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Long-term, Prolonged-release Tacrolimus-based Immunosuppression in De Novo Liver Transplant Recipients: 5-year Prospective Follow-up of Patients in the DIAMOND Study

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Background. Immunosuppression with calcineurin inhibitors (CNIs) is reportedly associated with risk of renal impairment in liver transplant recipients. It is believed that this can be mitigated by decreasing initial exposure to CNIs or delaying CNI introduction until 3–4 d posttransplantation. The ADVAGRAF studied in combination with mycophenolate mofetil and basiliximab in liver transplantation (DIAMOND) trial evaluated different administration strategies for prolonged-release tacrolimus (PR-T). **Methods.** DIAMOND was a 24-wk, open-label, phase 3b trial in de novo liver transplant recipients randomized to: PR-T 0.2 mg/kg/d (Arm 1); PR-T 0.15–0.175 mg/kg/d plus basiliximab (Arm 2); or PR-T 0.2 mg/kg/d delayed until day 5 posttransplant plus basiliximab (Arm 3). In a 5-y follow-up, patients were maintained on an immunosuppressive regimen according to standard clinical practice (NCT02057484). Primary endpoint: graft survival (Kaplan-Meier analysis). **Results.** Follow-up study included 856 patients. Overall graft survival was 84.6% and 73.5% at 1 and 5 y post transplant, respectively. Five-year rates for Arms 1, 2, and 3 were 74.7%, 71.5%, and 74.5%, respectively. At 5 y, death-censored graft survival in the entire cohort was 74.7%. Overall graft survival in patients remaining on PR-T for ≥ 30 d was 79.1%. Graft survival in patients who remained on PR-T at 5 y was 87.3%. Patient survival was 86.6% at 1 y and 76.3% at 5 y, with survival rates similar in the 3 treatment arms at 5 y. Estimated glomerular filtration rate at the end of the 24-wk initial study and 5 y posttransplant was 62.1 and 61.5 mL/min/1.73 m², respectively, and was similar between the 3 treatment arms at 5 y. Overall, 18 (2.9%) patients had ≥ 1 adverse drug reaction, considered possibly related to PR-T in 6 patients. **Conclusions.** In the DIAMOND study patient cohort, renal function, graft survival, and patient survival were similar between treatment arms at 5 y posttransplant.

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INTRODUCTION

Liver transplantation is a life-saving procedure that can restore patients with end-stage liver disease or acute liver failure to good health and normal activity.^{1,2} Data from the European Liver Transplant Registry (ELTR) indicate that the 1-y patient survival rate after liver transplantation is 86% (2010–2014 data); however, long-term outcomes remain a challenge, with 5-y patient survival reported as 74%.³

Liver transplant recipients require lifelong, controlled exposure to immunosuppressive therapy to prevent cellular and antibody-mediated graft rejection, while minimizing drug-related toxicity.⁴ Tacrolimus is a calcineurin inhibitor (CNI) that is the cornerstone of immunosuppression in solid organ transplantation. The most commonly used immunosuppressive regimen in liver transplantation consists of tacrolimus in combination with mycophenolate mofetil (MMF) and/or corticosteroids.⁵ Tacrolimus was originally marketed as a twice-daily, immediate-release formulation, but in 2007, a once-daily, prolonged-release formulation was marketed in many countries worldwide for use in stable liver transplant recipients or for administration to de novo patients.⁶

For liver transplant recipients, prolonged-release tacrolimus may offer several important clinical advantages over the traditional formulation. Tacrolimus has a narrow therapeutic index,⁷ and reducing inpatient variability in exposure^{8–10} via improved delivery of tacrolimus and potentially better adherence to the simplified once-daily regimen^{11,12} may improve long-term outcomes. In a retrospective analysis of data from the ELTR, patients who received prolonged-release tacrolimus following transplantation demonstrated a significantly higher rate of graft survival at 4 y posttransplant compared with those who received immediate-release tacrolimus (84% versus 79%, respectively). Patient survival at 4 y was also higher in the group receiving prolonged-release versus immediate-release tacrolimus (85% versus 81%, respectively).¹³

One of the drawbacks of administering CNIs post-liver transplantation is considered to be the risk of renal impairment,^{14,15} which is one of the main causes of poor long-term outcomes in liver transplant recipients.¹⁶ Strategies to minimize the adverse renal effects of CNIs include decreasing initial exposure^{17–20} or delaying their introduction until 3–4 d posttransplantation.²¹ For example, in the ReSpECT study, a regimen with low-dose, delayed initiation of immediate-release tacrolimus was associated with reduced renal function impairment at 52 wk compared with standard-dose, immediate-release tacrolimus-based treatment immediately posttransplant—without increased frequency of biopsy-confirmed acute rejection (BCAR), graft loss, or death.²¹ Furthermore, the phase 3b ADVAGRAF studied in combination with mycophenolate mofetil and basiliximab in liver transplantation (DIAMOND) trial evaluated renal function in de novo liver transplant patients receiving standard-dose, reduced-dose, or delayed initiation of prolonged-release

tacrolimus. Patients receiving the reduced- and delayed-dose regimens also received basiliximab.²² The reduced initial dose regimen administered immediately posttransplant was associated with significantly reduced renal function impairment and a significantly lower incidence of BCAR compared with the standard-dose regimen. The delayed tacrolimus regimen was also associated with significantly reduced renal function impairment compared with the standard-dose regimen, although BCAR incidence was comparable.

Findings from the DIAMOND trial suggest that delayed or reduced-dose prolonged-release tacrolimus regimens may improve renal outcomes compared with standard-dose regimens. However, DIAMOND was a 6-mo study, and, therefore, it is unclear whether these tacrolimus minimization strategies in the early post-liver transplant period have an impact on long-term transplant outcomes.

Herein, we report 5-y prospective follow-up data from the DIAMOND patient cohort. The primary objective of this follow-up study was to assess long-term graft survival in liver transplant recipients treated with regimens of standard-dose, reduced-dose, or delayed initiation of prolonged-release tacrolimus in the early posttransplant period. Secondary objectives included assessment of long-term patient survival, renal function, and the incidence of acute rejection (AR) and BCAR. Graft survival in patients receiving prolonged-release tacrolimus for ≥ 30 d was also assessed, as was the safety of long-term treatment with prolonged-release tacrolimus.

MATERIALS AND METHODS

Study Design

Details of the DIAMOND study (ClinicalTrials.gov: NCT01011205) have been described previously.²² In brief, DIAMOND was a 24-wk, randomized, open-label, phase 3b study of de novo liver transplant patients receiving once-daily, prolonged-release tacrolimus (Advagraf, Astellas Pharma Europe BV, Netherlands)-based immunosuppression regimens. Patients were not excluded if they had hepatocellular carcinoma. Eligible adult patients underwent primary orthotopic or partial liver transplantation. There were 3 randomized treatment arms: Arm 1, prolonged-release tacrolimus (initial dose 0.2 mg/kg/d); Arm 2, prolonged-release tacrolimus (0.15–0.175 mg/kg/d) plus basiliximab; and Arm 3, prolonged-release tacrolimus (0.2 mg/kg/d delayed until d 5 post transplant) plus basiliximab. All patients additionally received MMF plus a single bolus of corticosteroids (no maintenance corticosteroids).

The present study (ClinicalTrials.gov: NCT02057484) was a 5-y, noninterventional, prospective follow-up of patients who received a liver transplant and were assigned to treatment with prolonged-release tacrolimus as participants in the DIAMOND study. Patients who provided informed consent (written or verbal) were eligible to participate in the follow-up study.

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, at any time, without giving a reason for doing so and without penalty or prejudice. Patients were discontinued from the study if they died, were lost to follow-up, or withdrew consent.

Treatment

Patients were grouped according to their original randomized treatment arm in the DIAMOND study. Patients were maintained on their usual immunosuppressive regimen according to standard clinical practice.

Assessments

The follow-up period included 6 study visits. Patients had a baseline visit (visit 1) on their DIAMOND end of study (EOS) date, whereas those who had already completed DIAMOND had visit 1 at their next scheduled appointment (up to d 181 posttransplant). Subsequent visits were scheduled annually starting 1 y (\pm 4 mo) posttransplant.

Endpoints

The primary endpoint was overall graft survival, defined as time from transplantation to graft loss (retransplantation or death). Secondary endpoints included: overall patient survival, estimated glomerular filtration rate (eGFR; based on both the 4-variable Modification of Diet in Renal Disease [MDRD4] formula²³ and the Chronic Kidney Disease Epidemiology Collaboration formula²⁴) and AR and BCAR episodes (severity assessed by Banff classification²⁵⁻²⁷).

Tacrolimus dose and duration of treatment, and concomitant or other immunosuppressive therapy use were reported. Concomitant immunosuppressive medications included all medications administered to the patient during the follow-up study that may or may not have been administered concomitantly with tacrolimus. Adverse events (AEs) and adverse drug reactions (ADRs) were recorded throughout the follow-up period and were classified by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (version 16.1). An ADR was defined as a response to prolonged-release tacrolimus that was noxious and unintended. Response in this context implied that a causal relationship between prolonged-release tacrolimus and the AE was at least a reasonable possibility.

Statistical Analyses

Analysis Sets

The enrolled patient set (EPS) comprised all patients who enrolled in the DIAMOND study, had a liver transplant, and received at least 1 dose of prolonged-release tacrolimus. The follow-up patient set (FPS) comprised patients in the EPS who consented to the follow-up study or who died during DIAMOND or before the start of the follow-up study before they could give consent. Patients who were lost to follow-up between the DIAMOND EOS date and the start of the long-term follow-up study, or who did not provide informed consent for the long-term follow-up study, were included in the analysis up to the date when they discontinued or completed DIAMOND.

Descriptive Statistics

Data for patient demographics and clinical characteristics, tacrolimus dosing and exposure, use of other immunosuppressants, renal function, and safety and tolerability are presented using mean with SD or numbers and percentages, as appropriate.

Analysis of Time-to-Event Endpoints

The Kaplan-Meier method was used to analyze overall graft survival (the primary endpoint), as well as overall patient

survival, AR, and BCAR. Patients without graft loss were censored at the follow-up EOS date or last evaluation date. Post hoc analyses of death-censored graft survival (graft survival censored for death with a functioning graft), graft survival and death-censored graft survival in patients who remained on tacrolimus for \geq 30 d after transplantation, and graft and patient survival while receiving prolonged-release tacrolimus were also performed. Graft survival estimates at 1, 2, 3, 4, and 5 y posttransplant were calculated, with corresponding 2-sided 95% confidence intervals (CIs) using the normal approximation method. Kaplan-Meier analyses were performed on the EPS. Time-to-event endpoints were also analyzed using a Cox proportional hazards model, adjusted for treatment arm (Arm 1 versus Arm 3; Arm 2 versus Arm 3), donor age (\geq 50 y versus $<$ 50 y), sex, donor type (living versus deceased), and hepatitis C virus (HCV) status.

RESULTS

Patient Characteristics

A total of 856 patients who had previously enrolled in the DIAMOND study were included in the EPS. The FPS (patients who consented to the follow-up study or died before they could give consent) included 617 patients, of whom 443 (71.8%) completed the long-term follow-up study (Figure 1); 4 patients died after enrollment into the follow-up study. In the FPS, the mean (SD) age at baseline was 54.3 y (9.8 y), and 71.8% of patients were male (Table 1). Baseline demographics and clinical characteristics were similar in the 3 treatment arms (Arm 1, n=196; Arm 2, n=212; and Arm 3, n=209).

Tacrolimus Dosing and Exposure

The overall mean (SD) daily dose of prolonged-release tacrolimus decreased from 0.063 mg/kg (0.04 mg/kg) at 1-y post transplant to 0.039 mg/kg (0.03 mg/kg) at 5 y posttransplant. Mean daily doses of prolonged-release tacrolimus were similar in the 3 treatment arms at all time points (Table 2). The overall mean (SD) duration of prolonged-release tacrolimus from transplantation was 870.1 d (817.5 d). The mean duration of prolonged-release tacrolimus was higher in Arm 3 (940.7 d) than in Arms 1 (840.4 d) or 2 (831.4 d), suggesting that a lower proportion of patients in Arm 3 than in the other 2 arms discontinued treatment with prolonged-release tacrolimus. Of 856 patients in the EPS, 381 remained on prolonged-release tacrolimus at 1 y, 355 at 3 y, and 134 at 5 y. After the first year of treatment, few patients discontinued prolonged-release tacrolimus because of graft loss or death.

In accordance with the decreasing tacrolimus daily dose over time, overall mean (SD) tacrolimus trough levels were 7.4 ng/mL (2.8 ng/mL) at 1 y and 5.2 ng/mL (2.1 ng/mL) at 5 y posttransplant. Mean tacrolimus trough levels were similar in the 3 treatment arms at all time points (Table 3).

Concomitant and Other Immunosuppressants

Almost two-thirds of patients (64.2%) took at least 1 concomitant immunosuppressive medication during the follow-up study (Table 4). The most common concomitant immunosuppressant in the FPS was MMF (57.4%). Other immunosuppressive medications taken by $>$ 5% of patients in any treatment arm in the FPS were systemic corticosteroids (14.6%), the mammalian target of rapamycin inhibitors, everolimus or sirolimus (12.2%), and ciclosporin (5.2%; not administered

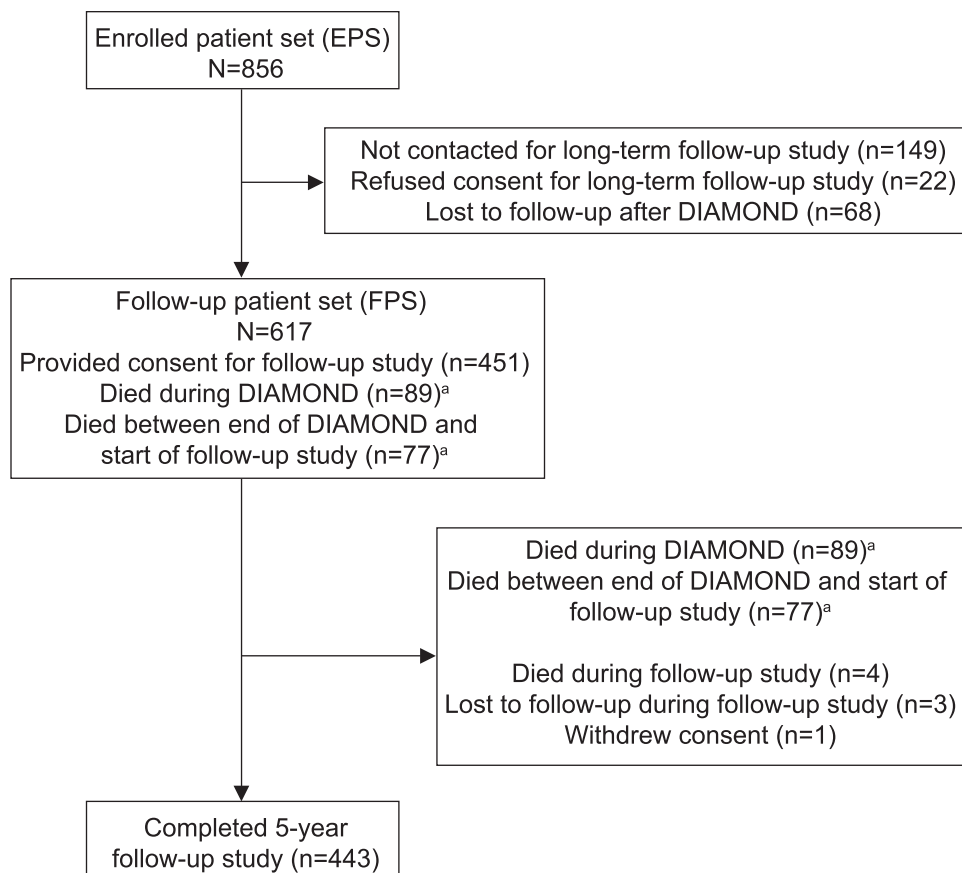


FIGURE 1. Patient disposition and analysis sets. ^aPatients who died during DIAMOND or between DIAMOND and the start of the follow-up study were included in the FPS but were not considered to have completed the follow-up study. DIAMOND, ADVAGRAF studied in combination with mycophenolate mofetil and basiliximab in liver transplantation; EPS, enrolled patient set; FPS, follow-up patient set.

with tacrolimus). Concomitant or other immunosuppressive medication use was similar between treatment arms, except for everolimus, which was taken less frequently in Arm 2 (4.7%) than in Arm 1 (10.2%) or Arm 3 (10.5%).

Primary Efficacy Endpoint: Graft Survival

At 1-y posttransplant, overall graft survival was 84.6% (95% CI, 82.0%-87.1%), decreasing to 73.5% (95% CI, 70.2%-76.8%) at 5 y posttransplant (Figure 2A). Graft survival rates

TABLE 1.
Baseline demographics and clinical characteristics (FPS)

Parameter	Arm 1 ^a (n = 196)	Arm 2 ^b (n = 212)	Arm 3 ^c (n = 209)	Total (N = 617)
Age, y, mean (SD)	54.4 (9.1)	54.0 (10.1)	54.4 (10.0)	54.3 (9.8)
Male sex, n (%)	142 (72.4)	155 (73.1)	146 (69.9)	443 (71.8)
Ethnicity, White, n (%)	189 (96.4)	200 (94.3)	201 (96.2)	590 (95.6)
Body mass index, kg/m ² , mean (SD)	26.5 (4.8)	26.9 (5.5)	26.4 (4.4)	26.6 (4.9)
eGFR (MDRD4), mL/min/1.73 m ² , mean (SD) ^d	66.9 (26.7)	73.55 (34.1)	68.5 (28.9)	69.7 (30.2)
Last measured tacrolimus trough level (ng/mL), mean (SD) ^d	8.1 (3.9)	8.5 (4.6)	7.8 (4.0)	8.1 (4.2)
Patients with graft loss before start of follow-up study, n (%)	36 (18.4)	34 (16.0)	31 (14.8)	101 (16.4)
Recipient viral status, n (%)				
CMV positive	130 (66.3)	150 (70.8)	140 (67.0)	420 (68.1)
HBV negative	170 (86.7)	180 (84.9)	185 (88.5)	535 (86.7)
HCV negative	134 (68.4)	154 (72.6)	149 (71.3)	437 (70.8)
HIV negative	195 (99.5)	212 (100.0)	206 (98.6)	613 (99.4)
Donor age, y, mean (SD)	51.8 (17.5)	51.3 (18.0)	51.3 (17.9)	51.5 (17.8)
Organ donor type, n (%)				
Deceased	190 (96.9)	207 (97.6)	202 (96.7)	599 (97.1)
Living nonrelated	2 (1.0)	1 (0.5)	2 (1.0)	5 (0.8)
Living related	4 (2.0)	4 (1.9)	5 (2.4)	13 (2.1)

^aArm 1: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d) + MMF.

^bArm 2: prolonged-release tacrolimus (initial dose 0.15–0.175 mg/kg/d) + MMF + basiliximab.

^cArm 3: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d delayed until day 5) + MMF + basiliximab.

^dMeasured at DIAMOND EOS (d 168 ± 42 d).

CMV, cytomegalovirus; DIAMOND, ADVAGRAF studied in combination with mycophenolate mofetil and basiliximab in liver transplantation; eGFR, estimated glomerular filtration rate; EOS, end of study; FPS, follow-up patient set; HBV, hepatitis B virus; HCV, hepatitis C virus; MDRD4, 4-variable Modification of Diet in Renal Disease; MMF, mycophenolate mofetil.

TABLE 2.**Total daily dose of prolonged-release tacrolimus over time (FPS)**

Visit	Time point	Arm 1 ^a (n = 196)	Arm 2 ^b (n = 212)	Arm 3 ^c (n = 209)	Total (N = 617)
1	DIAMOND EOS (d 181)	0.09 (0.06)	0.09 (0.07)	0.09 (0.06)	0.09 (0.06)
	N	190	207	192	589
2	1 y (d 182–547)	0.06 (0.03)	0.06 (0.04)	0.07 (0.05)	0.06 (0.04)
	n	122	125	132	379
3	2 y (d 548–913)	0.04 (0.03)	0.05 (0.03)	0.05 (0.04)	0.05 (0.03)
	n	118	124	125	367
4	3 y (d 914–1278)	0.04 (0.02)	0.04 (0.03)	0.05 (0.03)	0.04 (0.03)
	n	110	117	120	347
5	4 y (d 1279–1643)	0.04 (0.02)	0.04 (0.03)	0.04 (0.03)	0.04 (0.03)
	n	110	115	119	344
6/EOS	5 y (d 1644–2009)	0.04 (0.02)	0.04 (0.03)	0.04 (0.03)	0.04 (0.03)
	n	110	113	119	342

^aArm 1: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d) + MMF.

^bArm 2: prolonged-release tacrolimus (initial dose 0.15–0.175 mg/kg/d) + MMF + basiliximab.

^cArm 3: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d delayed until d 5) + MMF + basiliximab.

Data are mean (SD) mg/kg/d.

DIAMOND, ADVAGRAF studied in combination with mycophenolate mofetil and basiliximab in liver transplantation; EOS, end of study; FPS, follow-up patient set; MMF, mycophenolate mofetil.

TABLE 3.**Whole-blood trough levels of tacrolimus over time (FPS)**

Visit	Time point	Arm 1 ^a (n = 196)	Arm 2 ^b (n = 212)	Arm 3 ^c (n = 209)	Total (N = 617)
1	DIAMOND EOS (d 181)	8.2 (4.0)	8.5 (4.6)	7.9 (4.0)	8.2 (4.2)
	n	185	205	191	581
2	1 y (d 182–547)	7.4 (3.0)	7.3 (3.0)	7.6 (2.6)	7.4 (2.8)
	n	133	140	135	408
3	2 y (d 548–913)	6.7 (2.6)	6.2 (2.4)	6.8 (3.2)	6.6 (2.8)
	n	126	130	127	383
4	3 y (d 914–1278)	5.4 (1.8)	5.7 (2.7)	5.7 (2.3)	5.6 (2.3)
	n	120	124	125	369
5	4 y (d 1279–1643)	5.1 (1.8)	5.4 (2.7)	6.3 (5.3)	5.6 (3.7)
	n	116	122	127	365
6/EOS	5 y (d 1644–2009)	5.4 (1.9)	4.9 (2.0)	5.4 (2.4)	5.2 (2.1)
	N	117	122	121	360

^aArm 1: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d) + MMF.

^bArm 2: prolonged-release tacrolimus (initial dose 0.15–0.175 mg/kg/d) + MMF + basiliximab.

^cArm 3: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d delayed until d 5) + MMF + basiliximab.

Data are mean (SD) ng/mL.

DIAMOND, ADVAGRAF studied in combination with mycophenolate mofetil and basiliximab in liver transplantation; EOS, end of study; FPS, follow-up patient set; MMF, mycophenolate mofetil.

TABLE 4.**Concomitant or other immunosuppressive medications taken by ≥5% of patients in 1 of the treatment arms (FPS)**

Medication	Arm 1 ^a (n = 196)	Arm 2 ^b (n = 212)	Arm 3 ^c (n = 209)	Total (N = 617)
≥1 concomitant immunosuppressant	129 (65.8)	130 (61.3)	137 (65.6)	396 (64.2)
Mycophenolate mofetil	115 (58.7)	122 (57.5)	117 (56.0)	354 (57.4)
Systemic corticosteroid	33 (16.8)	24 (11.3)	33 (15.8)	90 (14.6)
Everolimus	20 (10.2)	10 (4.7)	22 (10.5)	52 (8.4)
Ciclosporin	10 (5.1)	13 (6.1)	9 (4.3)	32 (5.2)
Sirolimus	10 (5.1)	8 (3.8)	5 (2.4)	23 (3.7)

^aArm 1: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d) + MMF.

^bArm 2: prolonged-release tacrolimus (initial dose 0.15–0.175 mg/kg/d) + MMF + basiliximab.

^cArm 3: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d delayed until day 5) + MMF + basiliximab.

Data are n (%).

DIAMOND, ADVAGRAF studied in combination with mycophenolate mofetil and basiliximab in liver transplantation; FPS, follow-up patient set; MMF, mycophenolate mofetil.

at 5 y for treatment Arms 1, 2, and 3 were comparable: 74.7% (95% CI, 68.9%–80.4%), 71.5% (95% CI, 65.5%–77.4%), and 74.5% (95% CI, 68.8%–80.2%), respectively (Figure 2B). A post hoc analysis of overall death-censored graft survival

showed similar results to the primary analysis: 85.9% (95% CI, 83.5%–88.4%) at 1 y and 74.7% (95% CI, 71.4%–78.0%) at 5 y posttransplant (Figure S1, SDC, <http://links.lww.com/TXD/A331>).

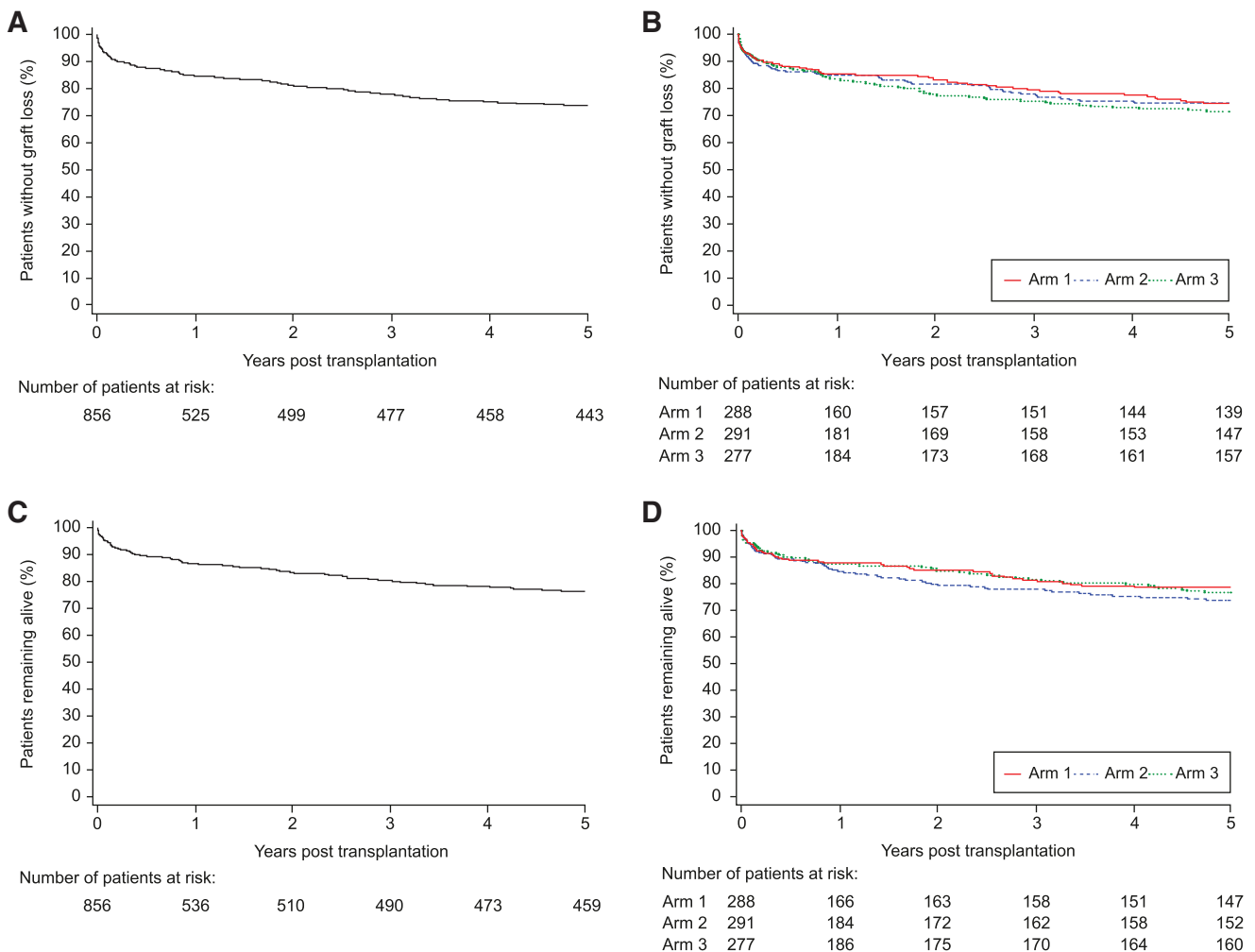


FIGURE 2. Kaplan-Meier plots of graft and patient survival (EPS). A, Overall graft survival. B, Graft survival by treatment arm. C, Overall patient survival. D, Patient survival by treatment arm. Arm 1: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d) + MMF; Arm 2: prolonged-release tacrolimus (initial dose 0.15–0.175 mg/kg/d) + MMF + basiliximab; and Arm 3: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d delayed until d 5 post transplant) + MMF + basiliximab. Time to graft loss was defined as the time from transplantation to graft loss, including graft loss events that occurred in DIAMOND. Graft loss was defined as retransplantation or death. Patients were censored at last evaluation if no event. DIAMOND, ADVAGRAF studied in combination with mycophenolate mofetil and basiliximab in liver transplantation; EPS, enrolled patient set; MMF, mycophenolate mofetil.

At 5 y posttransplant, graft survival and death-censored graft survival in patients who remained on prolonged-release tacrolimus for ≥ 30 d were 79.1% (95% CI, 75.8%–82.4%) and 79.3% (95% CI, 76.0%–82.6%), respectively (Figure S1, SDC, <http://links.lww.com/TXD/A331>). Graft survival over 5 y in patients who remained on prolonged-release tacrolimus was 87.3% (95% CI, 84.8%–89.7%) (Figure S1, SDC, <http://links.lww.com/TXD/A331>).

Cox proportional hazards model analysis of overall graft survival (Table 5) showed that patients with positive HCV status at baseline had a higher hazard of graft loss than patients with negative HCV status: hazard ratio (HR) 1.93 (95% CI, 1.44–2.58). There were no differences in the risk of graft loss between treatment arms, donor age, donor type, or sex.

Graft Survival by 12-mo eGFR

Kaplan-Meier estimated graft survival at 5 y was generally comparable in patients with 12-mo eGFR 30–60 mL/min/1.73 m² or ≥ 60 mL/min/1.73 m², irrespective of treatment arm (range between 91.0% and 98.1%). In Arms 1 and 2, posttransplant eGFR < 30 mL/min/1.73 m² at 12 mo was associated with numerically worse 5-y graft survival rates

(88.9% and 88.2%, respectively) compared with eGFR 30–60 or ≥ 60 mL/min/1.73 m². No patients in Arm 3 with eGFR < 30 mL/min/1.73 m² lost their graft. However, the findings in patients with eGFR < 30 mL/min/1.73 m² should be interpreted with caution because of small patient numbers ($n = 18$, $n = 17$, and $n = 14$ in Arms 1–3, respectively).

Secondary Efficacy Endpoints

Patient Survival

At 1 y posttransplant, overall patient survival was 86.6% (95% CI, 84.1%–89.0%), decreasing to 76.3% (95% CI, 73.1%–79.6%) at 5 y posttransplant (Figure 2C). Patient survival rates for treatment Arms 1, 2, and 3 were similar at 5 y: 78.6% (95% CI, 73.2%–84.1%), 73.8% (95% CI, 68.1%–79.6%), and 76.7% (95% CI, 71.2%–82.3%), respectively (Figure 2D). In a post hoc analysis of survival in patients who remained on prolonged-release tacrolimus, survival rate was 90.6% (95% CI, 88.5%–92.8%) (Figure S2, SDC, <http://links.lww.com/TXD/A331>).

Cox proportional hazards model analysis of overall patient survival (Table 5) showed that patients with a positive baseline

TABLE 5.**Cox proportional hazards model analysis of overall graft and patient survival (EPS)**

Model parameter	Subgroups	Hazard ratio (95% CI)	
		Graft survival	Patient survival
HCV status	Positive vs negative	1.93 (1.44-2.58)	2.01 (1.47-2.74)
Sex	Male vs female	1.37 (0.98-1.92)	1.59 (1.10-2.32)
Donor age	≥50 y vs <50 y	1.33 (0.99-1.79)	1.22 (0.89-1.67)
Donor type	Living vs deceased	1.22 (0.50-2.98)	0.78 (0.25-2.47)
Treatment arm	Arm 1 ^a vs Arm 3 ^b	1.01 (0.71-1.45)	0.93 (0.63-1.36)
	Arm 2 ^c vs Arm 3 ^b	1.14 (0.81-1.62)	1.16 (0.81-1.67)

^aArm 1: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d) + MMF.

^bArm 3: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d delayed until d 5) + MMF + basiliximab.

^cArm 2: prolonged-release tacrolimus (initial dose 0.15–0.175 mg/kg/d) + MMF + basiliximab. CI, confidence interval; EPS, enrolled patient set; HCV, hepatitis C virus; MMF, mycophenolate mofetil.

HCV status had a higher hazard of death than patients with a negative baseline HCV status (HR, 2.00; 95% CI, 1.47-2.74). Male patients had a higher risk of death than female patients (HR, 1.59; 95% CI, 1.01-2.32). There was no difference in the risk of death between treatment arms, donor age, or donor type.

Overall Survival by Baseline eGFR

Kaplan-Meier estimated 5-y overall survival was numerically lower in patients with baseline eGFR <30 mL/min/1.73 m² than in patients with baseline eGFR ≥60 mL/min/1.73 m², irrespective of treatment arm (EPS). Overall survival at 5 y in patients with eGFR <30 mL/min/1.73 m² versus ≥60 mL/min/1.73 m² was 56.5% (95% CI, 32.2%-80.8%) versus 85.3% (95% CI, 79.1%-91.6%) in Arm 1, 48.4% (95% CI, 23.1%-73.7%) versus 77.0% (95% CI, 70.0%-83.9%) in Arm 2, and 16.7% (95% CI, 0.0%-43.3%) versus 82.1% (95% CI, 75.5%-88.8%) in Arm 3.

Renal Function

Mean (SD) overall eGFR (MDRD4) was similar at the DIAMOND EOS and at 5 y posttransplant: 62.1 mL/min/1.73 m² (37.6 mL/min/1.73 m²) and 61.5 mL/min/1.73 m² (30.4 mL/min/1.73 m²), respectively (Table 6). Although mean eGFR (MDRD4) was numerically lower in Arm 1 than in Arms 2 and 3 at the DIAMOND EOS, eGFR was comparable between arms by year 1, and there were no obvious differences between the 3 treatment arms at the end of the observation period. Similar results were observed for calculation of eGFR using the Chronic Kidney Disease Epidemiology Collaboration method (Table 6). Mean (SD) eGFR (MDRD4) for patients who remained on prolonged-release tacrolimus was similar at the DIAMOND EOS and at 5 y posttransplant (62.3 mL/min/1.73 m² [35.6 mL/min/1.73 m²] and 64.5 mL/min/1.73 m² [29.9 mL/min/1.73 m²], respectively).

Acute Rejection

Most AR episodes occurred in the first 6 mo posttransplant (Figure 3A and B). The overall AR-free survival rate was 82.2% at 6 mo, and 78.7% at 5 y posttransplant. At 6 mo posttransplant, a greater proportion of patients were AR-free in Arm 2 (86.8%) versus Arm 1 (80.0%) or Arm 3 (79.7%). At 5 y posttransplant, the AR-free survival rate remained higher in Arm 2 (83.5%) versus Arm 1 (76.6%) or Arm 3 (75.8%).

Biopsy-confirmed Acute Rejection

As seen with AR, most BCAR episodes were reported in the first 6 mo posttransplant (Figure 3C and D). The overall BCAR-free survival rate was 84.8% at 6 mo, and 81.9% at 5 y posttransplant. BCAR-free survival at 6 mo was higher in Arm 2 (89.0%) than in Arm 1 (82.2%) or Arm 3 (83.1%), and remained higher at 5 y posttransplant (86.3%) compared with Arm 1 (79.5%) and Arm 3 (79.9%). In most patients, BCAR was classified as mild or moderate; severe BCAR was experienced by 10 patients (1.2%) at baseline (visit 1) and 1 patient (0.1%) at 2 y posttransplant.

Safety and Tolerability

In the FPS, 1 or more AEs were experienced by 93 patients (15.1%) (Table 7). The most common AEs were asthenia (1.0%) and incisional hernia (1.0%). No patients had AEs leading to discontinuation of tacrolimus. In total, 18 patients (2.9%) had at least 1 ADR, of whom 6 (1.0%) had at least 1 ADR classified as “probably tacrolimus-related,” as assessed by the investigator. The most common probably tacrolimus-related ADR was renal failure, which was the only ADR that occurred in >1 patient (n=2). No patients experienced ADRs leading to death. A total of 22 patients developed diabetes, including 21 patients between the end of the DIAMOND study and provision of informed consent for the follow-up study and 1 patient during the follow-up study.

DISCUSSION

In this 5-y, prospective follow-up of a large patient cohort (n=856) from the 24-wk DIAMOND study, we evaluated long-term graft survival in liver transplant recipients treated with prolonged-release tacrolimus-based immunosuppression. Overall, graft and patient survival rates at 5 y posttransplant were 73.5% and 76.3%, respectively, and were similar in the 3 treatment arms. The overall death-censored graft survival rate was 74.7%. Graft survival and death-censored graft survival rates were 79.1% and 79.3%, respectively, for patients who remained on prolonged-release tacrolimus for ≥30 d. Both graft and patient survival were numerically highest in the group of patients who remained on prolonged-release tacrolimus (87.3% and 90.6%, respectively, at 5 y). Graft survival rates for patients who remained on prolonged-release tacrolimus for ≥30 d were comparable with the 4-y graft survival rates in patients receiving prolonged-release tacrolimus following liver transplantation reported by the ELTR (79% and 84%, respectively).¹³ In both instances, patients who received prolonged-release tacrolimus for <1 mo were excluded. In our study, graft survival rates were numerically higher in the cohort receiving prolonged-release tacrolimus for ≥30 d than in the overall cohort. This highlights the impact of graft loss resulting from causes other than failed immunosuppression that can occur within the first month after liver transplantation.

Cox proportional hazards analysis showed that patients with a positive baseline HCV status had a higher risk of graft loss and death than patients with a negative HCV status. This finding is well known and consistent with historic data showing that a positive HCV status is a major risk factor for reduced long-term graft and patient survival.²⁸ However, HCV recurrence of the transplanted liver is no longer a major clinical concern, because of the inception of direct-acting antiviral agents. Our analysis

TABLE 6.**Renal function (eGFR) over time by MDRD4 and CKD-EPI (FPS)**

Visit	Time point	Arm 1 ^a (n = 196)	Arm 2 ^b (n = 212)	Arm 3 ^c (n = 209)	Total (N = 617)
1	DIAMOND EOS (d 181)				
	n	195	212	209	616
	MDRD4	57.6 (36.2)	66.0 (40.8)	62.5 (35.2)	62.1 (37.6)
	CKD-EPI	56.7 (34.0)	63.6 (34.9)	61.6 (32.9)	60.7 (34.0)
2	1 y (d 182–547)				
	n	146	150	151	447
	MDRD4	62.5 (32.7)	65.6 (30.9)	62.8 (28.8)	63.6 (30.8)
	CKD-EPI	62.1 (31.0)	65.6 (30.3)	63.2 (29.0)	63.6 (30.1)
3	2 y (d 548–913)				
	n	145	145	147	437
	MDRD4	63.9 (32.2)	63.7 (29.4)	61.3 (28.0)	63.0 (29.9)
	CKD-EPI	63.5 (32.2)	63.7 (28.8)	62.1 (28.7)	63.1 (29.2)
4	3 y (d 914–1278)				
	n	145	142	147	434
	MDRD4	63.3 (32.8)	62.0 (29.2)	59.6 (27.8)	61.6 (30.0)
	CKD-EPI	62.4 (30.2)	61.9 (28.8)	60.0 (28.5)	61.5 (29.1)
5	4 y (d 1279–1643)				
	n	141	146	145	432
	MDRD4	61.9 (31.7)	62.4 (29.6)	61.9 (32.1)	62.1 (31.1)
	CKD-EPI	61.3 (30.4)	61.9 (28.9)	60.9 (29.5)	61.4 (29.5)
6/EOS	5 y (d 1644–2009)				
	n	139	145	145	429
	MDRD4	62.3 (32.8)	62.5 (30.0)	59.8 (28.5)	61.5 (30.4)
	CKD-EPI	61.1 (29.9)	61.6 (28.7)	59.7 (28.5)	60.8 (29.0)

^aArm 1: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d) + MMF.

^bArm 2: prolonged-release tacrolimus (initial dose 0.15–0.175 mg/kg/d) + MMF + basiliximab.

^cArm 3: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d delayed until d 5) + MMF + basiliximab.

Data are mean (SD) mL/min/1.73 m².

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DIAMOND, ADVAGRAF studied in combination with mycophenolate mofetil and basiliximab in liver transplantation; eGFR, estimated glomerular filtration rate; EOS, end of study; FPS, follow-up patient set; MDRD4, 4-variable Modification of Diet in Renal Disease; MMF, mycophenolate mofetil.

also showed that male patients appear to have a higher risk of death than female patients. This difference only emerged during the long-term follow-up period as, in the original 24-wk DIAMOND study, there were no significant differences in mortality between male and female patients.²² Although the findings from our follow-up study are consistent with long-term survival data from the ELTR,¹³ other studies report a higher mortality rate in female patients compared with male patients,^{29,30} or no difference between sexes in liver graft survival.³¹ Given the inconsistency in survival between sexes, results from the Cox analysis in our study should be interpreted with caution.

A decline in renal function is one of the main causes of poor long-term outcomes in liver transplant recipients.¹⁶ Data from the US National Institute of Diabetes and Digestive and Kidney Diseases liver transplantation database showed that the effect of renal failure on patient mortality increases over time (HR was 2.4 at 1 y posttransplant, increasing to 7.5 at 5 y).¹⁶ In the present study, renal function as measured by mean eGFR (MDRD4) remained stable from 1 y (63.6 mL/min/1.73 m²) to 5 y (61.5 mL/min/1.73 m²) posttransplant, in line with the high rates of patient survival observed. Although there was a gradual decline in mean eGFR over 5 y in Arm 2 (from 66.0 mL/min/1.73 m² at DIAMOND EOS to 62.5 mL/min/1.73 m² at 5 y) and there was a numeric improvement in Arm 1 (from 57.6 mL/min/1.73 m² at DIAMOND EOS to 62.3 mL/min/1.73 m² at 5 y), the clinical significance of these findings is unclear. After the initial tacrolimus dose, as per the randomized regimen, investigators were allowed to

adjust the dose to maintain target tacrolimus trough levels, and the patients were observed in the real world after the first 6 mo of treatment. Therefore, as the initial tacrolimus dosing regimens were not maintained long-term and tacrolimus trough levels were subsequently managed by the sites as per the drug label, this may account for the generally comparable tacrolimus trough levels during follow-up and similar 5-y renal function between study arms. Overall, the data suggest that the immunosuppressive regimens utilized in the original DIAMOND study, and subsequent long-term prolonged-release tacrolimus use, do not negatively affect long-term renal function, which is encouraging for clinical practice.

AR after liver transplantation is associated with a significantly increased risk of graft failure, all-cause mortality, and graft failure-related death.³² In this study, AR- and BCAR-free survival rates were high at 5 y posttransplant (78.7% and 81.9%, respectively), with most episodes occurring within the first 6 mo posttransplant. We found that AR- and BCAR-free survival rates at 6 mo in Arm 2 (prolonged-release tacrolimus 0.15–0.175 mg/kg/d immediately posttransplant plus basiliximab) were numerically higher than those in Arm 1 (prolonged-release tacrolimus 0.2 mg/kg/d immediately posttransplant) or Arm 3 (prolonged-release tacrolimus 0.2 mg/kg/d delayed until day 5 posttransplant plus basiliximab), and the difference was maintained through to 5 y posttransplantation. It should be noted that Arms 2 and 3 received induction therapy with basiliximab, which might have impacted outcomes

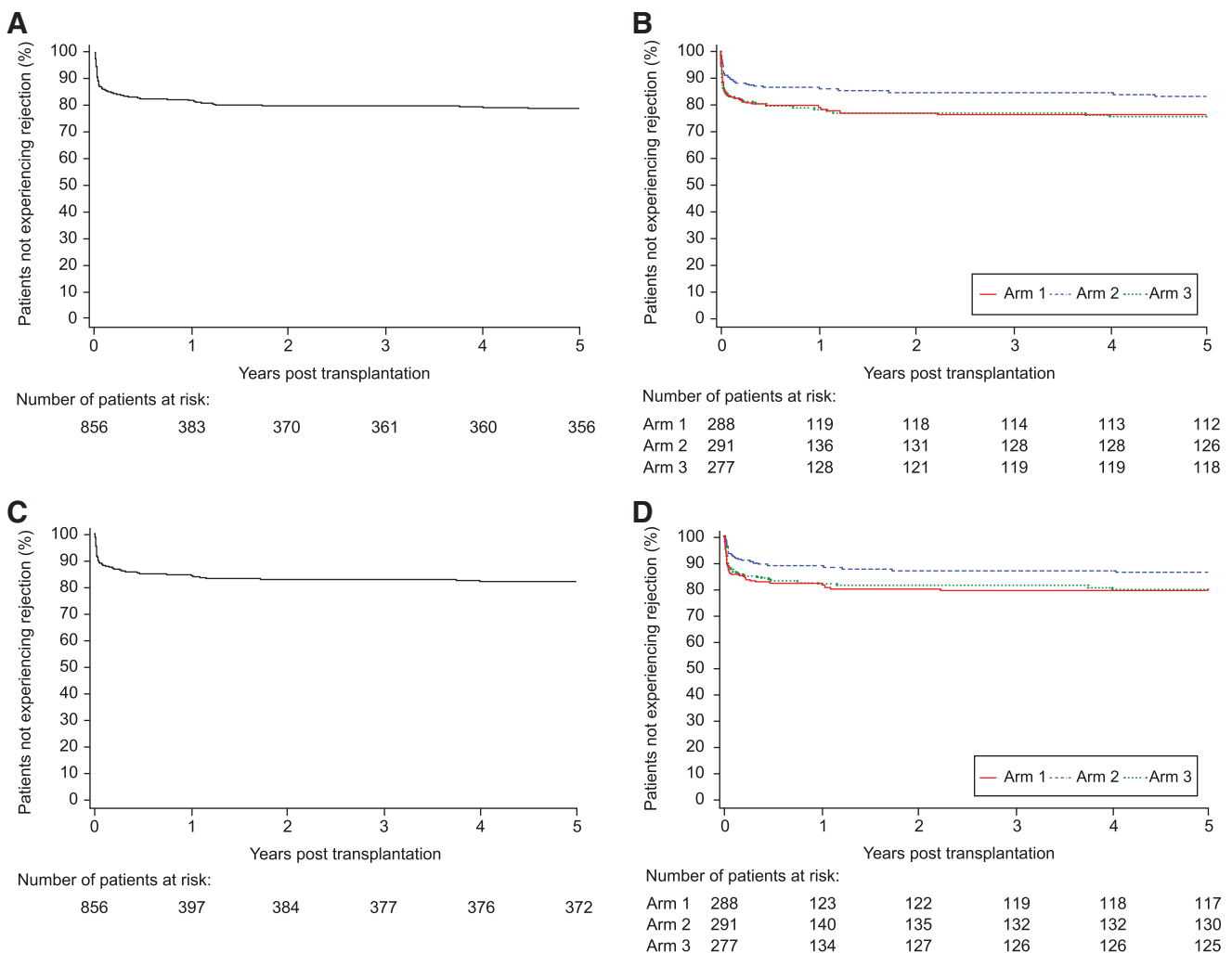


FIGURE 3. Kaplan-Meier plots of first episode of AR and BCAR (EPS). A, Overall AR-free survival. B, AR-free survival by treatment arm. C, Overall BCAR-free survival. D, BCAR-free survival by treatment arm. Arm 1: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d) + MMF; Arm 2: prolonged-release tacrolimus (initial dose 0.15–0.175 mg/kg/d) + MMF + basiliximab; and Arm 3: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d delayed until d 5 posttransplant) + MMF + basiliximab. AR, acute rejection; BCAR, biopsy-confirmed acute rejection; EPS, enrolled patient set; MMF, mycophenolate mofetil.

in the immediate posttransplant period. However, despite the link between AR and rates of graft and patient survival,³² the higher rate of AR-free survival in Arm 2 compared with Arms 1 and 3 did not translate into improved rates of graft or patient survival in Arm 2. Whether this might be linked with the gradual decline in renal function or the lower tacrolimus trough levels at 5 y (4.9 ng/mL) observed in Arm 2 versus Arms 1 and 3 is unclear.

Over the 5-y follow-up period, tacrolimus daily dose and trough levels decreased. At the end of the original DIAMOND study and during long-term follow-up, the mean tacrolimus daily dose and trough levels were similar between arms. This might be expected as the recommended tacrolimus trough levels were the same in all 3 treatment arms, and tacrolimus dose was titrated according to trough levels. During follow-up, approximately 35% of patients received monotherapy with prolonged-release tacrolimus. Furthermore, while all patients received MMF at the start of the DIAMOND study, ~40% of patients stopped MMF at some stage during DIAMOND or the follow-up study. The first 6 mo of the study were protocol-driven, and tacrolimus monotherapy was not permitted. During follow-up,

patients were treated according to standard clinical practice, individual patient preference and medical need (eg, to treat a concomitant disease), which may have enabled cessation of MMF and subsequent monotherapy with prolonged-release tacrolimus.

Overall, the safety profile of the patients in the follow-up study was consistent with those of the primary DIAMOND study,²² and no new safety signals were detected. A small proportion of patients (1.0%) had ADRs that were considered probably tacrolimus-related during this follow-up study. In contrast to the observed high incidence of diabetes in the ReSpECT study (39%–48%),²¹ only 3.6% of patients in the FPS developed diabetes. The low incidence of diabetes during the follow-up study was probably related to the low proportion of patients (15%) taking systemic corticosteroids.³³

The present study has several limitations. Firstly, this study was not powered to statistically compare treatment arms. Furthermore, the open-label design of both the randomized phase and the long-term follow-up study means that results from both periods were susceptible to bias, including selection bias regarding enrollment into the follow-up

TABLE 7.**AEs and ADRs reported during the long-term follow-up period (FPS)**

AE/ADR	Patients, n (%), N=617
At least 1 AE	93 (15.1)
AEs in ≥3 patients	
Asthenia	6 (1.0)
Incisional hernia	6 (1.0)
Diarrhea	3 (0.5)
Hypertension	3 (0.5)
Urinary tract infection	3 (0.5)
At least 1 ADR ^a	18 (2.9)
At least 1 probably tacrolimus-related ADR	6 (1.0)
Renal failure	2 (0.3)
Papillary thyroid cancer	1 (0.2)
Acute prerenal failure	1 (0.2)
Leukoencephalopathy	1 (0.2)
Toxicity to various agents	1 (0.2)

^aAn ADR is defined as a response to a medicinal product that is noxious and unintended. Response in this context implies that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.

ADR, adverse drug reaction; AE, adverse event; FPS, follow-up patient set.

study. Many patients with a functioning graft at the end of the initial DIAMOND trial did not enter the long-term follow-up study. Some sites (including those in Norway and Turkey) from the initial DIAMOND study did not participate because they lacked the resources, their patients did not respond to requests to participate, or they were not approached for logistical reasons. One site was not included because its ethics committee considered the study design interventional.

An additional limitation is that key factors associated with long-term graft survival in liver transplant recipients, including the development of de novo donor-specific antibodies^{34,36} and adherence to medication^{11,12} were not assessed here. Future studies that evaluate these factors are warranted. Additionally, as this was an observational study, factors associated with local clinical practice could have impacted the proportion of patients discontinuing treatment with prolonged-release tacrolimus—and these factors were not assessed.

CONCLUSIONS

In this long-term follow-up of a large cohort of patients who had previously enrolled in the DIAMOND study, renal function, graft survival, and patient survival were similar between treatment arms at 5 y posttransplant. Renal function remained generally stable through 5 y posttransplantation, and rates of AR- and BCAR-free survival were high, with most episodes reported during the first 6 mo posttransplant. The safety and tolerability profile was consistent with the DIAMOND study, and no new safety signals were reported over 5 y.

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