visit 1 was at 6 mo posttransplantation. Patients still participating in ADVANCE had visit 1 on the ADVANCE end of study day, whereas patients who had already completed ADVANCE had visit 1 at their next scheduled review appointment. The subsequent visits (visits 2–6) were scheduled annually starting at 1 y (±4 mo) posttransplantation.

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, International Conference on Harmonisation guidelines, and applicable national laws and regulations. An independent ethics committee at each center granted approval of the follow-up study before initiation. Patients could withdraw from the study for any reason and provided written or verbal informed consent to participate in the follow-up study.

Treatment

In the primary ADVANCE study, patients received prolonged-release tacrolimus (0.1 mg/kg preoperatively and 0.2 mg/kg initially postoperatively) with oral MMF for 24 wk; intravenous basiliximab (20 mg) was also administered at day 0 (within 2 h prior to surgery) and at day 4.[17] Patients randomized to arm 1 received an intraoperative corticosteroid bolus plus tapered corticosteroids that were stopped after day 10, whereas patients in arm 2 only received an intraoperative corticosteroid bolus.[17] The recommended target trough levels for tacrolimus in both arms were 11 to 15 ng/mL for days 0 to 21, 8 to 12 ng/mL for days 22 to 42, and 5 to 9 ng/mL for day 43 until the end of the study.[17]

During the subsequent 4.5-y noninterventional follow-up period, patients were maintained on their usual immunosuppressive and tacrolimus regimen according to the investigator site's standard clinical practice. Patients did not have to receive prolonged-release tacrolimus at the time of study enrollment or to have completed ADVANCE to participate in the follow-up study because the primary objective was to evaluate long-term graft survival in patients currently or previously treated with prolonged-release tacrolimus.

Endpoints

The primary endpoint was overall graft survival. Graft loss was defined as retransplantation, graft nephrectomy, death, or ongoing dialysis at the end of study participation.

Secondary endpoints included overall patient survival, renal function, acute rejection (AR)– and biopsy-confirmed AR (BCAR)–free survival (AR and BCAR severity was assessed by Banff 2007 classification[18]), and emergence of de novo donor-specific antibodies (DSAs). Renal function was assessed by 3 methods: estimated glomerular filtration rate (eGFR) using the 4-variable modification of diet in renal disease (MDRD4) formula[19] and the chronic kidney disease epidemiology collaboration formula,[20] and estimated creatinine clearance calculated with the Cockcroft-Gault formula.[21] DSAs were detected as per local practice, and measurements were made at the investigators' discretion to meet the needs of individual patient care. Additional secondary endpoints included tacrolimus daily dose and trough level and current immunosuppressive regimen. Safety endpoints included diagnosis of medical conditions or infections of interest, AEs, and adverse drug reactions (ADRs). AEs were collected prospectively from the time of enrollment into the follow-up study and were defined as any untoward medical occurrence that did not necessarily have a causal relationship with the treatment. ADRs were defined as a noxious and unintended response to any treatment in the immunosuppressive regimen.

Statistical Analysis

The enrolled patient set (EPS) included all patients who enrolled in the ADVANCE study and received a kidney transplant along with prolonged-release tacrolimus treatment.

The follow-up patient set (FPS) included patients in the EPS who consented to the follow-up study or who died before they could consent. Patients who died before the start of the follow-up study had only their original trial data and date of death included in the analyses, provided the date of death was available. Patients who did not provide informed consent for the follow-up study had their original ADVANCE trial data included in the analysis until the point they discontinued or completed ADVANCE. As this was a noninterventional follow-up study, no power calculations for sample size were performed.

The Kaplan-Meier method was used to estimate overall graft survival, patient survival, and AR- and BCAR-free survival in the EPS. Time-to-event analysis was performed for 1, 2, 3, 4, and 5 y posttransplantation, and 2-sided confidence intervals (CIs) were calculated using the normal approximation method, with standard error estimated by Greenwood's formula.[22] Patients without graft loss were censored at the end of study date or their last evaluation date. In addition, a post hoc analysis of graft survival censored for death was performed. A Cox proportional hazards model was used to analyze endpoints adjusted for randomized treatment arm (arm 1 versus arm 2), donor age (≥50 versus <50 y), sex, and donor type (living versus deceased). SAS versions 9.2 and 9.4 were used to process, summarize, and analyze data.

RESULTS

Patient Characteristics

Overall, 1125 patients who had previously enrolled in ADVANCE were included in the EPS. A total of 814 patients consented to the follow-up study and were included in the FPS, of whom 734 (90%) completed the 5-y follow-up (Figure 1). In the FPS, the mean ± SD age was 50.5 ± 13.2 y, and most patients were White (88.3%) and male (65.1%). Baseline demographics and clinical characteristics were similar in both treatment arms (Table 1).

Tacrolimus Dosing and Exposure

The mean ± SD total daily dose of prolonged-release tacrolimus in the FPS was 0.07 ± 0.05 mg/kg at 1 y posttransplantation, which decreased to 0.06 ± 0.04 mg/kg at 5 y posttransplantation in both arms 1 and 2 (Table 2). The mean ± SD duration of prolonged-release tacrolimus from transplantation was 1384.9 ± 710.4 d and was numerically higher in arm 2 than in arm 1, 1423.5 ± 688.6 and 1344.2 ± 731.4 d, respectively (Table 2).

Mean ± SD values of whole blood trough levels of tacrolimus were 7.05 ± 2.26 ng/mL at 1 y posttransplantation and 6.30 ± 2.19 ng/mL at 5 y posttransplantation. Whole blood tacrolimus trough levels were 6.43 ± 2.29 and 6.17 ± 2.09 ng/mL in arms 1 and 2, respectively, at 5 y posttransplantation (Table 2).

Concomitant Immunosuppressants

Overall, 92.9% of patients took at least 1 concomitant immunosuppressant during the follow-up study. The most commonly used concomitant medication was MMF, which was taken by 84.9% of patients. Corticosteroids were taken by 31.9% of patients. The only other concomitant medication taken by ≥5% of patients was MPA (12.3%). MMF and MPA use was numerically higher in arm 2 than in arm 1. Usage of other concomitant immunosuppressants was similar between treatment arms (Table 3).

Graft Survival

Graft survival in the EPS was 93.8% (95% CI, 92.4-95.2) at 1 y, which decreased to 91.8% (95% CI, 90.0-93.5) and 88.1% (95% CI, 86.0-90.2) at 3 and 5 y, respectively (Figure 2A). Post hoc analysis of graft survival censored for

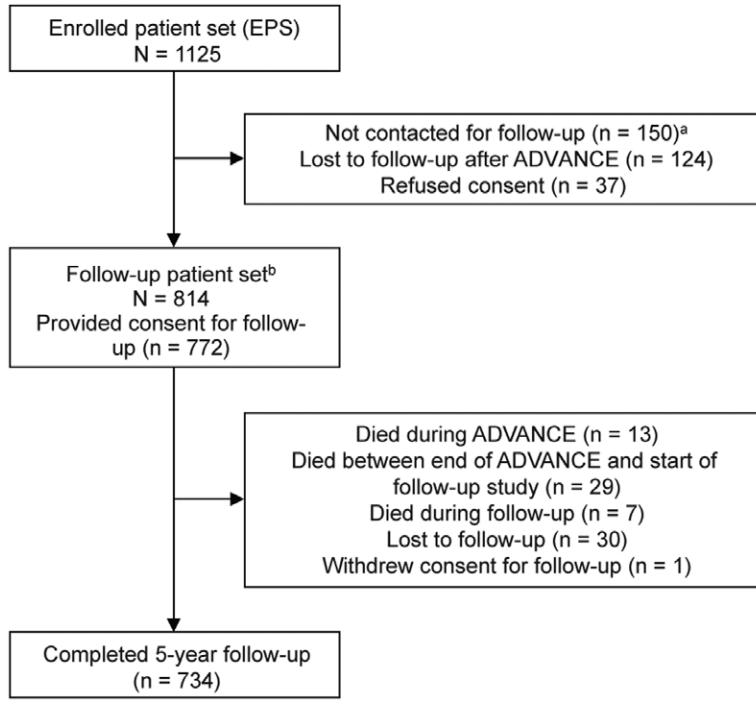

FIGURE 1. Patient population flow and analysis sets. [a]Excludes patients who died during the feeder trial (n = 13). [b]The follow-up patient set includes patients who died before giving consent for the follow-up study. ADVANCE, Advagraf-based Immunosuppression Regimen Examining New Onset Diabetes Mellitus in Kidney Transplant Recipients.

TABLE 1.

Baseline demographics and clinical characteristics in the FPS

Parameter	Arm 1[a] (n = 396)	Arm 2[b] (n = 418)	Total (N = 814)
Age (y), mean ± SD	50.4 ± 13.3	50.6 ± 13.1	50.5 ± 13.2
Male gender, n (%)	257 (64.9)	273 (65.3)	530 (65.1)
Race, n (%)			
Asian (native)	8 (2.0)	13 (3.1)	21 (2.6)
Black/African American	4 (1.0)	1 (0.2)	5 (0.6)
Other	34 (8.6)	35 (8.4)	69 (8.5)
White	350 (88.4)	369 (88.3)	719 (88.3)
Body mass index (kg/m^2), mean ± SD	25.6 ± 4.0	25.8 ± 4.4	25.7 ± 4.2
Renal function, mean ± SD			
eGFR (MDRD4) (mL/min/1.73 m^2)	49.8 ± 20.0	49.4 ± 19.4	49.6 ± 19.7
eGFR (CKD-EPI) (mL/min/1.73 m^2)	50.7 ± 21.6	50.2 ± 20.5	50.4 ± 21.0
eCC (Cockcroft-Gault) (mL/min)	59.1 ± 23.0	59.5 ± 23.0	59.3 ± 23.0
Last measured tacrolimus trough levels (ng/mL), mean ± SD	8.3 ± 3.5	8.3 ± 3.3	8.3 ± 3.4
Recipient viral status, n (%)			
CMV positive	259 (65.4)	291 (69.6)	550 (67.6)
HBV negative	386 (97.5)	411 (98.3)	797 (97.9)
HCV negative	387 (97.7)	406 (97.1)	793 (97.4)
HIV negative	394 (99.5)	416 (99.5)	810 (99.5)
Donor age (y), mean ± SD	51.3 ± 15.4	51.0 ± 15.1	51.1 ± 15.2
Organ donor type, n (%)			
Deceased	341 (86.1)	357 (85.4)	698 (85.7)
Living nonrelated	17 (4.3)	12 (2.9)	29 (3.6)
Living related	38 (9.6)	49 (11.7)	87 (10.7)

[a]Arm 1: prolonged-release tacrolimus + MMF + basiliximab + intraoperative corticosteroid bolus + tapered corticosteroids to day 10.
[b]Arm 2: prolonged-release tacrolimus + MMF + basiliximab + intraoperative corticosteroid bolus.
CKD-EPI, chronic kidney disease epidemiology collaboration; CMV, cytomegalovirus; eCC, estimated creatinine clearance; eGFR, estimated glomerular filtration rate; FPS, follow-up patient set; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MDRD4, 4-variable modification of diet in renal disease; MMF, mycophenolate mofetil; SD, standard deviation.

TABLE 2.

Prolonged-release tacrolimus daily dose, trough levels, and duration of treatment in the FPS

Time period (posttransplantation)	Arm 1[a] (n = 396)	Arm 2[b] (n = 418)	Total (N = 814)
Prolonged-release tacrolimus total daily dose (mg/kg), mean ± SD			
6 mo	0.09 ± 0.06	0.09 ± 0.06	0.09 ± 0.06
1 y	0.07 ± 0.05	0.07 ± 0.05	0.07 ± 0.05
2 y	0.07 ± 0.04	0.06 ± 0.04	0.07 ± 0.04
3 y	0.06 ± 0.04	0.06 ± 0.04	0.06 ± 0.04
4 y	0.06 ± 0.04	0.06 ± 0.04	0.06 ± 0.04
5 y	0.06 ± 0.04	0.06 ± 0.04	0.06 ± 0.04
Tacrolimus trough levels (ng/mL), mean ± SD			
6 mo	8.30 ± 3.51	8.27 ± 3.28	8.28 ± 3.39
1 y	6.91 ± 2.35	7.18 ± 2.16	7.05 ± 2.26
2 y	6.64 ± 2.02	6.88 ± 2.25	6.76 ± 2.14
3 y	6.54 ± 2.31	6.51 ± 2.24	6.52 ± 2.27
4 y	6.55 ± 2.10	6.48 ± 2.02	6.51 ± 2.06
5 y	6.43 ± 2.29	6.17 ± 2.09	6.30 ± 2.19
Duration of prolonged-release tacrolimus treatment, mean ± SD			
Days posttransplantation	1344.2 ± 731.4	1423.5 ± 688.6	1384.9 ± 710.4

[a]Arm 1: prolonged-release tacrolimus + MMF + basiliximab + intraoperative corticosteroid bolus + tapered corticosteroids to day 10.
[b]Arm 2: prolonged-release tacrolimus + MMF + basiliximab + intraoperative corticosteroid bolus.
FPS, follow-up patient set; MMF, mycophenolate mofetil.

death showed comparable results; graft survival was 94.8% (95% CI, 93.4-96.1) and 89.0% (95% CI, 87.0-91.1) at 1 and 5 y posttransplantation, respectively (**Table S1, SDC,** http://links.lww.com/TXD/A485). In patients who remained on prolonged-release tacrolimus, graft survival was 94.3% (95% CI, 92.9-95.7) at 1 y posttransplantation and 91.5% (95% CI, 89.7-93.3) at 5 y posttransplantation (post hoc analysis; **Table S2, SDC,** http://links.lww.com/TXD/A485). Graft survival was similar between treatment arms (Figure 2B). At 5 y posttransplantation, graft survival was 86.2% (95% CI, 83.0-89.5) and 89.9% (95% CI, 87.2-92.6) for arms 1 and 2, respectively.

Cox proportional hazards model analysis showed that the risk of graft loss was higher in patients with donors ≥50 y than with

TABLE 3.

Concomitant immunosuppressive medication use, eGFR, and the incidence of de novo DSAs in the FPS

Medication	Arm 1[a] (n = 396)	Arm 2[b] (n = 418)	Total (N = 814)
Concomitant immunosuppressive medications used by ≥5% of patients in the FPS, n (%)			
Patients taking ≥1 concomitant immunosuppressive medication	358 (90.4)	398 (95.2)	756 (92.9)
MMF	328 (82.8)	363 (86.8)	691 (84.9)
MPA	43 (10.9)	57 (13.6)	100 (12.3)
Corticosteroids	128 (32.3)	132 (31.6)	260 (31.9)
eGFR (mL/min/1.73 m^2) by MDRD4, mean ± SD			
6 mo	49.6 ± 20.2	48.7 ± 20.4	49.2 ± 20.3
1 y	53.5 ± 18.9	51.9 ± 20.0	52.7 ± 19.5
2 y	52.8 ± 19.3	52.0 ± 20.4	52.4 ± 19.8
3 y	51.5 ± 20.7	51.9 ± 21.6	51.7 ± 21.2
4 y	51.7 ± 22.0	52.0 ± 21.8	51.9 ± 21.9
5 y	51.4 ± 22.6	50.8 ± 22.2	51.1 ± 22.4
Incidence of de novo DSAs, n (%)			
6 mo	2 (50) n = 4	0 (0) n = 0	2 (50) n = 4
1 y	5 (5.2) n = 96	4 (3.7) n = 107	9 (4.4) n = 203
2 y	3 (3.1) n = 98	3 (2.9) n = 103	6 (3.0) n = 201
3 y	6 (7.2) n = 83	7 (7.3) n = 96	13 (7.3) n = 179
4 y	6 (9.2) n = 65	7 (9.5) n = 74	13 (9.4) n = 139
5 y	5 (8.6) n = 58	7 (10.4) n = 67	12 (9.6) n = 125

Medications taken during the follow-up study include medications that were initiated before the start of the follow-up study and had an end date on or after the first day of the follow-up study.
[a]Arm 1: prolonged-release tacrolimus + MMF + basiliximab + intraoperative corticosteroid bolus + tapered corticosteroids to day 10.
[b]Arm 2: prolonged-release tacrolimus + MMF + basiliximab + intraoperative corticosteroid bolus.
DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; FPS, follow-up patient set; MDRD4, 4-variable modification of diet in renal disease; MMF, mycophenolate mofetil; MPA, mycophenolic acid.

donors <50 y of age (hazard ratio [HR]: 2.13; 95% CI, 1.40-3.23) and was lower in patients with a living donor than with a deceased donor (HR: 0.21; 95% CI, 0.08-0.58). The risk of graft loss was similar between treatment arms and between sexes.

Patient Survival

In the EPS, overall patient survival was 97.8% (95% CI, 96.8-98.7), 96.2% (95% CI, 94.9-97.4), and 94.4% (95% CI, 92.8-95.9) at 1, 3, and 5 y posttransplantation, respectively (Figure 3A). In patients who remained on prolonged-release tacrolimus, post hoc analysis showed patient survival rates of 99.0% (95% CI, 98.4-99.6) and 98.2% (95% CI, 97.3-99.1) at 1 and 5 y posttransplantation, respectively (**Table S3, SDC,** http://links.lww.com/TXD/A485). Patient survival rates were similar between the 2 treatment arms; Kaplan-Meier analysis showed that estimated survival rates at 5 y were 93.2% (95% CI, 90.8-95.6) and 95.5% (95% CI, 93.5-97.4) in arms 1 and 2, respectively (Figure 3B). Cox proportional hazards model analysis showed that the risk of death was higher in patients with donors ≥50 y versus donors <50 y of age (HR: 2.23; 95% CI, 1.16-4.28). The risk of death was similar between treatment arms and between sexes.

Renal Function

Renal function, as assessed by mean ± SD eGFR (MDRD4), was stable posttransplantation in the FPS: 52.7 ± 19.5 and 51.1 ± 22.4 mL/min/1.73 m^2 at 1 and 5 y posttransplantation, respectively (Table 3). The eGFR (MDRD4) was similar across treatment arms (Table 3). The eGFR (chronic kidney disease epidemiology collaboration) and estimated creatinine clearance (Cockcroft-Gault) showed similar trends to those observed with eGFR (MDRD4; **Table S4, SDC,** http://links.lww.com/TXD/A485).

AR- and BCAR-free Survival

Most AR and BCAR episodes in the EPS occurred in the first 6 mo posttransplantation; the overall AR-free survival rate was 78.4% (95% CI, 76.0-80.8) at 6 mo and 74.2% (95% CI, 71.5-76.9) at 5 y (Figure 4A). The BCAR-free survival rate was 88.8% (95% CI, 86.9-90.7) at 6 mo and 84.1% (95% CI, 81.8-86.4) at 5 y (Figure 5A). AR-free survival was numerically higher in arm 1 than in arm 2. This difference arose at 6 mo posttransplantation and was maintained through to 5 y (82.1% [95% CI, 78.9-85.3] and 74.8% [95% CI, 71.2-78.4] at 6 mo and 76.9% [95% CI, 73.1-80.7] and 71.6% [95% CI, 67.7-75.4] at 5 y for arms 1 and 2, respectively; Figure 4B). A similar trend to AR was observed for BCAR-free survival (91.3% [95% CI, 88.9-93.7] and 86.4% [95% CI, 83.6-89.2] at 6 mo and 86.2% [95% CI, 83.1-89.4] and 82.1% [95% CI, 78.7-85.4] at 5 y for arms 1 and 2, respectively; Figure 5B).

Incidence of De Novo DSAs

At 5 y posttransplantation, 12 (9.6%) of the 125 patients tested were positive for de novo DSAs. In patients who were tested for de novo DSAs, the incidence was 8.6% and 10.4% at 5 y posttransplant in arms 1 and 2, respectively (Table 3).

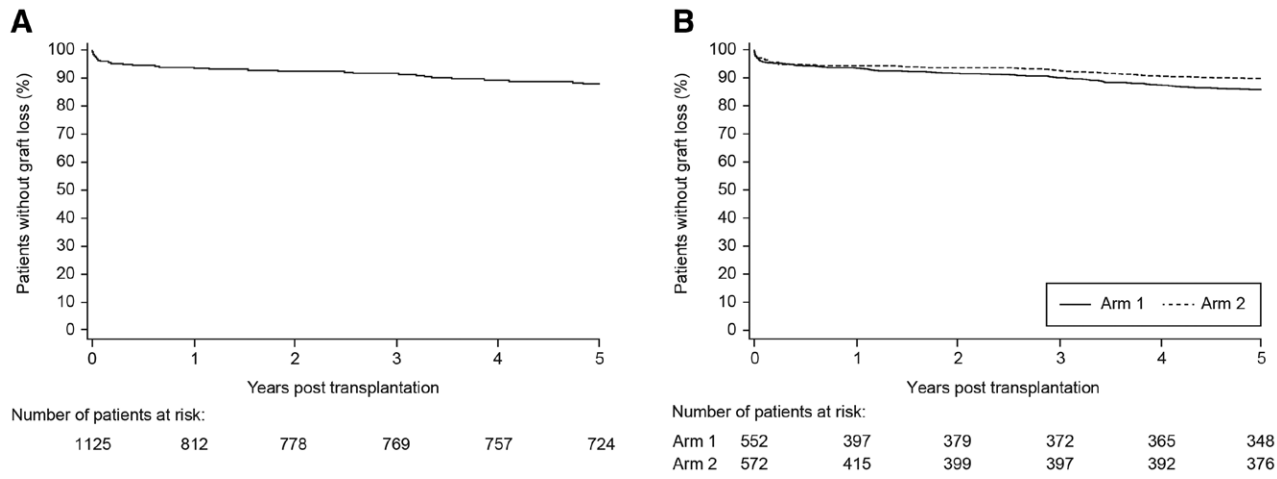

FIGURE 2. Kaplan-Meier plots of graft survival in the EPS, (A) in all patients and (B) by treatment arm. Arm 1: prolonged-release tacrolimus + MMF + basiliximab + intraoperative corticosteroid bolus + tapered corticosteroids to day 10. Arm 2: prolonged-release tacrolimus + MMF + basiliximab + intraoperative corticosteroid bolus. One patient in the EPS was screened but not randomized; hence, n = 1125 in (A) and n = 1124 in (B) at 0 y posttransplantation. EPS, enrolled patient set; MMF, mycophenolate mofetil.

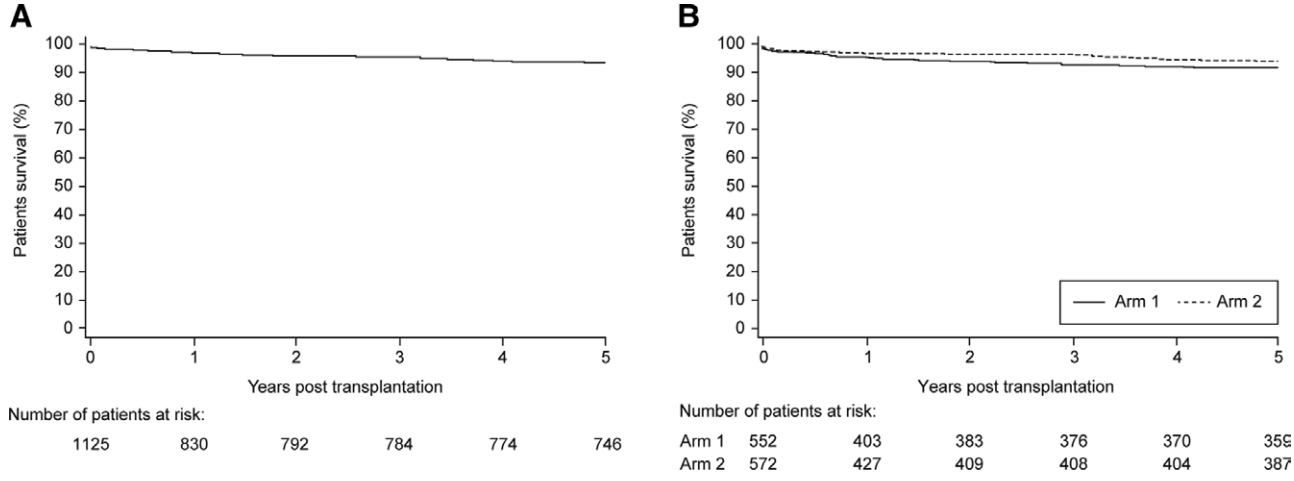

FIGURE 3. Kaplan-Meier plots of patient survival in the EPS, (A) in all patients and (B) by treatment arm. Arm 1: prolonged-release tacrolimus + MMF + basiliximab + intraoperative corticosteroid bolus + tapered corticosteroids to day 10. Arm 2: prolonged-release tacrolimus + MMF + basiliximab + intraoperative corticosteroid bolus. One patient in the EPS was screened but not randomized; hence, n = 1125 in (A) and n = 1124 in (B) at 0 y posttransplantation. EPS, enrolled patient set; MMF, mycophenolate mofetil.

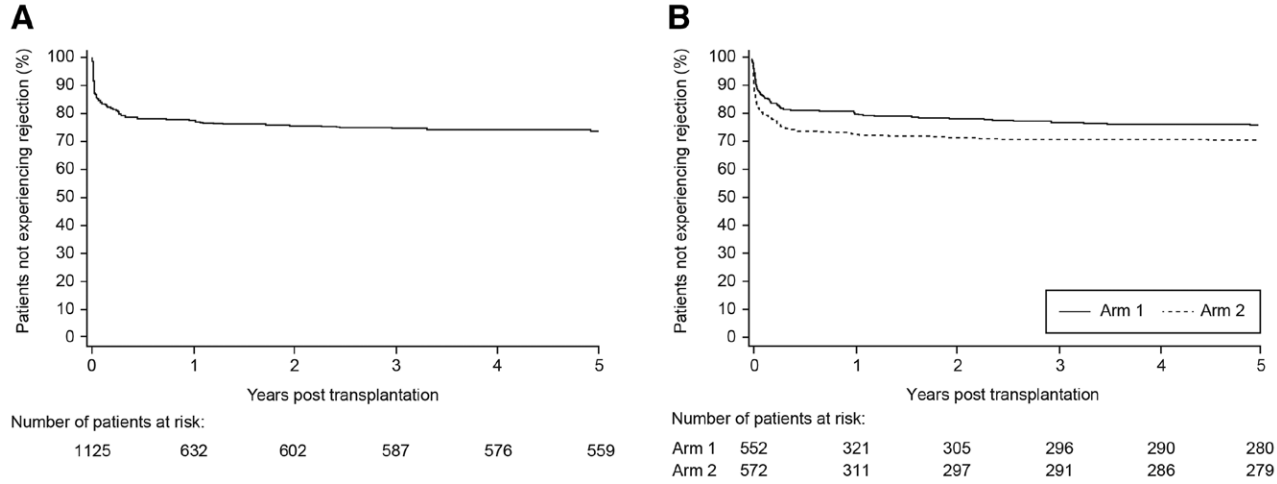

FIGURE 4. Kaplan-Meier plots showing time to first episode of AR in the EPS, (A) in all patients and (B) by treatment arm. Arm 1: prolonged-release tacrolimus + MMF + basiliximab + intraoperative corticosteroid bolus + tapered corticosteroids to day 10. Arm 2: prolonged-release tacrolimus + MMF + basiliximab + intraoperative corticosteroid bolus. One patient in the EPS was screened but not randomized; hence, n = 1125 in (A) and n = 1124 in (B) at 0 y posttransplantation. AR, acute rejection; EPS, enrolled patient set; MMF, mycophenolate mofetil.

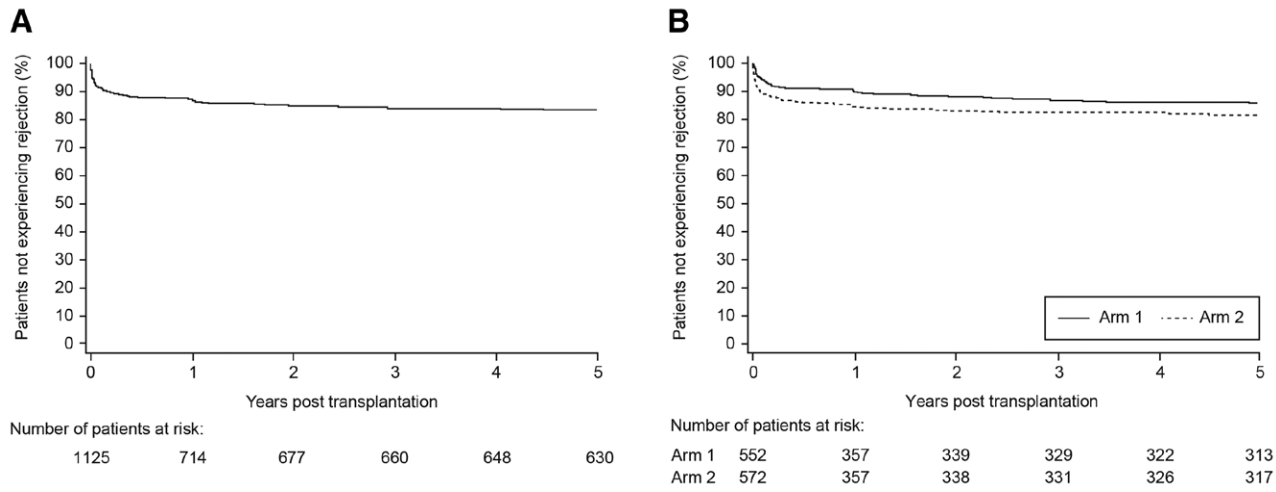

FIGURE 5. Kaplan-Meier plots showing time to first episode of BCAR in the EPS, (A) in all patients and (B) by treatment arm. Arm 1: prolonged-release tacrolimus + MMF + basiliximab + intraoperative corticosteroid bolus + tapered corticosteroids to day 10. Arm 2: prolonged-release tacrolimus + MMF + basiliximab + intraoperative corticosteroid bolus. One patient in the EPS was screened but not randomized; hence, n = 1125 in (A) and n = 1124 in (B) at 0 y posttransplantation. BCAR, biopsy-confirmed acute rejection; EPS, enrolled patient set; MMF, mycophenolate mofetil.

Safety

Overall, 269 patients (33.0%) in the FPS reported at least 1 AE. Rates of AEs were similar between treatment arms (34.6% and 31.6% in arms 1 and 2, respectively). AEs experienced by ≥1% of patients are displayed in Table 4. The most frequent AEs were urinary tract infection (4.7% of patients) and diarrhea (2.2%). AEs leading to discontinuation of tacrolimus occurred in 2 patients: 1 was a moderate removal of renal transplant (renal transplantectomy, nonrejection) occurring 3 y and 8 mo after transplantation and was considered not related to tacrolimus, and the other was a case of mild alopecia, which started 4 y and 1 mo after transplantation and was considered possibly related to tacrolimus. Fifty ADRs (6.1%) were recorded, and 12 patients (1.5%) experienced at least 1 probably tacrolimus-related ADR: sepsis (0.2%), toxic nephropathy (0.2%), actinic cheilitis (0.1%), acute pyelonephritis (0.1%), bronchitis (0.1%), diabetes (0.1%), diarrhea (0.1%), *Escherichia* urinary tract infection (0.1%), pneumonia (0.1%), prostatic abscess (0.1%), septic shock (0.1%), streptococcal sepsis (0.1%), and upper respiratory tract infection (0.1%).

Diabetes was considered a medical condition of special interest and was recorded in 38 patients (4.7%; 5.1% in arm 1 and 4.3% in arm 2) between the end of ADVANCE and the beginning of the follow-up study. Subsequently, 2 patients, one from each treatment arm, developed nonserious diabetes during the follow-up period.

TABLE 4.

AEs experienced by ≥1% of patients and ADRs in the FPS

AE/ADR	Patients (N = 814), n (%)
At least 1 AE	269 (33.0)
AEs in ≥1% of patients	
Urinary tract infection[a]	38 (4.7)
Diarrhea	18 (2.2)
Edema peripheral	13 (1.6)
Anemia	9 (1.1)
Renal impairment	8 (1.0)
Hypertension	8 (1.0)
Cough	8 (1.0)
At least 1 ADR	50 (6.1)
At least 1 probably tacrolimus-related ADR	12 (1.5)

Data are presented as number of patients (%).
[a]Composite of the preferred terms *Escherichia* urinary tract infection, urinary tract infection, and urinary tract infection bacterial.
AE, adverse event; ADR, adverse drug reaction; FPS, follow-up patient set.

DISCUSSION

In this 5-y follow-up study, long-term graft survival was evaluated in kidney transplant recipients who were treated with prolonged-release tacrolimus-based immunosuppression during the ADVANCE study. Five-year graft and patient survival rates were high, as were AR- and BCAR-free survival rates, and renal function remained stable for 5 y posttransplantation. The incidence of de novo DSAs was low in patients who were evaluated, and no new safety signals were identified in patients for the 5-y period.

Five-year graft and patient survival rates (88.1% and 94.4%, respectively) in this study were generally comparable with those reported in other long-term studies.[10,23-25] For example, in a 5-y follow-up of 539 kidney transplant patients (of 838 patients enrolled and included in the EPS) who received prolonged-release tacrolimus-based immunosuppression in the ADHERE (Advagraf in Combination With Sirolimus Evaluating Renal Function) study, graft and patient survival rates were 84.0% and 90.8%, respectively.[24] High graft and patient survival rates were also reported in a 5-y postmarketing surveillance study of prolonged-release tacrolimus in Japan (93.4% and 96.7%, respectively, at 5 y posttransplantation in the efficacy analysis set).[25] Additionally, in a 4-y follow-up study of de novo kidney transplant patients prescribed prolonged-release tacrolimus and MMF, graft survival was 88.1%, and patient survival was 93.8%.[10] By contrast, van Hooff et al[23] reported higher graft and patient survival rates of 100% at 4 y posttransplantation in de novo kidney transplant recipients prescribed prolonged-release tacrolimus. This may be because of the lower-risk population in the van

Hooff study because patients with a contraindication for corticosteroids or tacrolimus were excluded. Although 32% of patients were taking corticosteroids during the follow-up study, the data suggest that corticosteroid minimization was suitable for most of the study population and was associated with good long-term patient and graft outcomes. Collectively, the data suggest that the use of prolonged-release tacrolimus in combination with a corticosteroid-minimization regimen is suitable for use in clinical practice.

AR after kidney transplantation is associated with increased rates of graft loss and patient death.[26] AR- and BCAR-free survival were both high at 6 mo in the primary ADVANCE study; AR-free survival rates in arms 1 and 2 were 81.8% and 74.1%, respectively, whereas BCAR-free survival rates were 91.3% and 86.4%, respectively.[17] In this follow-up study, AR- and BCAR-free survival in the overall study population at 5 y posttransplantation were 74.2% and 84.1%, respectively, showing that most rejection episodes occurred during the first 6 mo after transplantation. Rejection rates in this study are comparable with those in the 5-y ADHERE follow-up study, which reported AR- and BCAR-free survival rates of 77.4% and 86.0% at 5 y posttransplantation,[24] and in the Japanese postmarketing surveillance study (overall 5-y rejection-free rate of 73.1%).[25] BCAR-free survival rates in patients treated with prolonged-release tacrolimus de novo were higher in a study by van Hooff et al[23] (90.9% at 4 y) than in those reported here. However, as previously mentioned, the lower-risk population in that study may account for the observed difference. In our study, AR- and BCAR-free survival rates at 5 y posttransplantation were both numerically higher in arm 1 than in arm 2. This difference was maintained from the primary ADVANCE trial, which reported a significantly lower incidence of AR and BCAR in arm 1 versus arm 2. These findings suggest that, after transplantation, a 10-d corticosteroid regimen may be beneficial in terms of long-term rejection rates compared with a 1-d regimen.

DSAs were not routinely measured in this study, and only 15% of patients in the FPS were evaluated for DSAs at 5 y posttransplantation. However, the incidence of de novo DSAs in those tested was low at 5 y posttransplantation. According to the Banff 2007 criteria, acute antibody-mediated rejection is classed as BCAR,[18] and although the small sample size means that reliable conclusions cannot be drawn, the low incidence of de novo DSAs is consistent with the high BCAR-free survival rates observed. The low rate of de novo DSA development is encouraging for clinicians because kidney transplant recipients with de novo DSAs have been reported to experience ~40% lower graft survival at 10 y posttransplantation than patients without de novo DSAs (59% versus 96%, respectively; $P < 0.0001$).[27]

Renal function remained stable throughout the 5-y follow-up study. Stable renal function was also reported in the ADHERE follow-up study, with a mean eGFR of 52.3 mL/min/1.73 m^2 at 6 mo and 52.5 mL/min/1.73 m^2 at 5 y posttransplantation—values comparable with our study.[24] Furthermore, in a postmarketing surveillance study of prolonged-release tacrolimus, eGFR was comparable at 4 wk (48.3 mL/min/1.73 m^2) and 5 y (48.7 mL/min/1.73 m^2) posttransplantation.[25] Stable long-term renal function has also been reported in other studies after 4 y of prolonged-release tacrolimus treatment.[10,23] Because poor renal function has been shown to predict long-term graft loss,[28,29] it is encouraging that long-term use of prolonged-release tacrolimus can be renal sparing.

Studies have demonstrated that steroid reduction/withdrawal typically increases tacrolimus trough levels soon after and may reduce tacrolimus dose requirements.[30-32] Herein, the daily dose of tacrolimus was similar between treatment arms during follow-up, suggesting that the initial steroid regimen did not impact long-term tacrolimus dosing requirements. Over the 5-y follow-up period, tacrolimus daily dose decreased from 0.07 mg/kg at 1 y to 0.06 mg/kg at 5 y posttransplantation. The same pattern was also observed with tacrolimus trough levels. This reduction in tacrolimus daily dose and trough levels over time mirrors results that have been described in previous studies of a similar length.[24,25] In this study, mean tacrolimus trough levels were slightly higher than those reported in the ADHERE follow-up study. At 5 y posttransplantation, trough levels were 5.5 and 6.3 ng/mL in the ADHERE and ADVANCE follow-up studies, respectively.[24] This was expected because target trough levels for patients in arm 2 of the ADHERE study were lower than those specified in the ADVANCE study (4–5 versus 5–9 ng/mL from day 42 onward, respectively).[24]

In this follow-up study, approximately 75% of patients were receiving steroid-free double immunosuppressive therapy, consisting of prolonged-release tacrolimus plus MMF/MPA. The AR- and BCAR-free survival rates observed in the present study are consistent with published data from the Collaborative Transplant Study, which showed that long-term patient and graft survival rates at 5 to 7 y posttransplantation were higher in patients on steroid-free maintenance immunosuppression than in those on regimens including steroids.[33,34] However, the literature contains conflicting evidence on the risks and benefits of steroid withdrawal/avoidance. Meta-analyses have consistently reported that steroid withdrawal/avoidance significantly increases the risk of AR in kidney transplant recipients.[35,36] However, this increase tends to be observed in patients treated with cyclosporine rather than with tacrolimus[37,38] and does not seem to impact graft survival.[37] We observed a lower incidence of AR in arm 1 than in arm 2, which may reflect a benefit of the 10-d tapered corticosteroid regimen. Overall, the high AR- and BCAR-free survival rates in this study, in combination with the graft and patient survival rates and low rates of PTD, suggest that steroid withdrawal (particularly a 10-d regimen) is not associated with detrimental outcomes up to 5 y posttransplantation. Therefore, early steroid withdrawal may be an acceptable strategy in clinical practice for patients with low immunological risk.

Overall, the safety results reported here are broadly consistent with those in the primary ADVANCE study,[17] and importantly, no new safety signals were identified during this long-term study. A small proportion of patients (1.5%) had ADRs that were considered probably tacrolimus-related. In addition, the rate of diabetes was low (40/814 patients; 4.9%) in comparison with that during the primary 6-mo ADVANCE trial (17.4% and 16.6% in arms 1 and 2, respectively).[17] This is not surprising because development of PTD primarily occurs within the first 6 mo posttransplantation,[39] and the rate of corticosteroid use was low in the follow-up patient cohort.[40] Although short-term steroid use has been linked with an increased risk of PTD early in the posttransplantation period,[39,41] the link between long-term steroid use and the development of type 2 diabetes is less clear. Indeed, a study

comparing early steroid withdrawal with long-term, low-dose corticosteroid treatment in kidney transplant recipients found that—although the incidence of diabetes was similar between regimens—significantly more patients receiving long-term corticosteroids required insulin treatment.[42] The findings from the current study suggest that early steroid withdrawal in combination with long-term, prolonged-release tacrolimus use may minimize the risk of developing PTD and type 2 diabetes and, consequently, the need for pulse steroids.

A strength of this study is that it was a long-term, 5-y prospective study of a large cohort of kidney transplant recipients; however, the study also had several limitations. First, this noninterventional follow-up study was not powered to statistically compare treatment arms. The open-label design of both the randomized phase and the long-term follow-up study rendered results from both periods susceptible to bias, such as selection bias regarding enrollment into the follow-up study. A further limitation is that neither adherence with tacrolimus medication nor variability in tacrolimus trough levels were assessed, despite their important association with long-term graft survival.[43,44] In addition, detailed information on the tacrolimus formulation patients were receiving throughout the follow-up study was not available. Assessment of DSAs was only conducted in patients whose treatment center included DSA measurement as part of routine clinical practice; therefore, DSA assessment was only conducted in a limited subset of patients and without systematic screening. This meant that detailed analysis of antibody-mediated rejection was not possible, despite its recognition as the leading cause of kidney allograft loss.[45] Further long-term studies of the key factors associated with graft and patient survival are warranted.

In conclusion, in this long-term follow-up of the ADVANCE study, prolonged-release tacrolimus-based immunosuppression was associated with high rates of both graft and patient survival at 5 y posttransplantation. Renal function remained stable for 5 y, and rates of AR and BCAR were low, with most cases being reported during the first 6 mo posttransplantation. The safety profile was consistent with that of the primary ADVANCE study, and no new safety signals were identified during follow-up. These findings support the long-term administration of once-daily, prolonged-release tacrolimus-based immunosuppression in combination with MMF in kidney transplant recipients.

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