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Efficacy of Prolonged-release Tacrolimus After Conversion From Immediate-release Tacrolimus in Kidney Transplantation: A Retrospective Analysis of Long-term Outcomes From the ADMIRAD Study

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Background. Prolonged-release tacrolimus (PRT) may offer improved outcomes after kidney transplantation compared with immediate-release tacrolimus (IRT). However, data on outcomes beyond 5-y posttransplantation are lacking. **Methods.** A retrospective, noninterventional chart review study examined long-term graft survival in adult kidney transplant participants in the Adherence Measurement in Stable Renal Transplant Patients Following Conversion From Prograf to Advagraf (ADMIRAD) clinical trial at 4 Belgian sites. Patients were randomized to receive once-daily PRT or twice-daily IRT for 6 mo, followed by treatment as per real-world clinical practice. Data were collected retrospectively from randomization day until December 31, 2018. Primary endpoints included efficacy failure, defined as a composite endpoint of graft loss, biopsy-confirmed acute rejection, and graft dysfunction. Secondary endpoints included overall patient survival and course of kidney function. **Results.** This analysis included 78.5% of patients from ADMIRAD (n = 108 PRT; n = 64 IRT). The Kaplan–Meier survival rate without efficacy failure from randomization to year 5 was 0.741 (95% confidence interval [CI]: 0.647, 0.813) for the PRT group (n = 80), and 0.667 (95% CI: 0.536, 0.768) for the IRT group (n = 42) and remained higher for PRT throughout 10 y follow-up (P = 0.041). The Kaplan–Meier estimate of overall survival from the time of last transplant was 0.981 (95% CI: 0.928, 0.995) and 0.880 (95% CI: 0.802, 0.928) at 5 and 10 y in the PRT group. Kidney function parameters and tacrolimus trough levels remained stable over the follow-up period. **Conclusions.** Patients in the ADMIRAD study who received PRT for up to 10 y had improved long-term outcomes compared with patients receiving IRT, with a consistent effect on both graft and patient survival.

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Long-term immunosuppression following kidney transplant is ideally maintained by treatments with predictable and stable pharmacokinetic profiles that reduce variability in trough drug levels.[1,2] Additionally, good medication adherence,

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Researchers may request access to anonymized participant level data, trial level data and protocols from Astellas sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

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defined by the World Health Organization as the extent to which a person's behavior regarding their medical treatment corresponds to the agreed recommendations from their healthcare professionals, is vital to achieve effective immunosuppression.[3,4] Treatments that offer improved convenience, through once-daily versus twice-daily dosing, can improve treatment adherence.[5] Because nonadherence is known to contribute substantially to graft loss,[6,7] once-daily dosing may improve transplantation outcomes.

Immunosuppressive therapy following kidney transplant generally includes a calcineurin inhibitor (CNI) and an antiproliferative agent such as mycophenolate mofetil (MMF) with or without corticosteroids.[8] CNIs induce immunosuppression via impairment of T-cell activation, proliferation, and differentiation.[9] Tacrolimus is the most widely used CNI for the long-term maintenance of kidney transplants.[10]

Tacrolimus is available both as twice-daily immediate-release tacrolimus (IRT; PROGRAF [PROGRAFT in Belgium], Astellas Pharma Ltd., Surrey, UK) and as once-daily prolonged-release tacrolimus (PRT; ADVAGRAF, Astellas Pharma Ltd.).[11,12] Compared with the twice-daily formulation, PRT may offer clinical advantages, which in turn could improve long-term outcomes. Firstly, PRT can reduce intrapatient variability in drug exposure via improved delivery compared with IRT.[1,2,12] Secondly, the improvement in treatment convenience with once- versus twice-daily dosing means that treatment adherence is improved.[5,11]

There are limited data available regarding long-term outcomes with PRT-based immunosuppressive regimens, with few studies providing information beyond 5-y post-transplantation.[8,13] The randomized, controlled, open-label trial, Adherence Measurement in Stable Renal Transplant Patients Following Conversion From Prograf to Advagraf (ADMIRAD), was conducted in Belgium to compare medication adherence between IRT and PRT in kidney transplant recipients.[11] Among participants who were still receiving treatment after 6 mo, the PRT-based regimen was associated with significantly better medication adherence than IRT (P = 0.0009).[11]

This 10-y, retrospective analysis of data from the ADMIRAD trial aimed to address the lack of long-term outcome data in adult kidney transplant patients receiving either PRT- or IRT-based immunosuppressive therapy.

MATERIAL AND METHODS

Study Design and Patients

This was a retrospective, non-interventional chart review study to examine long-term graft survival in adult kidney transplant patients treated with PRT following conversion from IRT in the ADMIRAD trial (Figure 1).[11] The original ADMIRAD randomized controlled trial was performed between October 2008 and September 2009.[11] For this retrospective data analysis, the start date for data collection was the date of the last transplant before ADMIRAD study enrollment, and the end date was December 31, 2018. Data extraction was performed between December 2019 and January 2021.

The retrospective analysis included all adult kidney transplant patients who were previously enrolled and randomized from 4 of the 6 original centers that participated in the ADMIRAD trial. The remaining 2 sites were unable to participate in the follow-up study. All participants from the original trial who had been treated for at least 3 mo with IRT before randomization, had their first or second renal transplantation between 6 mo and 6 y before inclusion, and had a stable health status at the time of entry into ADMIRAD, were included in the analysis. Long-term data were not included in the retrospective analysis for patients who had no follow-up data, or for whom consent was not granted, either by the study site or the patient. The analysis was conducted in compliance with national and European Union requirements for ensuring the rights of participants in noninterventional studies. Before any patient data were entered into the electronic case report form (eCRF), the written informed consent statement was reviewed and signed by the patient or his/her guardian or legal representative. Data were only extracted for patients who were newly consented; 2 of the 6 original study sites were not used owing to the lack of consent. Written informed consent was not required for patients who were deceased at the time of data extraction.

The original ADMIRAD study was designed and conducted in accordance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference on Harmonization, the local regulatory requirements, and the approval of the local medical ethics committee. Before treatment, all patients signed a written informed consent document.[11] Institutional Review Board/Independent Ethics Committee

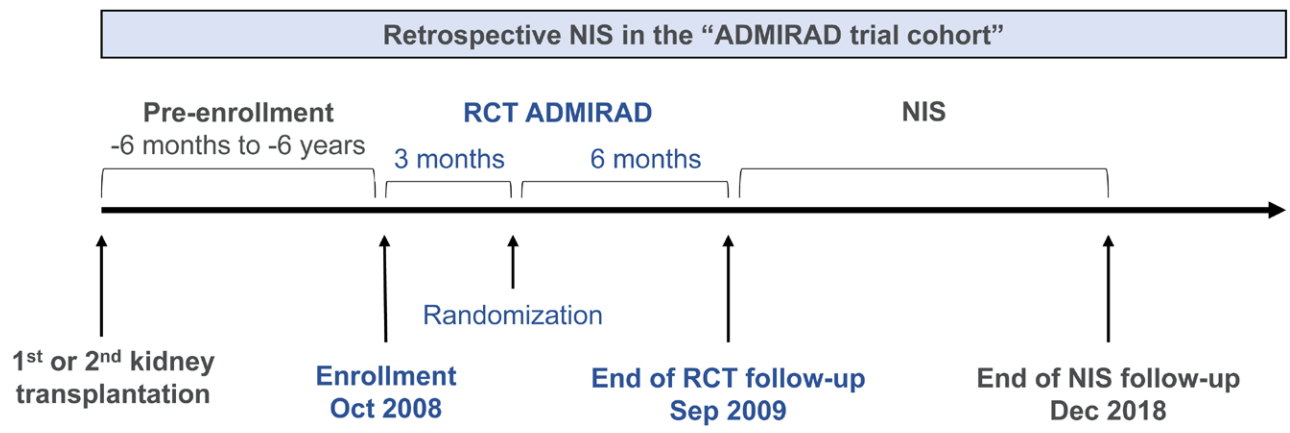


FIGURE 1. Study design. ADMIRAD, Adherence Measurement in Stable Renal Transplant Patients Following Conversion From Prograf to Advagraf; IRT, immediate-release tacrolimus; NIS, noninterventional study; PRT, prolonged-release tacrolimus; RCT, randomized controlled trial.

approval was also obtained for the retrospective chart review study.

Data Collection

Anonymized data from the medical charts of eligible patients were extracted by study personnel using an eCRF.

Treatment

The randomized treatment regimen has been described previously.[11] Briefly, following enrollment, participants continued with twice-daily IRT for 3 mo to provide baseline adherence data. Participants were then randomized 2:1 to receive once-daily oral PRT or twice-daily oral IRT for 6 mo. PRT was available in strengths of 0.5, 1, 3, and 5 mg, and IRT was available in strengths of 0.5, 1, and 5 mg. There were no restrictions on the dose that could be prescribed or switching to other treatments. At the end of the ADMIRAD study, patients were treated as per real-world clinical practice. Data were retrospectively collected at time points every 6 mo (±2 mo) up to a maximum of 10 y (±2 mo) following the end of the study.

Primary Endpoint

The primary aim of the study was to assess the long-term outcomes in patients with kidney transplants who participated in the ADMIRAD study. This was assessed using a composite endpoint consisting of the earliest date of any of the following: graft loss (defined as any of the following events: retransplantation, nephrectomy, death, or return to dialysis); biopsy-confirmed acute rejection; and graft dysfunction (defined as estimated glomerular filtration rate [eGFR] modification of diet in renal disease-4 [MDRD-4] of <40 mL/min/1.73 m^2, or investigator-defined dysfunction, which did not include proteinuria alone). Delayed graft function was not included as a graft dysfunction outcome for the purposes of this composite endpoint. The primary analysis was conducted from time of randomization into the ADMIRAD trial.

Association Between Independent Variables and the Composite Endpoint

Multivariable analysis of independent risk factors that might have an impact on the primary composite endpoint were modeled, adjusting for potential confounders. The final model included serum creatinine at time of randomization (mg/dL), patient age at transplant (years), first implant biopsy finding, panel reactive antibodies (%), patient sex, and donation after circulatory death as explanatory variables.

Secondary Endpoints

Secondary assessments included the following: overall patient survival, course of kidney function (including serum creatinine levels, eGFR [MDRD-4], and creatinine clearance using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] in mL/min/1.73 m^2 equation),[14] and tacrolimus dosing and trough levels. All secondary analyses were conducted from time of randomization into the ADMIRAD trial, except for patient survival, which was defined as time from transplantation to date of death from any cause.

Safety

The study intended to collect adverse drug reactions (ADRs), defined as events with at least a reasonable possibility of being related to the study drug. However, one site reported adverse events (AEs), with no requirement for reporting causal relationship.

Statistical Analysis

Because this was a noninterventional chart review study, no power calculation for sample size estimation was performed. The analysis included patients who had been enrolled in the ADMIRAD study and it was determined that 200 patients would allow the proportion of patients who experienced the primary composite endpoint to be estimated with a precision of ±6.2%. This estimate was based on the half-width of the 95% confidence interval (CI), and as worst case, the true rate of composite endpoint being 25%. The "All patients" cohort included all patients who fulfilled the inclusion criteria subject to data availability and consent, whereas the PRT and IRT cohorts included all patients who were randomized to PRT and IRT, respectively, in the ADMIRAD trial.

Continuous variables were described by either their mean value with SD, or their median value with upper and lower quartiles, extreme values (minimum and maximum), and the number of missing data. Categorical variables were described by the number and percentage of each response and the number of missing data.

The primary endpoint was analyzed using Kaplan–Meier (KM) estimates and 95% CI of the time from randomization into the ADMIRAD to the first incidence of the primary endpoint. Greenwood's formula was used to calculate the standard error of survival function. This analysis provided the rate and 95% CI of the composite endpoint for all years of follow-up.

Time-dependent treatment covariates calculated in the multivariable Cox proportional hazards model were time on PRT since randomization, proportion of time on PRT relative to IRT since randomization, time on IRT before enrollment, time from transplant to randomization, and time from randomization to conversion.

Time to event was presented graphically. The 95% CI values for median time to event were derived from the standard errors and calculated using the Greenwood formula.

For all KM analyses, patients lost to follow up for any reason or alive at study end without occurrence of the endpoint in question were censored on the day of the last available follow-up visit. Patients who died or were otherwise lost between randomization and end of the original study were censored at that date.

Sensitivity analyses were performed on the primary endpoint to test the robustness of the findings. This included providing KM estimates for the composite endpoint but censoring individuals who discontinued using either IRT or PRT at any time point. Also, KM estimates for each clinical endpoint of the composite were analyzed separately; survival estimates are potentially biased because of the competing risks of occurrence of the other primary endpoint components.

Secondary endpoints were analyzed using KM methods (overall survival) or the Cox proportional hazard model (multivariable analysis) and were summarized by descriptive statistics for all other secondary endpoints. Variables in the multivariable analysis were selected using a forward selection model (P value threshold, 0.05); all variables with a P value <0.2 in a univariate analysis were eligible for model entry.

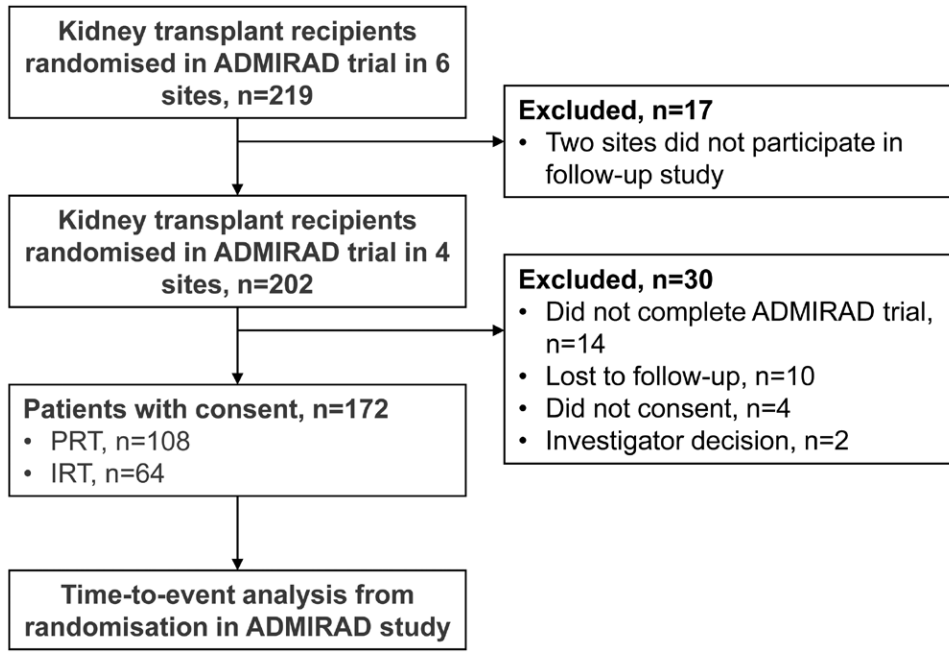


FIGURE 2. Patient flow. ADMIRAD, Adherence Measurement in Stable Renal Transplant Patients Following Conversion From Prograf to Advagraf; IRT, immediate-release tacrolimus; PRT, prolonged-release tacrolimus.

There was no imputation for missing data. In accordance with recommended best practice,[15] to minimize cases of missing data, the eCRF form was designed to be as clear as possible, the data extractors received suitable training, and there was ongoing data monitoring to address any issues in data extraction. Statistical analysis was performed using the software package SAS 9.4.1 or higher.

RESULTS

Patient Characteristics

In total, 172 of 219 patients (78.5%) were included in this retrospective analysis (Figure 2). Seventeen participants were not included because consent to participate in the analysis was not received from 2 of the 6 original study sites, and a further 30 patients were excluded for various reasons (see Figure 2). Of the 172 patients included in the retrospective analysis, 108 patients were randomized to PRT in the original ADMIRAD trial and 64 were randomized to IRT; 123 were alive at time of data extraction. Long-term follow-up data for 10 y were available in 43.6% of all patients included in this analysis.

Patient demographics and clinical characteristics at randomization were generally similar between arms, although there were more males in the IRT than the in PRT group (71.9% and 55.6%, respectively; Table 1). Additionally, a greater proportion of patients had diabetes (includes pre-transplant diabetes and/or new-onset diabetes between transplantation and randomization) in the IRT than in the PRT group (42.2% and 27.8%, respectively; Table 1). This was consistent with higher rates of diabetes in the IRT versus PRT groups at time of transplant (20.3% [13/64] versus 9.3% [10/108], respectively). Post-randomization, a similar proportion of patients in the PRT group (5.6% [6/108]) and IRT group (4.7% [3/64]) developed new-onset diabetes.

The overall donor characteristics from the most recent transplant were similar between the PRT and IRT groups. Most donors were deceased (95% in both groups) with mean ages of 42 (PRT) and 45 y (IRT). There were differences between the PRT and IRT groups in the proportion of standard criteria donors (91.7% versus 84.4%) and donor cytomegalovirus positivity in patients who were cytomegalovirus-positive at follow-up (75% and 60%, respectively; Table 2).

Treatment

Mean time from transplant to randomization was similar in both the PRT (40.5 mo) and the IRT groups (38.1 mo) (Table 3). Almost all patients who converted to PRT (99%) stayed on treatment, with a mean time to discontinuation or loss to follow-up of 91.6 mo. In the IRT group, 41% converted to PRT and had a mean time on PRT from conversion to discontinuation or loss to follow-up of 61.0 mo. Of the patients randomized to convert to PRT, the mean time from transplant to conversion was 41.0 mo in the PRT group and 77.4 mo in the IRT group (Table 3). Mean prescribed PRT and IRT doses remained stable over time (Figure 3). Most patients received concomitant corticosteroids or MMF/mycophenolic acid during the follow-up period (Table 3).

Primary Efficacy Endpoint

The proportion of patients experiencing composite efficacy failure at year 5 was lower in the PRT (25.9% [28/108]) compared with the IRT group (32.8% [21/64]) (Figure 4). The KM estimate of the survival rate without experiencing efficacy failure at year 5 was 0.741 (95% CI: 0.647, 0.813) for patients in the PRT group (n = 80), and 0.667 (95% CI: 0.536, 0.768) for patients in the IRT group (n = 42) (Table 4). The proportion of patients experiencing composite efficacy failure remained lower for PRT than for IRT throughout follow-up (Figure 4; $P = 0.041$).

TABLE 1.

Demographic characteristics

Parameter	PRT (n = 108)	IRT (n = 64)	All (n = 172)
Mean (SD) age, y[a]	51.6 (13.4)	54.4 (13.6)	52.7 (13.5)
Male sex, n (%)[a]	60 (55.6)	46 (71.9)	106 (61.6)
Ethnicity, n (%)[a]			
White or Caucasian	96 (88.9)	54 (84.4)	150 (87.2)
Black/African American/Caribbean	0	5 (7.8)	5 (2.9)
Other	1 (0.9)	0	1 (0.6)
Not available	11 (10.2)	5 (7.8)	16 (9.3)
Mean (SD) weight, kg[a]	73.2 (17.5)	69.6 (14.8)	71.9 (16.6)
Adherence during ADMIRAD trial			
Adherent	50 (46.3)	29 (45.3)	79 (45.9)
Nonadherent	1 (0.9)	0	1 (0.6)
Not available	57 (52.8)	35 (54.7)	92 (53.5)
Comorbidities, n (%)[a]			
None	18 (16.7)	9 (14.1)	27 (15.7)
Diabetes type 1	5 (4.6)	2 (3.1)	7 (4.1)
Diabetes type 2	25 (23.1)	25 (39.1)	50 (29.1)
Posttransplant diabetes[b]	30 (27.8)	27 (42.2)	57 (33.1)
Hypertension	77 (71.3)	46 (71.9)	123 (71.5)
Malignant tumors	5 (4.6)	6 (9.4)	11 (6.4)
Coronary heart disease	10 (9.3)	7 (10.9)	17 (9.9)
Not available	2 (1.9)	0	2 (1.2)
Co-infections, n (%)[c]			
No infections	76 (70.4)	42 (65.6)	118 (68.6)
At least one infection	28 (25.9)	22 (34.4)	50 (29.1)
HBV infection	4 (3.7)	3 (4.7)	7 (4.1)
HCV infection	1 (0.9)	2 (3.1)	3 (1.7)
CMV infection	24 (22.2)	18 (28.1)	42 (24.4)
Not available	1 (0.9)	0	1 (0.6)
Missing	4 (3.7)		4 (2.3)
First transplant, n (%)	94 (87.0)	54 (84.4)	148 (86.0)
Mean (SD) PRA, %[d]	3.9 (15.9)[a]	4.0 (13.3)[a]	4.0 (15.0)[a]
HLA mismatch with donor, n (%)			
Yes	94 (87.0)	57 (89.1)	151 (87.8)
No	14 (13.0)	6 (9.4)	20 (11.6)
Not available	0	1 (1.6)	1 (0.6)
Number of HLA mismatches with donor, n (%)			
0	14 (13.0)	6 (9.4)	20 (11.6)
1	10 (9.3)	5 (7.8)	15 (8.7)
2	26 (24.1)	13 (20.3)	39 (22.7)
>2	58 (53.7)	39 (60.9)	97 (56.4)
Not available	0	1 (1.6)	1 (0.6)
Patient receiving antibody induction therapy at time of transplant, n (%)			
Yes	54 (50.0)	29 (45.3)	83 (48.3)
No	54 (50.0)	34 (53.1)	88 (51.2)
Not available	0	1 (1.6)	1 (0.6)
Patient receiving ACE inhibitors at time of transplant, n (%)			
Yes	27 (25.0)	19 (29.7)	46 (26.7)
No	73 (67.6)	44 (68.8)	117 (68.0)
Not available	8 (7.4)	1 (1.6)	9 (5.2)

[a] Data collected at randomization into ADMIRAD trial.
[b] PTDM includes pretransplant diabetes and/or new-onset diabetes between transplantation and randomization.
[c] Data collected at most recent transplantation.
[d] PRT, n = 87; IRT, n = 51; all patients, n = 138.
ACE, angiotensin-converting enzyme; ADMIRAD, Adherence Measurement in Stable Renal Transplant Patients Following Conversion From Prograf to Advagraf; CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; IRT, immediate-release tacrolimus; PRA, panel reactive antibody; PRT, prolonged-release tacrolimus; PTDM, posttransplant diabetes.

Multivariable Analysis of Independent and Time-dependent Variables

A multivariable Cox proportional hazards model identified 3 covariates associated significantly with an increased risk of efficacy failure: (1) serum creatinine at time of randomization (hazard ratio [HR] 2.146; 95% CI: 1.531, 3.010; $P < 0.001$) , (2) patient age at transplant (HR 1.038; 95% CI [1.015, 1.061]; p=0.001), and (3) female versus male sex (HR 1.858;

TABLE 2.

Donor characteristics at the most recent transplant

Parameter	PRT (n = 108)	IRT (n = 64)	All (n = 172)
Donor vital status, n (%)			
Living	5 (4.6)	3 (4.7)	8 (4.7)
Deceased	103 (95.4)	61 (95.3)	164 (95.3)
Mean (SD) donor age, y	42.0 (13.3)	45.2 (13.8)	43.2 (13.5)
Donor quality, n (%)			
SCD	99 (91.7)	54 (84.4)	153 (89.0)
ECD	9 (8.3)	9 (14.1)	18 (10.5)
Not available	0	1 (1.6)	1 (0.6)
Donation after circulatory death, n (%)			
Yes	20 (18.5)	9 (14.1)	29 (16.9)
No	87 (80.6)	55 (85.9)	142 (82.6)
Not available	1 (0.9)	0	1 (0.6)
Donor CMV status (in patients CMV positive at follow-up), n (%)			
Positive	6 (75.0)	3 (60.0)	9 (69.2)
Negative	1 (12.5)	2 (40.0)	3 (23.1)
Not available	1 (12.5)	0	1 (7.7)

CMV, cytomegalovirus; ECD, expanded criteria donor; IRT, immediate-release tacrolimus; PRT, prolonged-release tacrolimus; SCD, standard criteria donor.

95% CI: 1.077, 3.203; $P = 0.026$). Time-dependent treatment covariates had no statistically significant association with an increased risk of efficacy failure, including the proportion of time on PRT relative to IRT since randomization (HR 0.520; 95% CI: 0.284, 0.950; $P = 0.033$).

Sensitivity Analyses

Censoring individuals at discontinuation of either PRT or IRT resulted in findings similar to the primary analysis. Five-year survival rates without reaching the composite endpoint were 0.743 (95% CI: 0.646, 0.818) for the PRT group and 0.655 (95% CI: 0.496, 0.775) for the IRT group. PRT demonstrated improved survival over IRT over the whole follow-up period ($P = 0.018$) (Figure 5). Sensitivity analyses of the primary endpoint were also performed on the individual components of the composite endpoint. The KM analyses of graft loss from randomization showed improved survival probability with PRT versus IRT (eg, a 5-y survival rate of 0.889 [95% CI: 0.813, 0.935] with PRT and 0.792 [95% CI: 0.669, 0.874] with IRT). The difference was smaller, however, when patients were censored at their death date, particularly during earlier years of follow-up (Figure 5).

Patients Converting to PRT Versus Remaining on IRT

Twenty-six patients randomized to IRT converted to PRT during follow-up, with a median time of 66.43 mo (Q1–Q3: 50.96–103.0) from transplant to conversion. Of the PRT cohort, 1% converted to another immunosuppressive therapy. The proportion of patients with composite efficacy failure was lower for patients randomized to and receiving PRT compared with those who were randomized to and maintained on IRT (did not convert to PRT, n = 38; $P = 0.001$, Figure 6). At year 5, the KM estimate of the survival rate without experiencing efficacy failure was 0.738 (95% CI: 0.644, 0.811) for PRT patients and 0.541 (95% CI: 0.369, 0.684) for IRT patients not converting to PRT.

TABLE 3.

Treatment during follow-up

Parameter	PRT (n = 108)	IRT (n = 64)	All (n = 172)
Time since transplant on IRT, mo, n			
n	108 (100.0)	64 (100.0)	172 (100.0)
Mean (SD)	46.2 (33.7)	95.9 (41.8)	64.7 (44.0)
Median (min, max)	37.4 (7.3, 171.8)	97.1 (17.7, 191.6)	52.5 (7.3, 191.6)
Q1, Q3	23.4, 57.8	62.2, 127.1	29.9, 91.6
Time from transplant to conversion to PRT, mo			
n (%)	107 (99.1)	26 (40.6)	133 (77.3)
Mean (SD)	41.0 (24.2)	77.4 (38.5)	48.11 (31.0)
Median (min, max)	35.9 (7.3, 171.8)	66.4 (17.7, 173.9)	39.2 (7.3, 173.9)
Q1, Q3	23.3, 54.6	51.0 103.0	25.8, 59.4
Time on PRT from conversion to discontinuation or loss to follow-up, mo			
n (%)	107 (99.1)	26 (40.6)	133 (77.3)
Mean (SD)	91.6 (34.7)	61.0 (36.7)	85.6 (37.1)
Median (min, max)	110.9 (1.6, 118.7)	50.8 (1.0, 112.5)	107.1 (1.0, 118.7)
Q1, Q3	79.2, 114.3	30.1, 101.5	63.0, 113.7
Time from randomization to conversion to PRT, mo			
n (%)	107 (99.1)	26 (40.3)	133 (77.3)
Mean (SD)	0.2 (1.2)	39.1 (35.0)	7.8 (21.8)
Median (min, max)	0.0 (-1.0, 12.4)	19.4 (-0.1, 94.6)	0.0 (-1.0, 94.6)
Q1, Q3	0.0, 0.03	7.9, 73.40	0.0, 0.30
Time from transplant to randomization, mo			
n (%)	108 (100.0)	64 (100.0)	172 (100.0)
Mean (SD)	40.5 (24.3)	38.1 (20.1)	39.6 (22.8)
Median (min, max)	35.9 (7.3, 171.8)	35.0 (9.0, 83.9)	35.9 (7.3, 171.8)
Q1, Q3	22.8, 53.7	21.5, 50.7	22.1, 52.7
Concomitant immunosuppressants used after randomization, n (%)[a]			
MMF or MPA	103 (95.4)	60 (93.8)	163 (94.8)
Everolimus or sirolimus	15 (13.9)	4 (6.3)	19 (11.0)
Corticosteroids	107 (99.1)	64 (100.0)	171 (99.4)
Azathioprine	8 (7.4)	6 (9.4)	14 (8.1)
Belatacept	1 (0.9)	1 (1.6)	2 (1.2)

[a] Immunosuppressants used in addition to tacrolimus at any time the during follow-up period.
IRT, immediate-release tacrolimus; MMF, mycophenolate mofetil; MPA, mycophenolic acid; PRT, prolonged-release tacrolimus.

Secondary Efficacy Endpoints

Overall Survival

Overall survival from the time of last transplant was 0.981

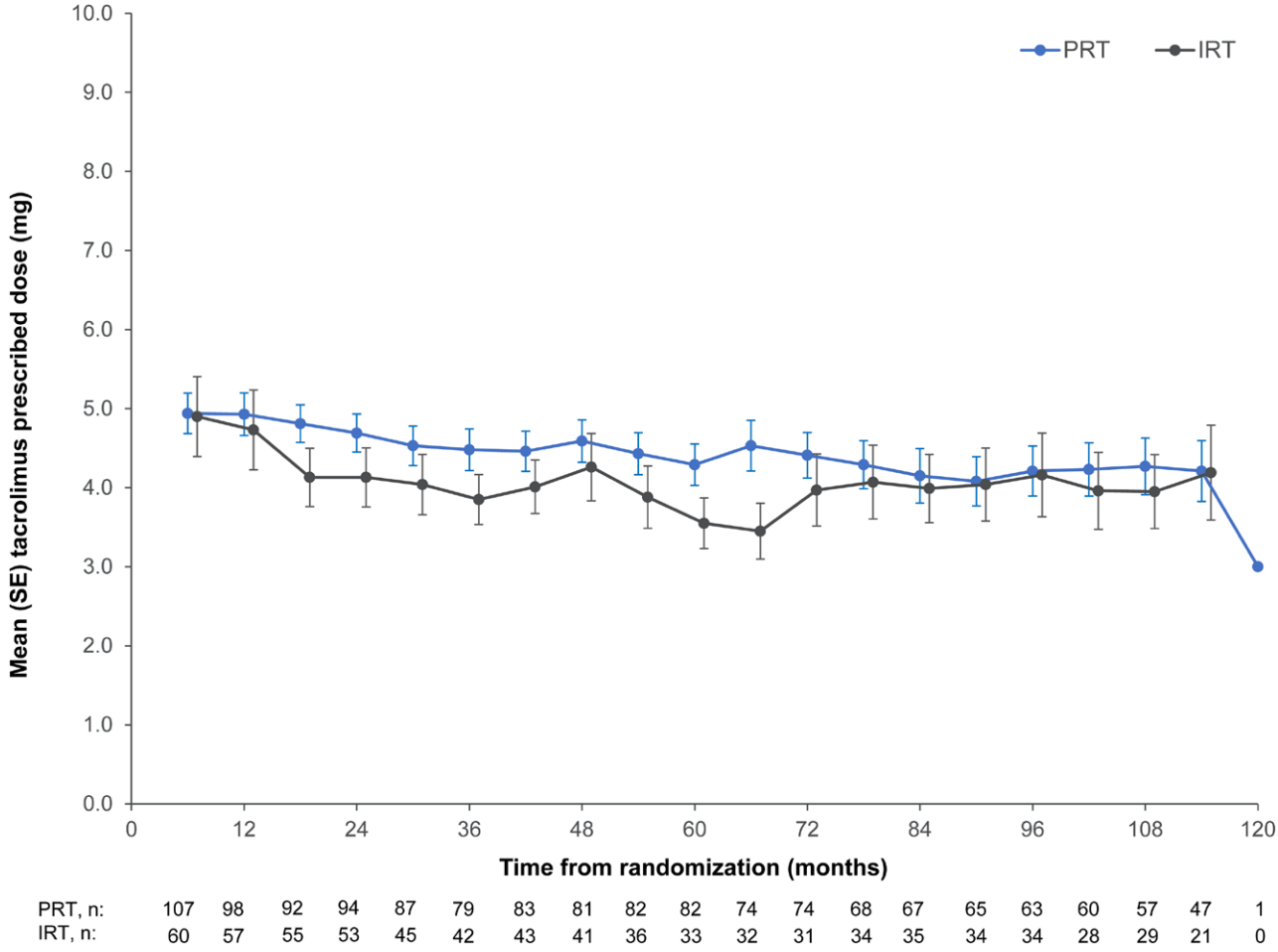


FIGURE 3. Mean daily prescribed tacrolimus dose. IRT, immediate-release tacrolimus; PRT, prolonged-release tacrolimus; SE, standard error.

(95% CI: 0.928, 0.995) and 0.880 (95% CI: 0.802, 0.928) at 5 and 10 y with PRT, and 0.953 (95% CI: 0.862, 0.985) and 0.750 (95% CI: 0.625, 0.839) at 5 and 10 y with IRT. The improved survival with PRT versus IRT was observed throughout the follow-up period (P = 0.008) but became more pronounced after year 8 (Figure 7).

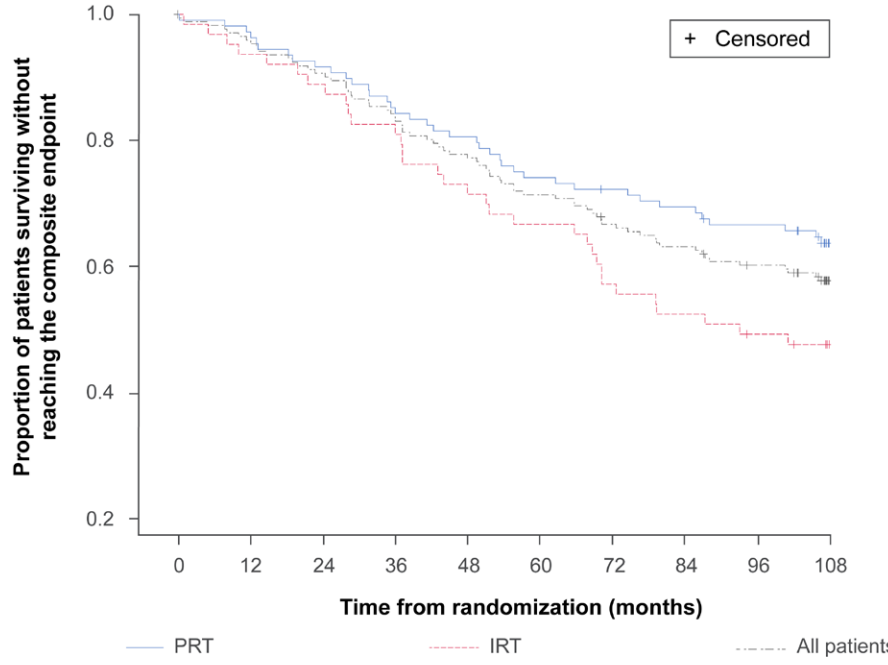
Kidney function as estimated by serum creatinine-based equations (MDRD-4 or CKD-EPI) was stable throughout treatment. From baseline (enrollment into ADMIRAD study) to 6 mo following randomization, median creatinine values ranged between 1.28 and 1.35 mg/dL for PRT and 1.52 and 1.57 mg/dL for IRT. Following the end of the original 6-mo ADMIRAD study period, median creatinine values were 1.38 and 1.37 mg/dL with PRT and 1.48 and 1.50 mg/dL with IRT at the 5- and 9-y follow-up visits (before a marked drop in patient numbers, Figure 8). For eGFR over the same time-points (baseline to year 5 or 9 of follow-up), median values were 50.45 and 48.10 mL/min/1.73 m^2 for PRT and 44.60 and 46.80 mL/min/1.73 m^2 for IRT. CKD-EPI values were in a similar range as the eGFR values and remained stable over the study and follow-up periods.

Safety and Tolerability

Of 172 participants across the four study sites, 151 (87.79%) reported ≥1 ADR (or AE) during the study period. Safety data collected upon retrospective review were generally consistent with the known safety profile of the product. However, inconsistency in the collection of AEs and ADRs in this study makes any interpretation of safety information difficult. BK virus nephropathy was reported as a new-onset disease after randomization in 11 patients (10.2%) receiving PRT and 7 patients (10.9%) receiving IRT.

Tacrolimus Dose and Trough Levels

Prescribed tacrolimus doses remained relatively constant over time and were similar for PRT and IRT (Figure 3). During the original ADMIRAD trial, mean tacrolimus trough levels were stable from baseline, randomization, and follow-up at months 3 and 6 with PRT (range, 7.18–7.87 ng/mL) and IRT (range, 6.84–8.31 ng/mL) (Figure 9). From the end of the ADMIRAD trial to the end of study follow-up (month 120 for PRT and month 114 for IRT), mean trough levels ranged between 4.40 and 8.34 ng/mL with PRT and 5.65 and 8.03 ng/mL with IRT. The low values in each group were from the final data collection time point, for which there were only 2 of 108 patients in the PRT group at 120 wks poststudy and 21 of 61 in the IRT group at 114 wks poststudy. The mean (SD) intraindividual coefficients of variation in tacrolimus trough levels, calculated across the time from the end of the ADMIRAD trial follow-up to 60 mo after randomization,



PRT, n	108	105	99	92	87	80	77	74	70	60
IRT, n	64	59	56	52	46	42	36	33	30	26
All patients, n	172	164	155	144	133	122	113	107	100	86

FIGURE 4. KM plot of time from randomization to efficacy failure (composite endpoint). Plot truncated at 108 mo, that is, the follow-up period achieved by a reasonable proportion of patients, as per recommendations.[16] IRT, immediate-release tacrolimus; KM, Kaplan–Meier; PRT, prolonged-release tacrolimus.

were 24.28% (11.42) and 29.65% (15.30) in the PRT and IRT groups, respectively.

DISCUSSION

This long-term retrospective analysis of data from the ADMIRAD trial in Belgium addresses the lack of long-term outcome data in adult kidney transplant patients receiving tacrolimus-based immunosuppressive therapy. This analysis indicates that PRT treatment was associated with a decreased likelihood of experiencing kidney graft failure over the long-term, up to 10 y, compared with IRT. Importantly, survival rates were higher among those randomized to PRT versus IRT in the original ADMIRAD study, particularly in later years of follow-up. Additionally, this analysis indicated that the long-term safety profile of tacrolimus over 10 y is consistent with the well-characterized safety profile of tacrolimus in terms of the overall proportion of participants experiencing ADRs and AEs.

At 5 y of follow-up, 74.1% of individuals in the PRT group had kidney allograft survival based on the composite efficacy endpoint. This level of kidney allograft survival is comparable to the 4-y kidney allograft survival rates reported previously with PRT in combination with MMF (82.7%, n = 113).[13] The current data are also consistent with the 5-y acute rejection-free survival rate of 77.4% (n = 270) with PRT plus MMF in the long-term follow-up of the ADHERE study.[8] In a smaller prospective observational study of tacrolimus plus MMF (n = 45) conducted by Chhabra et al, kidney allograft survival was 91% at 8.5 y.[17] The lower graft survival rate in this study versus data from the Chhabra study may reflect differences in study design. In contrast to the composite endpoint, which included graft loss, acute rejection and graft dysfunction, used in the current study, the graft survival measure used in the Chhabra study was biopsy-proven rejection.[17] Additionally, the original study for the Chhabra long-term follow-up described their transplant population as "low risk,"[18] and included younger patients compared to the current study (42–46 y old versus 51–54 y old). There was also a substantially lower proportion of grafts from deceased donors (27%–33% versus 95% in the current study).[17,18] The incidence of BK virus nephropathy was similar in the PRT and IRT groups and likely did not affect graft outcome.

TABLE 4.

KM estimate of survival rate for efficacy failure (95% CIs) for all years

	KM estimate of rate of efficacy (95% CI)		
Year of event	Randomized to PRT cohort (n = 108)	Randomized to IRT cohort (n = 64)	All patient (n = 172)
1	0.972 (0.916; 0.991)	0.937 (0.840; 0.976)	0.959 (0.916; 0.980)
2	0.917 (0.846; 0.956)	0.889 (0.781; 0.945)	0.906 (0.852; 0.942)
3	0.852 (0.770; 0.906)	0.825 (0.707; 0.899)	0.842 (0.778; 0.889)
4	0.806 (0.718; 0.869)	0.730 (0.602; 0.823)	0.778 (0.708; 0.833)
5	0.741 (0.647; 0.813)	0.667 (0.536; 0.768)	0.713 (0.639; 0.775)
6	0.722 (0.627; 0.797)	0.571 (0.440; 0.683)	0.667 (0.590; 0.732)
7	0.694 (0.598; 0.772)	0.524 (0.394; 0.638)	0.631 (0.554; 0.699)
8	0.666 (0.568; 0.746)	0.492 (0.364; 0.608)	0.602 (0.524; 0.671)
9	0.637 (0.538; 0.720)	0.476 (0.349; 0.592)	0.577 (0.499; 0.647)

CI, confidence interval; IRT, immediate-release tacrolimus; KM, Kaplan–Meier; PRT, prolonged-release tacrolimus.

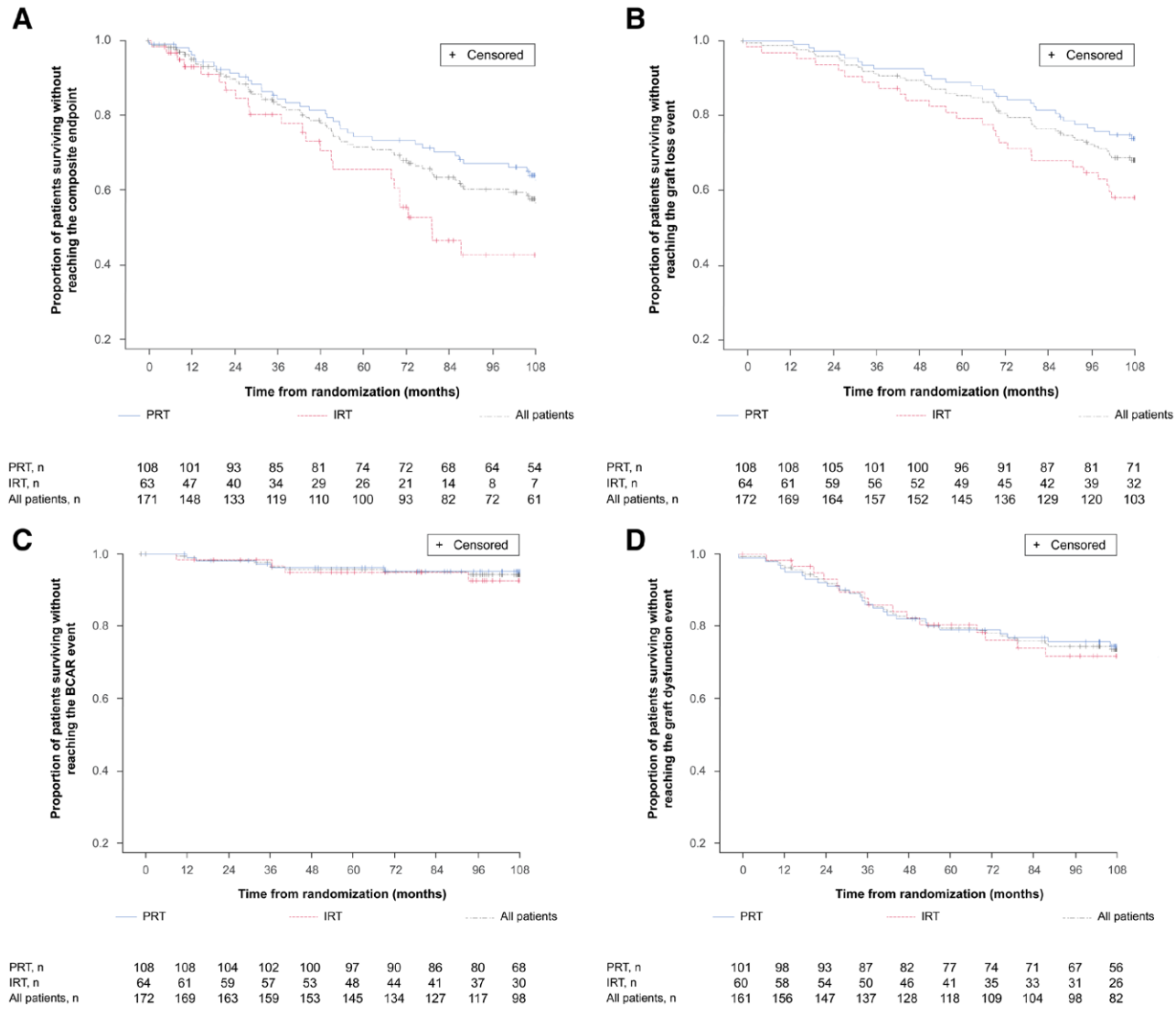
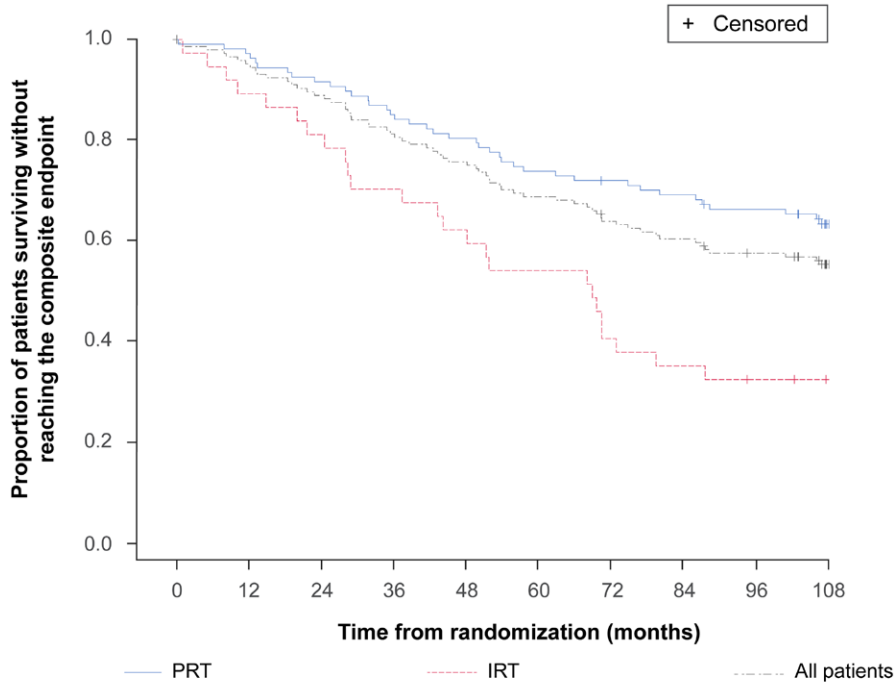


FIGURE 5. Sensitivity Analysis: KM plots of the individual components of the primary composite endpoint from time of randomization. A, Censored discontinuation of PRT or IRT. B, Time to graft loss. C, Time to BCAR. D, Time to graft dysfunction. Plot truncated at 108 mo, that is, the follow-up period achieved by a reasonable proportion of patients, as per recommendations.[16] BCAR, biopsy-confirmed acute rejection; IRT, immediate-release tacrolimus; KM, Kaplan–Meier; PRT, prolonged-release tacrolimus.

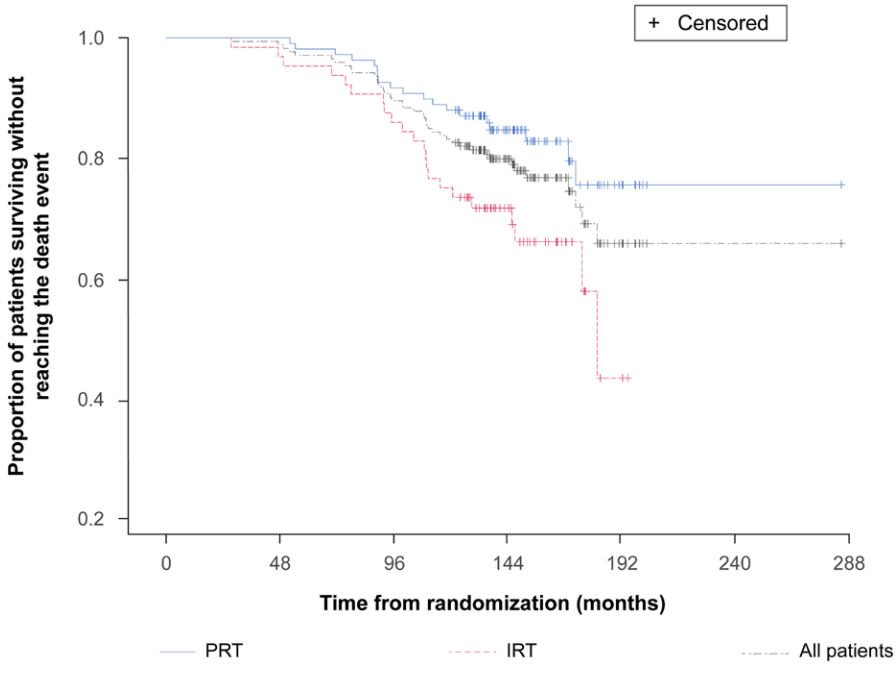
This study further extends the follow-up period for PRT immunosuppression following conversion from IRT after kidney allograft and provides support for the long-term efficacy of PRT up to 10 y posttransplant. The data on graft survival were supported by the observed long-term stable kidney function. At 5 and 10 y, overall survival was 98% and 88% with PRT, which is consistent with previously reported 4- and 5-y overall survival rates of 91.2% and 90.8%, respectively, with PRT plus MMF.[8,13] The smaller prospective observational study of tacrolimus plus MMF (n = 45) reported 100% overall survival at 8.5 y; as discussed previously, however, the demographic and clinical characteristics of that population were potentially more favorable for better long-term survival than those in the current analysis.[17,18] It should be noted that there was a higher proportion of diabetes in the IRT group at randomization into the ADMIRAD trial, which could possibly have contributed to the difference in outcomes between IRT and PRT.

As expected, trough tacrolimus levels decreased gradually throughout 10 y of follow-up in both treatment groups, although there appeared to be more variability in trough values with IRT versus PRT treatment. This reflects findings from previous studies, which showed improvements in intrapatient coefficient of variability for tacrolimus exposure from 14.1% to 10.9% ($P = 0.012$),[2] and from 14.0% to 8.5% ($P < 0.05$) with a switch from twice- to once-daily tacrolimus dosing.[1] Trough tacrolimus levels provide a good surrogate marker for overall tacrolimus exposure.[2] As tacrolimus needs to be maintained within a tight therapeutic range to balance the potential for allograft rejection at lower levels and additional toxicity at higher levels,[1] the more predictable pharmacokinetics and improved trough levels with PRT may partially explain the improved long-term treatment outcomes observed with the PRT versus IRT in this study. Thus, composite efficacy failure at year 5 was significantly higher in those participants randomized to IRT who did not convert to PRT versus those who received PRT. Of note, because of the retrospective nature of this analysis, this finding may be subject to bias as those not converting from IRT to PRT may have been prevented from doing so owing to a higher frequency of complications.



PRT, n	107	104	98	91	86	79	76	73	69	59
IRT, n	38	33	30	26	23	20	15	13	11	9
All patients, n	145	137	128	117	109	99	91	86	80	68

FIGURE 6. KM plot of time from randomization to efficacy failure for those randomized to PRT or randomized to IRT and did not convert to PRT (composite endpoint). Plot truncated at 108 mo, that is, the follow-up period achieved by a reasonable proportion of patients, as per recommendations.[16] IRT, immediate-release tacrolimus; KM, Kaplan–Meier; PRT, prolonged-release tacrolimus.



PRT, n	108	108	99	61	9	1	0
IRT, n	64	62	55	28	2	0	
All patients, n	172	170	154	89	11	1	0

FIGURE 7. Overall survival from time of most recent transplant. IRT, immediate-release tacrolimus; PRT, prolonged-release tacrolimus.

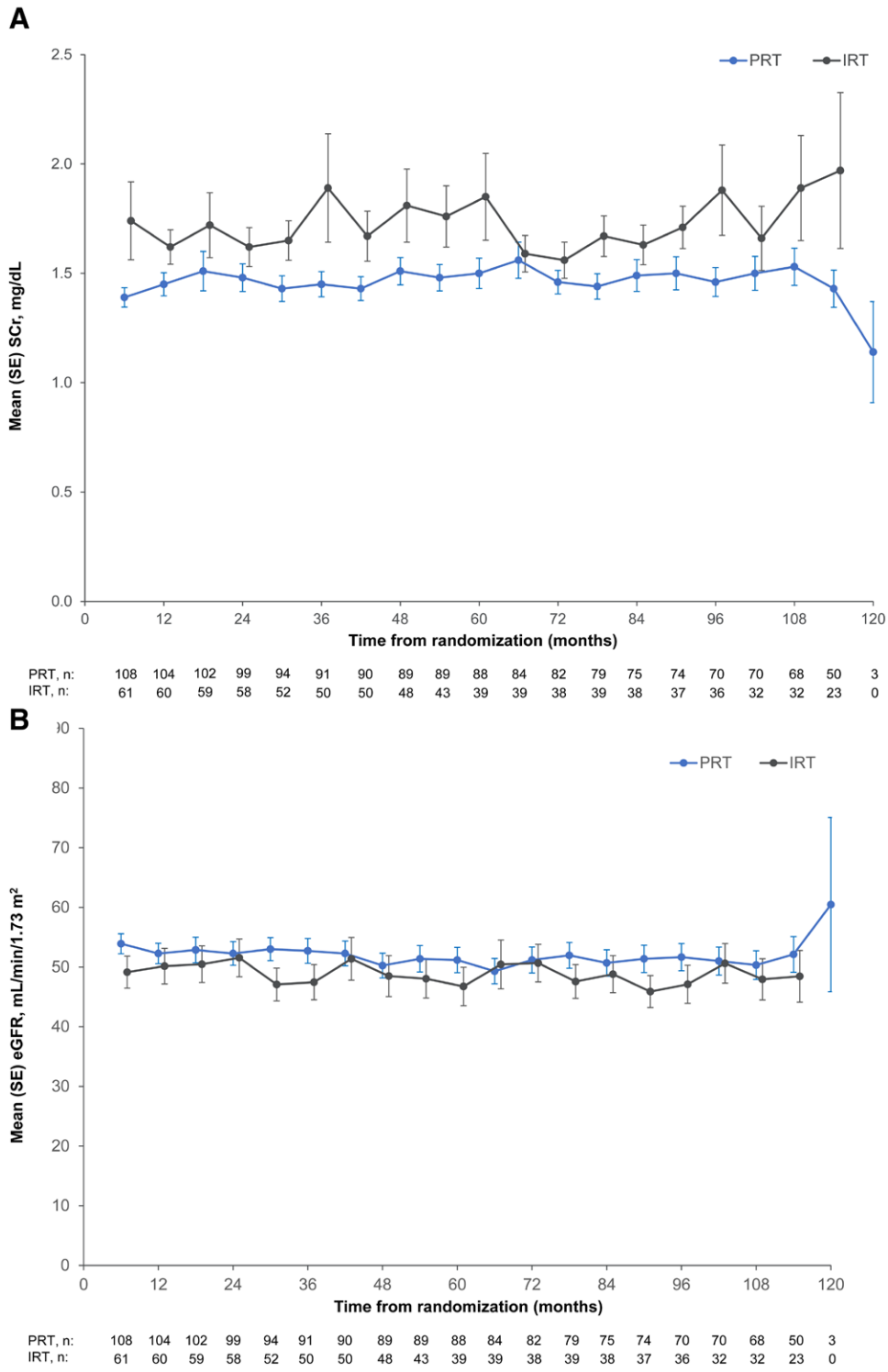


FIGURE 8. Kidney function. A, Serum creatinine. B, eGFR (MDRD-4). eGFR, estimated glomerular filtration rate; IRT, immediate-release tacrolimus; MDRD-4, modification of diet in renal disease-4; PRT, prolonged-release tacrolimus; sCR, serum creatinine; SE, standard error.

Interestingly, only 1% of patients on PRT changed to another immunosuppressive therapy during the study.

Owing to a misunderstanding regarding which safety data to record, 1 site recorded all AEs, for which no causal link to study drug was required, and the other 3 sites recorded ADRs, which required investigators to determine that a link to study drug was possible. In general, the safety data appeared to be consistent with the well-established safety profile of tacrolimus formulations.

The improved outcomes with PRT versus IRT may also, in part, reflect better adherence to the once-daily versus twice-daily formulation. Although the impact of medication nonadherence on long-term outcomes could not be assessed in this study because of limited data, other studies have indicated clear improvements in adherence after conversion from twice- to once-daily tacrolimus.[5,19-22] In the original ADMIRAD study, numerically more participants in the PRT group than

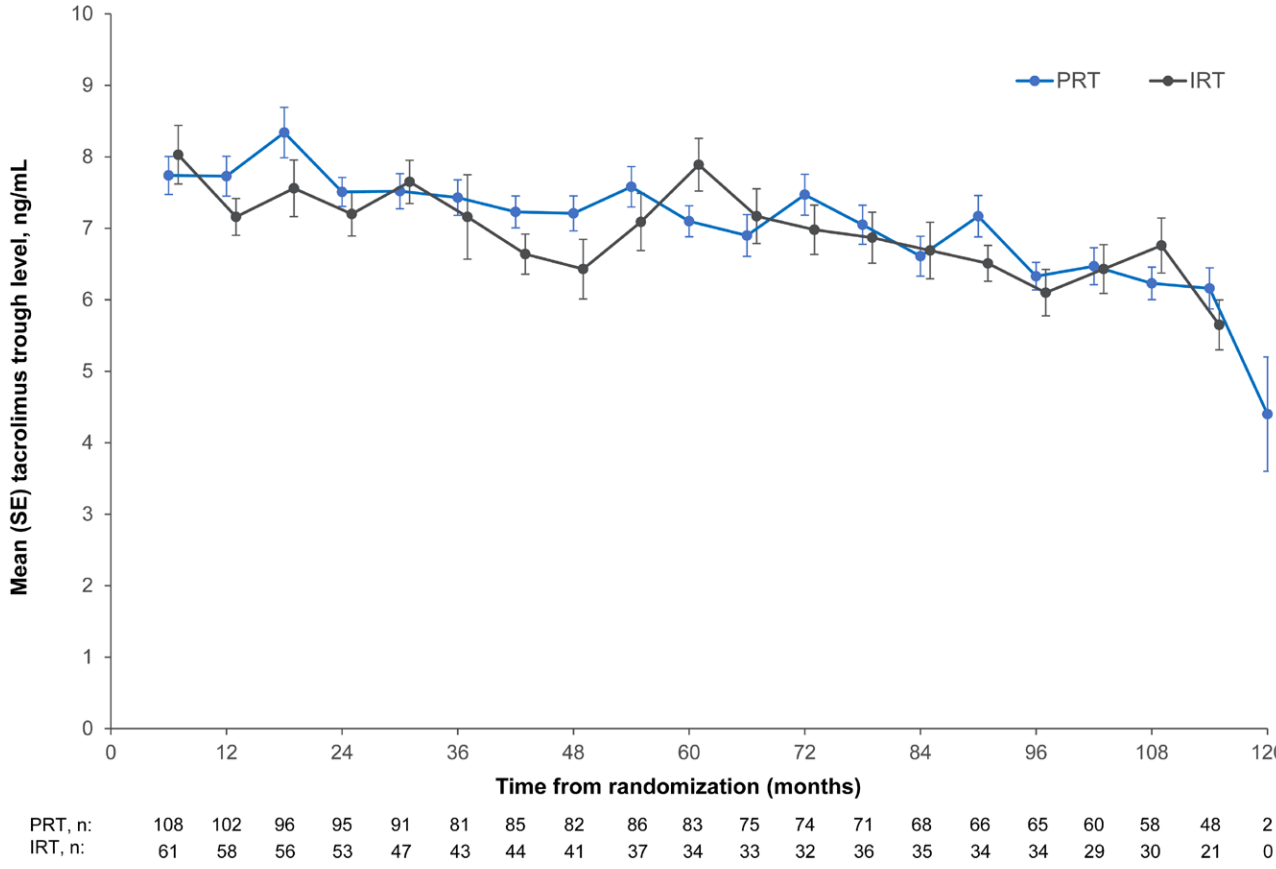


FIGURE 9. Tacrolimus trough levels. IRT, immediate-release tacrolimus; PRT, prolonged-release tacrolimus; SE, standard error.

the IRT group (81.5% versus 71.9%, respectively) persisted with treatment at 6 mo ($P = 0.0824$).[11] In those who persisted with treatment, statistically significantly more patients in the PRT versus IRT group (88.2% versus 78.8%, respectively) took the correct number of daily doses ($P = 0.0009$).[11] Among those receiving twice-daily doses, an average of 11.7% missed their morning dose and 14.2% missed their evening dose over each week.[11] It is important to note, however, that the data on missed doses for the once-daily dose were not reported in the ADMIRAD study.[11] The results of the ADMIRAD study were mirrored in a prospective cohort study (n = 75) that showed improved treatment convenience and self-reported adherence (94.6% and 79.7%) with once- versus twice-daily tacrolimus.[5]

A key strength of this analysis is that it helps to address the evidence gap in long-term graft and patient survival data for adult kidney transplant recipients receiving tacrolimus-based immunosuppression. Data were available for more than 78% of patients from the initial study; furthermore, data for long-term follow-up (10 y since enrollment) were available for almost half of all patients (75/172). A potential limitation of this study is that participants from only 4 of the original 6 sites involved in the ADMIRAD trial were able to participate in the follow-up analysis. Also, patients who discontinued in the original trial were not eligible for this analysis, which may have introduced selection bias owing to the exclusion of patients at a higher risk of ADRs. Additionally, although the original ADMIRAD study was a randomized trial, this retrospective assessment was based on real-world data in a noninterventional, open-label setting. It should also be noted that, owing to pharmacokinetic differences, the outcomes with PRT in this analysis are not generalizable to other once-daily formulations.[23] Although the lack of detailed data on drug accountability (owing to the retrospective nature of the methodology) prevented the assessment of long-term adherence, the stability of tacrolimus dose and trough levels over an extended period in a real-world setting is suggestive of good long-term adherence to treatment. The randomization process used in this study may also act as a source of bias between patient cohorts. Following randomization, more patients in the IRT cohort had diabetes, expanded criteria donors, >1 previous transplantations, >2 HLA-mismatches, and were older (>65 y) versus the PRT cohort. Subsequently, differences can also be observed in our estimations of kidney function (primarily serum creatinine and eGFR) for patients at baseline and at randomization.

In conclusion, this analysis indicates that for up to 10 y PRT is associated with greater long-term kidney allograft survival and higher overall patient survival than IRT. Kidney function remained stable with both PRT and IRT for up to 10 y. Thus, transferring adult kidney transplant recipients from twice- to once-daily tacrolimus-based immunosuppression is a reliable clinical option with consistent efficacy results including stable long-term renal function. Future studies should aim to improve the efficiency of the randomization process which complicates the interpretation of these results.

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