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Renal Function and Patient-Reported Outcomes in Stable Kidney Transplant Patients Following Conversion From Twice-Daily Immediate-Release Tacrolimus to Once-Daily Prolonged-Release Tacrolimus: A 12-Month Observational Study in Routine Clinical Practice in Germany (ADAGIO)

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ABSTRACT

Introduction. This 12-month, noninterventional study on routine clinical practice in Germany evaluated renal function in stable kidney transplant recipients converted from immediate-release tacrolimus (IR-T) to prolonged-release tacrolimus (PR-T).

Methods. Renal function was assessed in 183 patients by estimated glomerular filtration rate using the modification of diet in renal disease-4 formula. Self-reported gastrointestinal health-related quality of life, adherence, satisfaction with PR-T, suspected rejection episodes, and safety were also assessed at conversion and at 3, 6, and 12 months.

Results. Conversion from IR-T to PR-T resulted in stable kidney function over 12 months, with a difference in estimated glomerular filtration rate between the first and final visits of 0.1 mL/min/1.73 m^2 (95% confidence interval, −1.6, 1.8). Eight patients experienced an acute

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rejection episode (4.4%). At each assessment, gastrointestinal health-related quality of life was low and adherence was high. Most patients reported that they were very satisfied (69.8%) or satisfied (28.1%) with PR-T at the final visit. Among patients reporting a preference, 78.4% preferred PR-T, 2.2% preferred IR-T, and 19.4% reported no preference. The safety profile of PR-T was consistent with that previously described.

Conclusion. Conversion of stable kidney transplant recipients from IR-T to PR-T provided stable kidney and graft function over 12 months (Verband Forschender Arzneimittelhersteller–registered study: NIS ADV-02).

TACROLIMUS is the most widely used core component of immunosuppressive therapy in kidney transplant recipients. It is usually combined with mycophenolate mofetil and/or corticosteroids as a dual- or triple-therapy regimen [1]. Although this triple-therapy combination has been effective in reducing the incidence of acute rejection at 1 year post kidney transplant to less than 10%, long-term graft and patient outcomes remain a challenge [2,3]. Risk factors that have been identified as contributing to graft rejection include intrapatient variability in tacrolimus trough levels and nonadherence to the immunosuppressant regimen [4].

Contemporary oral formulations of tacrolimus approved in many countries worldwide for the prevention of graft rejection in kidney transplant recipients include twice-daily immediate-release (IR-T) and once-daily prolonged-release (PR-T) formulations [5,6]. Both formulations are effective immunosuppressant treatments and have well-established safety profiles in kidney transplant recipients [5–8]. For example, a European study of 976 kidney transplant recipients showed PR-T-based immunosuppression (0.2 mg/kg/day), without induction, to be noninferior to IR-T (0.2 mg/kg/day), with acute rejection rates low and comparable for both formulations [8]. However, significant improvements in renal graft function after conversion from IR-T to PR-T have been reported in several studies [9–11]. After conversion, kidney transplant recipients are reported to have stable kidney function in the medium term [12].

The clinical benefits of PR-T compared to IR-T may be associated with the intrinsic pharmacokinetic properties of PR-T that help reduce intra- and interpatient variability, as well as improved adherence to the simplified once-daily regimen [13–15].

We conducted a 12-month, noninterventional study in stable kidney transplant recipients, with the aim of evaluating renal function in patients converted from IR-T to PR-T in routine clinical practice in Germany.

PATIENTS AND METHODS

Design and Patients

This was a national multicenter 12-month noninterventional study conducted at 15 hospitals and 1 office-based dialysis practice in Germany (ADAGIO) between December 2013 and August 2017. The study was registered with the German Association of Research-Based Pharmaceutical Companies for noninterventional studies (Verband Forschender Arzneimittelhersteller) under the study number NIS ADV-02. All data reported in this study originated from routine diagnostic and therapeutic procedures; no additional diagnostic or therapeutic interventions were permitted. The study was conducted in accordance with the Declaration of Helsinki and the International Council of Harmonisation Good Clinical Practice guidelines. In accordance with German regulations, the independent ethics committee at the principal investigator's institution (Medizinische Klinik und Poliklinik III, Dresden, Germany) granted approval before initiation of the study. Further ethics submissions were made at additional centers if required. All patients provided informed written consent with regard to collection, protection and analysis of their clinical data.

Eligible patients were adult (≥18 years) kidney transplant recipients who had received a renal graft ≥9 months previously and whose physician had independently chosen to convert them from IR-T (Prograf, Astellas Pharma GmbH, Munich, Germany) to PR-T (Advagraf, Astellas Pharma Europe BV, Leiden, Netherlands).

Assessments

The study period included 4 study visits. Visit 1 (baseline visit) took place at the time of treatment start with PR-T; visits 2, 3, and 4 (final visit) occurred 3, 6, and 12 months after visit 1, respectively. At visit 1, prior to switching to PR-T, trough levels and dose of IR-T were determined, and retrospective selected data were documented (including ≥3 trough levels and doses).

Immunosuppressive Treatment

Patients were converted from IR-T to PR-T according to standard practice at each participating center and were subsequently maintained on PR-T, which was administered once daily in the morning. Following conversion, tacrolimus trough levels were monitored and, if necessary, dose adjustments were made to maintain similar systemic exposure on an individual patient basis according to standard center practice. Tacrolimus trough levels were generally expected to be within the usual maintenance therapeutic range according to the Advagraf SmPC [16], unless there was a medical need for other tacrolimus trough levels. Concomitant immunosuppressant medications were administered as recommended in the relevant prescribing information. Medication was provided through insurance at no cost to the patient.

Patients recorded details of PR-T dose changes, tacrolimus blood trough levels, and concomitant immunosuppressive therapy dose changes in a diary. At each visit, all data recorded in the diary were checked and verified against the patient record by the investigator or his or her designee and were then transcribed into an electronic case report form (eCRF). Any dose changes or tacrolimus trough levels that had not been recorded by the patient in the diary were added to the eCRF by the investigator at this time. Data relating to

concomitant immunosuppressive therapy were not transferred from the patient diary but were transcribed directly from the patient record to the eCRF.

The time to tacrolimus steady state was defined as the number of days to achieve 2 consecutive target trough levels if the time between measurements was ≤2 days or 3 consecutive target trough levels if the time between measurements was >2 days. The tacrolimus target trough level for achievement of steady state was required to be 5 to 15 ng/mL or not more than 10% outside of this range (ie, 4.5-16.5 ng/mL). In clinical practice, tacrolimus trough concentrations during maintenance therapy with PR-T have generally been in the range of 5 to 15 ng/mL in kidney transplant recipients [16].

Primary Efficacy Variable

The primary efficacy variable was renal function, as assessed by estimated glomerular filtration rate (eGFR) using the 4-variable modification diet in renal disease (MDRD) formula [17]. Renal function was assessed at each study visit.

Secondary Efficacy Variables

Renal function was also assessed based on eGFR using the Chronic Kidney Disease Epidemiology Collaboration formula [18] and the Cockcroft-Gault (CG) formula [19].

Graft Rejection. Graft rejection was assessed at each study visit. Clinical, laboratory-based, or histologic confirmation of a suspected rejection episode was considered an acute rejection episode [20]. Acute rejection episodes diagnosed as acute antibody-mediated or T-cell-mediated rejection were considered biopsy-proven acute rejection [20].

Graft Failure. Graft failure (assessed at each study visit) was defined as retransplantation, nephrectomy, or death or as dialysis ongoing at end of study or at early discontinuation from the study (unless superseded by follow-up information).

Quality of Life. The Gastrointestinal Quality of Life Index (GIQLI) [21] includes 36 items that evaluate the impact of gastrointestinal (GI) symptoms on health-related quality of life. It includes 4 subscales: GI Symptoms (19 items), Physical Functioning (7 items), Emotional Functioning (5 items), and Social Functioning (5 items). Item scores range from 0 (zero quality of life) to 4 (high quality of life). The scores from each of the 36 items are summed to give a global score (0-144). The GIQLI was completed by patients at visits 1 and 3.

Therapy Adherence. Patient-reported adherence was assessed at visits 1 and 4 using the Basel Assessment of Adherence Scale for Immunosuppressives (BAASIS) [22], Essener adherence score (EAS), and visual analog scale (VAS) [23].

The BAASIS measures the adherence to immunosuppressive medication after kidney transplantation within the past 4 weeks based on 4 items. The questionnaire was adapted to specifically ask about tacrolimus immunosuppressive medication to determine whether and how often during the previous 4 weeks patients recalled nonadherence to their medication regimen under 4 dimensions: taking, drug holiday, timing, and dose alteration.

The EAS was used to assess self-reported current adherence with PR-T. It includes 23 questions, and a total score was calculated by summing up the values of the single items, resulting in a total score ranging from 0 to 92, with lower scores indicating better adherence. The total score was calculated for patients with ≥19 items available.

The VAS ranged from 0% (medication never taken as prescribed) to 100% (medication always taken as prescribed).

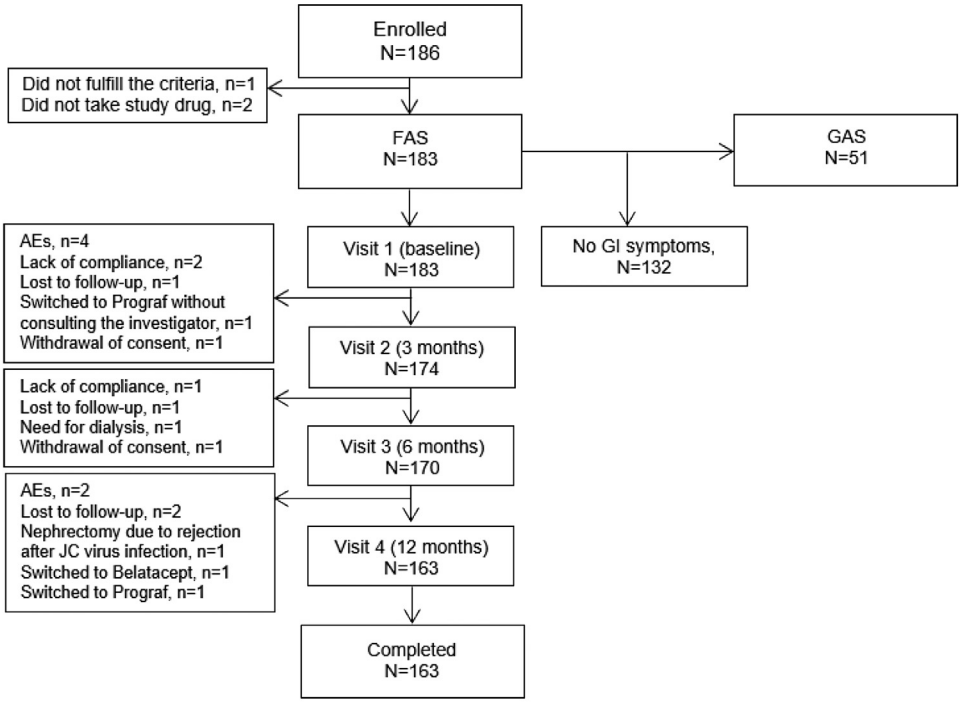

Fig 1. Flow of patients through the study. AE, adverse event; FAS, full analysis set; GAS, gastrointestinal analysis set; GI, gastrointestinal; JC, John Cunningham.

Table 1. Baseline Demographics and Clinical Characteristics (FAS)

Characteristic	N = 183
Sex, n (%)	
Male	112 (61.2)
Female	71 (38.8)
Mean (SD) age (years)	51.2 (12.7)
Ethnicity, White, n (%)	183 (100)
Mean (SD) time since last kidney transplant (months)	55.2 (53.7)
No. of kidney transplants, n (%)	
1	165 (90.2)
2	16 (8.7)
3	2 (1.1)
Occurrence of previous rejection episodes, n (%)	
Yes	60 (32.8)
No	123 (67.2)
Comorbidities, n (%)	
Hypertension	155 (84.7)
CMV	58 (31.7)
Diabetes mellitus	31 (16.9)
CHD	27 (14.8)
Malignant tumor	11 (6.0)
BK nephropathy	7 (3.8)
Biopsy-confirmed	3 (1.6)
Not biopsy-confirmed	4 (2.2)
No. of previous rejection episodes, n (%)*	
1	46 (76.7)
2	10 (16.7)
3	2 (3.3)
4	2 (3.3)

Abbreviations: CHD, coronary heart disease; CMV, cytomegalovirus; FAS, full analysis set; SD, standard deviation.
*Among patients with previous rejection episodes (n = 60).

Patient Satisfaction, Preferences, and Overall Assessment of the Effectiveness of Prolonged-Release Tacrolimus. Patients were questioned at the final visit to determine their satisfaction with once-daily dosing of PR-T; their assessment of whether once-daily dosing of tacrolimus is easier to remember than twice-daily dosing; their preference for therapy; whether there was a preference for once-daily dosing and their reason for the preference; and their assessment of the overall efficacy and tolerability of PR-T.

Safety

Treatment-emergent adverse events (TEAEs) were recorded throughout the study and were classified by system organ class and preferred term according to the *Medical Dictionary for Regulatory Activities* (MedDRA® v15.0; https://www.meddra.org). TEAEs were assessed by the investigators with respect to study treatment causality (probably, possibly, or not treatment related). Clinical laboratory parameters (hemoglobin, urine total protein, and urine albumin) and vital signs were monitored at each study visit.

Statistical Analyses

The full analysis set (FAS) included all patients with recorded core baseline characteristics (age, sex, and ethnicity) who received PR-T at visit 1 and serum creatinine assessments at visit 1 and at least once during visits 2 to 4. Intrapatient tacrolimus trough level variability was measured by the mean coefficient of variation (%CV) of trough levels. Renal function was evaluated in the FAS and according to donor type and the occurrence of prior rejection episodes. Safety was assessed in the FAS. GIQLI was assessed in the gastrointestinal analysis set, which included all patients with at least one GIQLI measurement. All statistical analyses were carried out using SAS (version 9.4; SAS, Cary, NC, United States).

RESULTS

Patient Characteristics

The FAS included a total of 183 patients, of whom 163 (89.1%) completed the study. The main reasons for discontinuation were adverse events (n = 5), lost to follow-up (n = 4), and lack of compliance (n = 3; Fig 1). All patients were White, 61.2% were men, and their mean age was 51.2 years. The mean time since last kidney transplant was 55.2 months and 9.8% of patients had received 2 or more previous kidney transplants (Table 1). The majority of patients had comorbidities, most commonly hypertension (84.7%), cytomegalovirus infection (31.7%), and diabetes mellitus (16.9%; Table 1). The main reason for a patient converting from IR-T to PR-T was convenience (70.5%).

Tacrolimus Dosing and Exposure and Concomitant Medications

Patients were converted from a mean total daily dose of IR-T 3.8 mg to PR-T 4.3 mg at the end of the study. Patients

Table 2. Tacrolimus Total Daily Dose and Blood Trough Levels Before and 12 Months After Conversion (FAS)

Tacrolimus Measures	Before Conversion: IR-T		After Conversion: PR-T	
	n	Mean (SD)	n	Mean (SD)
Number of trough level measurements	183	3.1 (0.4)	183	6.6 (5.1)
Blood trough levels (ng/mL)	183	6.8 (2.0)	178	5.6 (1.3)
CV for trough levels (%)	183	21.2 (12.9)	167	22.1 (11.8)
Range in trough levels (ng/mL)	183	2.8 (2.0)	167	3.5 (2.6)
Last IR-T dose before conversion (mg)	183	3.8 (2.3)	—	—
First PR-T dose after conversion (mg)	—	—	183	4.0 (2.4)
Last documented PR-T dose (mg)	—	—	178	4.3 (2.7)
Predominant dose of PR-T (mg)	—	—	177	4.1 (2.5)
Number of PR-T dose adaptations	—	—	179	1.9 (2.3)

Abbreviations: CV, coefficient of variation; FAS, full analysis set; IR-T, immediate-release tacrolimus; PR-T, prolonged-release tacrolimus; SD, standard deviation.

Table 3. Concomitant Medications (FAS)

Medication	n (%)
Any immunosuppressive medications	181 (98.9)
Mycophenolate mofetil	165 (90.2)
Corticosteroids	140 (76.5)
Sirolimus	4 (2.2)
Everolimus	3 (1.6)
Azathioprine	2 (1.1)
Other agent	1 (0.5)

Abbreviation: FAS, full analysis set.

underwent a mean of 1.9 PR-T dose adjustments during the study.

Mean tacrolimus trough levels were slightly higher before the study with IR-T (6.8 ng/mL) than during the 12-month PR-T study period (5.6 ng/mL; Table 2). Overall intrapatient tacrolimus trough level variability (mean %CV) was 21.2% before conversion to PR-T and 22.1% after conversion to PR-T. In the only patient to experience graft failure, the mean %CV was 38.5% (based on 29 trough level measurements). The median time to a steady trough level state was 110 days.

Concomitant medications during the study are presented in Table 3. Overall, 90.2% of patients were receiving concomitant mycophenolate mofetil and 76.5% were treated with corticosteroids.

Renal Function

Renal function as assessed by eGFR (MDRD) was stable during 12 months of treatment with PR-T (Table 4). Similar results were observed after assessment of eGFR by the Chronic Kidney Disease Epidemiology Collaboration and CG methods (Table 4).

Table 5 shows renal function over time by previous rejection episode and donor type. In patients without a prior rejection episode, mean renal function improved slightly between baseline and month 12. In contrast, mean renal function decreased slightly over time in patients with a prior rejection episode. Using eGFR (MDRD), renal function was comparable in patients with a living donor and those with a deceased donor. However, using the CG equation, renal function was better in patients with a living donor than in patients with a deceased donor.

Graft Rejection and Failure

Table 6 provides details of the 8 patients who experienced an acute rejection episode (4.4%). One patient experienced 2 acute rejection episodes. All but 1 of the acute rejection episodes were biopsy proven (Table 7). One patient had acute rejection and graft failure and received dialysis. This patient had a documented history of high tacrolimus trough level variability both before and during the study. The patient completed the study and at the final visit was still receiving PR-T and had not undergone nephrectomy or retransplantation. One patient required dialysis and 1 patient underwent nephrectomy because of transplant rejection after John Cunningham virus infection. No patients underwent retransplantation. One of the 8 patients with rejection had de novo donor-specific antibodies (DSA), and data were missing for 3 patients (Table 6).

The incidence of acute rejection episodes was higher among patients with time since transplantation <36 months (n = 7/90) compared to ≥36 months (n = 1/92) and also in patients with a prior rejection episode (n = 5/60) compared to no prior rejection (n = 3/122). Systemic corticosteroids were initiated during 7 acute rejection episodes, and the PR-T dose was increased in response to 3 acute rejection episodes.

Adverse Events

One or more TEAEs were experienced by 68 patients (37.2%). TEAEs occurring in ≥5% of patients were nasopharyngitis (n = 20; 10.9%), diarrhea (n = 16; 8.7%), and urinary tract infection (n = 12; 6.6%). Fifty-five patients experienced a serious TEAE (30.1%), most commonly urinary tract infection (n = 6; 3.3%), diarrhea (n = 4; 2.2%), and cytomegalovirus infection (n = 4; 2.2%; Table 8); however, there were no serious TEAEs considered to be probably related to PR-T. No patients died during the study. Laboratory parameter values and vital signs were generally unchanged throughout the 12-month follow-up period.

Quality of Life

Patients reported low GIQLI global scores and subscale scores with no change between visits (Table 9). The mean

Table 4. Renal Function Over Time (FAS)

Patient Visit (Time Point)	eGFR (MDRD) (mL/min/1.73 m^2)	eGFR (CKD-EPI) (mL/min/1.73 m^2)	eGFR (CG) (mL/min)
1 (Baseline)	N = 183	N = 183	N = 183
Mean (SD)	51.4 (18.4)	51.6 (18.8)	64.1 (24.1)
2 (Month 3)	N = 163	N = 163	N = 163
Mean (SD)	51.4 (18.4)	51.6 (18.8)	63.6 (23.1)
3 (Month 6)	N = 165	N = 165	N = 165
Mean (SD)	50.5 (16.5)	50.8 (17.5)	63.5 (22.6)
4 (Month 12)	N = 165	N = 165	N = 165
Mean (SD)	51.4 (19.1)	51.5 (19.3)	64.5 (24.8)

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CG, Cockcroft-Gault; eGFR, estimated glomerular filtration rate; FAS, full analysis set; MDRD, modification of diet in renal disease; SD, standard deviation.

Table 5. Renal Function Over Time: Subgroup Analysis According to Prior Rejection Episodes and Type of Donor (FAS)

Patient Visit (Time Point)	Prior Rejection Episode Mean (95% CI)	No Prior Rejection Episode Mean (95% CI)
eGFR (MDRD) (mL/min/1.73 m^2)		
1 (Baseline)	n = 60	n = 123
	48.4 (43.0, 53.8)	52.8 (49.8, 55.8)
2 (Month 3)	n = 52	n = 111
	48.4 (42.8, 53.9)	52.8 (49.5, 56.1)
3 (Month 6)	n = 56	n = 109
	47.8 (43.3, 52.3)	51.8 (48.7, 54.9)
4 (Month 12)	n = 56	n = 109
	47.2 (42.2, 52.2)	53.5 (49.9, 57.2)
eGFR (CKD-EPI) (mL/min/1.73 m^2)		
1 (Baseline)	n = 52	n = 111
	48.3 (43.0, 53.6)	53.2 (49.7, 56.7)
2 (Month 3)	n = 60	n = 123
	48.4 (43.1, 53.7)	53.2 (50.0, 56.3)
3 (Month 6)	n = 56	n = 109
	48.3 (43.5, 53)	52.2 (48.9, 55.4)
4 (Month 12)	n = 56	n = 109
	47.3 (42.3, 52.3)	53.7 (50.0, 57.4)
eGFR (CG) (mL/min)		
1 (Baseline)	n = 60	n = 123
	63.1 (55.3, 70.8)	64.6 (60.9, 68.3)
2 (Month 3)	n = 52	n = 111
	61.7 (54.8, 68.5)	64.5 (60.3, 68.7)
3 (Month 6)	n = 56	n = 109
	61.4 (55.4, 67.5)	64.5 (60.2, 68.9)
4 (Month 12)	n = 56	n = 109
	60.7 (54.0, 67.4)	66.4 (61.7, 71.1)
	Living donor	Deceased donor
eGFR (MDRD) (mL/min/1.73 m^2)		
1 (Baseline)	n = 74	n = 98
	52.2 (48.6, 55.8)	51.1 (47.0, 55.2)
2 (Month 3)	n = 65	n = 89
	53.4 (49.3, 57.5)	51.0 (46.8, 55.2)
3 (Month 6)	n = 65	n = 89
	51.5 (48.1, 55.0)	50.4 (46.6, 54.3)
4 (Month 12)	n = 67	n = 88
	53.1 (49.3, 56.9)	51.1 (46.6, 55.6)
eGFR (CKD-EPI) (mL/min/1.73 m^2)		
1 (Baseline)	n = 74	n = 98
	53.3 (49.4, 57.1)	50.8 (46.7, 54.8)
2 (Month 3)	n = 65	n = 89
	54.6 (50.3, 58.8)	50.7 (46.5, 54.9)
3 (Month 6)	n = 65	n = 89
	52.6 (48.9, 56.3)	50.3 (46.3, 54.3)
4 (Month 12)	n = 67	n = 88
	54.1 (50.1, 58.1)	50.6 (46.1, 55.1)
eGFR (CG) (mL/min)		
1 (Baseline)	n = 74	n = 98
	68.8 (62.9, 74.6)	61.3 (56.9, 65.7)
2 (Month 3)	n = 65	n = 89
	69.5 (63.8, 75.2)	61.2 (56.4, 65.9)
3 (Month 6)	n = 65	n = 89
	68.0 (62.6, 73.3)	61.3 (56.6, 65.9)
4 (Month 12)	n = 67	n = 88
	69.8 (64.5, 75.1)	61.8 (56.4, 67.2)

Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CG, Cockcroft-Gault; eGFR, estimated glomerular filtration rate; FAS, full analysis set; MDRD, modification of diet in renal disease.

global score (standard deviation) was similar at the first visit (12.6, ±1.6) and at visit 3 (12.5, ±1.8).

Therapy Adherence

Self-reported adherence measured by the BAASIS and EAS was similar at the first and final visits (Table 10). At the final visit, self-reported scores showed high adherence, including the mean EAS score (9 from a possible 92) and high adherence by the VAS (mean 99%).

Patient Satisfaction, Preferences, and Overall Assessment of the Effectiveness of PR-T

At the final visit, 97.8% of patients were satisfied or very satisfied with PR-T (Fig 2); 81.2% of patients reported that PR-T was easier to remember than IR-T. Most patients preferred PR-T to IR-T (78.4% preferred PR-T, 2.2% preferred IR-T, and 19.4% had no preference; Fig 2). The main reasons for preferring PR-T over IR-T included "I don't have to take tacrolimus in the evening anymore" (67.9%) and "Reduced pill burden" (65.1%; Table 11). Among 136 patients with data available, 99.3% assessed the effectiveness of PR-T as good or very good and 0.7% (1 patient) assessed the effectiveness of PR-T as moderate (Fig 2). The tolerability of PR-T among 136 patients with data available was rated as very good (39.0%), good (59.6%), or moderate (1.5%).

DISCUSSION

In this noninterventional study of 183 stable kidney transplant recipients in routine clinical practice in Germany, conversion from IR-T to PR-T resulted in negligible changes in renal function over 12 months of treatment. These findings are consistent with those of previous studies of PR-T in kidney transplant recipients [6,11,13,24]. For example, a randomized trial of PR-T and IR-T in 667 de novo kidney transplant recipients found that kidney function was stable in both treatment groups [6]. In the prospective observational EVOLUTION study of 1832 kidney transplant recipients in Spain, renal function remained stable after conversion from IR-T to PR-T during 12 months of treatment [11]. In the long-term follow-up of EVOLUTION, kidney function was very stable over the course of 4 years [12].

Patients were converted from a mean total daily dose of IR-T 3.8 mg to PR-T 4.3 mg at the end of the study (PR-T:IR-T dose ratio = 1.1). This is consistent with current clinical practice to convert from IR-T to PR-T on a 1 mg:1 mg total daily dose basis [16]. Mean tacrolimus trough levels were lower following conversion but remained within the expected maintenance therapeutic range. A decline in tacrolimus trough levels following conversion from IR-T to PR-T was expected based on clinical experience and previous studies. For example, in the EVOLUTION study, preconversion and 12-month mean tacrolimus trough levels were 7.5 ng/mL and 6.8 ng/mL, respectively [11].

Table 6. Acute Rejection Episodes and Treatments (FAS)

Characteristic	
Acute rejection episodes, n (%)	N = 183
Yes	8 (4.4)
No	174 (95.6)
Missing	1 (0.5)
De novo DSA	N = 8
Yes	1
No	4
Missing	3
Age group (by median age), n	N = 8
<51 years	4
≥51 years	4
Time since last renal graft, n	N = 8
<36 months	7
≥36 months	1
Previous acute rejection episodes, n	N = 8
Yes	5
No	3
Living or deceased donor, n	N = 8
Living	1
Deceased	7
Acute rejection episodes, n	N = 8
1	7
2	1
Biopsy-confirmed rejection episode, n	N = 9*
Yes	8
No	1
Treatment of acute rejection episodes	N = 9*
Any specification, n	9
Systemic corticosteroids	7
PR-T dose increased	3
Unknown treatment	1
Polyclonal/monoclonal antibodies	1
Other	1

Abbreviations: DSA, donor-specific antibodies; FAS, full analysis set; PR-T, prolonged-release tacrolimus.
*One patient experienced 2 acute rejection episodes.

Tacrolimus trough levels were measured according to real-life clinical practice and, as such, measurements were infrequent; therefore, the median time to 2 consecutive trough values within the target range was around 110 days.

Table 7. Description of Biopsy Results Among Patients With Acute Rejection Episodes

Patient	Biopsy Description
1	Banff classification I; interstitial fibrosis
2	Suspected acute rejection
3	Two rejection episodes: 1. borderline changes; 2. antibody-mediated changes, type II capillary and/or glomerular inflammation and/or thrombosis; C4d
4	Type 1B
5	Borderline changes and chronic active antibody mediated rejection
6	Type II capillary and/or glomerular inflammation and/or thrombosis; C4d+; interstitial fibrosis
7	T-cell-mediated type IB
8	Chronic active and acute humoral rejection

Table 8. Serious TEAEs by Preferred Term (FAS)

Preferred Term	N = 183,* n (%)
≥1 serious TEAE	55 (30.1)
Urinary tract infection	6 (3.3)
Diarrhea	4 (2.2)
CMV infection	4 (2.2)
Abdominal pain	3 (1.6)
Transplant rejection	3 (1.6)
Gastroenteritis	3 (1.6)
Pneumonia	3 (1.6)
Transplant dysfunction	3 (1.6)
Blood creatinine increased	3 (1.6)
Respiratory tract infection	2 (1.1)
Urosepsis	2 (1.1)
Shunt aneurysm	2 (1.1)
Biopsy kidney	2 (1.1)
HLA marker study positive	2 (1.1)
Hyperlipidemia	2 (1.1)
Squamous cell carcinoma	2 (1.1)
Proteinuria	2 (1.1)
Renal failure	2 (1.1)
Renal impairment	2 (1.1)
Surgical vascular shunt	2 (1.1)

Abbreviations: CMV, cytomegalovirus; FAS, full analysis set; TEAE, treatment-emergent adverse event.
*Only includes serious TEAEs that occurred in >1% of patients.

During the study, there were 8 biopsy-proven acute rejection episodes in 7 patients, and only 1 patient experienced graft failure. Among 7 patients who experienced an acute rejection episode, all had intrapatient trough level variability (%CV) that was numerically higher than the mean value. Of the 5 patients with biopsy-proven acute rejection episodes and DSA assessments, 1 had de novo DSA.

Lifelong immunosuppressant therapy represents a substantial burden to kidney transplant recipients, and studies show that adherence with immunosuppressant therapy declines over time and that acute graft loss and late acute rejection are correlated with nonadherence [4,25]. Factors contributing to nonadherence are numerous and complex [25,26]; however, in a recent study of 161 kidney transplant recipients, forgetfulness and skipped doses were identified as the main modifiable barriers leading to nonadherence [27].

The rates of nonadherence reported in the literature for solid organ transplant recipients are widely variable and

Table 9. GIQLI Global Scores and Subscale Scores (GAS)

	Visit 1 (Baseline) N = 51	Visit 3 (Month 6) N = 47
GIQLI	Mean (SD)	Mean (SD)
Global score	12.6 (1.6)	12.5 (1.8)
GI symptoms	3.5 (0.3)	3.5 (0.4)
Physical functioning	2.5 (0.7)	2.5 (0.7)
Emotional functioning	3.2 (0.6)	3.3 (0.6)
Social functioning	3.3 (0.5)	3.3 (0.7)

Abbreviations: GAS, Gastrointestinal Analysis Set; GI, gastrointestinal; GIQLI, gastrointestinal quality of life; SD, standard deviation.

Table 10. Self-Reported Adherence With Immunosuppressant Therapy (FAS)

Adherence Score, Mean (SD)	Visit 1 (Baseline) N = 183	Visit 4 (Month 12) N = 166
BAASIS total score* (0-4)	n = 176	n = 140
	0.4 (0.6)	0.3 (0.5)
EAS total score (0-92)	n = 153	n = 111
	8.9 (6.2)	8.6 (6.5)
VAS (0-100)	n = 179	n = 143
	98.7 (4.3)	98.8 (3.6)

Abbreviations: BAASIS, Basel Assessment of Adherence Scale for Immunosuppressives; EAS, Essen Adherence Score; FAS, full analysis set; N, number of patients in the FAS; n, number of patients with data available; SD, standard deviation; VAS, visual analog scale.
*With immediate-release tacrolimus at baseline and with prolonged-release tacrolimus at month 12.

dependent on the measure used [28]. For example, in a study of heart, liver, or lung transplant recipients, nonadherence rates ranged from 23.9% to 70.0% depending on the self-report and collateral report method used [29]. Furthermore, in a prospective, noninterventional study of 153 kidney transplant recipients in Germany, the nonadherence rate was 67.7% and the rate of adherence to the timing of medication was 58.3%, yet the patient-reported rate of medication taking adherence according to the BAASIS was 91.3% [28].

In our study, patients received medical care at hospital- or office-based dialysis practices in Germany, which routinely includes psychosocial support and psychosomatic care to optimize immunosuppressant therapy adherence [4]. Using the BAASIS to assess tacrolimus immunosuppressive medication, treatment adherence did not change between the first and final visits, with self-reported scores suggesting high adherence with IR-T and PR-T. Because study medication was provided through insurance, cost to the patient was not considered to influence assessment of adherence.

Kidney transplant recipients are at risk of GI disorders, with some reports showing that up to half of patients experience GI symptoms posttransplant [30]. In a pilot study, kidney transplant recipients who converted to PR-T had significant improvements in GI symptoms at 12 months compared to those who remained on IR-T [31]. In our study, 51 patients experienced GI symptoms, and these patients reported a low GI quality of life based on GIQLI global scores, with similar mean global and subscale scores observed between conversion and 6 months.

The decision to switch from IR-T to PR-T was made by participating physicians independent of the study and was most frequently undertaken for reasons of convenience (70.5%). Most patients reported that they were very satisfied (69.8%) or satisfied (28.1%) with PR-T at the final visit, and among patients who reported a preference the majority preferred PR-T to IR-T (78.4% and 2.2%, respectively). After conversion from PR-T to IR-T, patients reported improved tremor (14.7%), improved clinical tolerance (9.2%), and improved sleep (5.5%). In addition, 67.9% of patients reported that they preferred PR-T to IR-T because they did not have to take medication in the evening.

In a previous study of 219 stable kidney transplant recipients, at 6 months after randomization to PR-T or IR-T the adherence rates were 81.5% vs 71.9%, respectively, and in the PR-T group doses were more commonly missed in the evening than in the morning (14.2% and 11.7%, respectively) [14]. In our study, the patient narratives indicated that when evening meals did not have to be timed around the second dose of immunosuppressant therapy, there were fewer restrictions on evening activities.

Overall, the safety and tolerability profile of PR-T described here is consistent with that described in previous studies of PR-T in kidney transplant recipients [11,13]. TEAEs were experienced by 37.2% of patients, and the

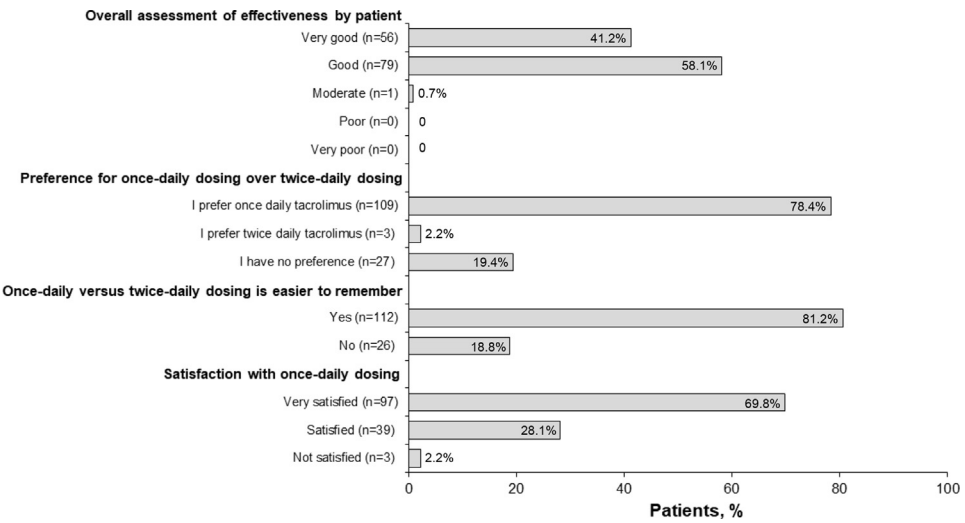

Fig 2. Patient satisfaction, preference, and overall assessment of effectiveness of conversion from immediate-release tacrolimus to prolonged-release tacrolimus after 12 months' treatment in the full analysis set.

Table 11. Reasons for Preference for Tacrolimus PR-T Over IR-T (FAS)

Specification	Patients n = 109
Any specification	109 (100.0)
I don't have to take tacrolimus in the evening anymore	74 (67.9)
Reduced pill burden	71 (65.1)
Before the switch, I had tremor; now I don't have tremor anymore or I experience less tremor than before	16 (14.7)
My tacrolimus drug levels and doses are more stable than before the switch	16 (14.7)
I tolerate once daily better than the twice-daily administration of tacrolimus	10 (9.2)
I can sleep better now than before the switch	6 (5.5)
Other	6 (5.5)
1. Less nausea than before	
2. Evening invitations; therefore, it is difficult not to eat 2 h before and 1 h after intake	
3. Alarm can be turned off in the evening; one thing less to consider	
4. Time to meals does not have to be considered twice daily	
5. Greater quality of life; less limited with dinners; less likely to forget	
6. Less limited in the evening	

Abbreviations: FAS, full analysis set; IR-T, immediate-release tacrolimus; PR-T, prolonged-release tacrolimus.

most common were nasopharyngitis, diarrhea, and urinary tract infection. There were no serious TEAEs considered to be probably related to PR-T.

The main limitations of this study were the observational, noninterventional design and the self-reporting methods used for some outcomes. In addition, recall bias was a limitation of the questionnaire method used to assess quality of life and treatment adherence [32].

CONCLUSIONS

In this real-world study conducted in routine clinical practice in Germany, the conversion of stable kidney transplant recipients from IR-T to PR-T provided stable kidney and graft function over 12 months. The safety profile of PR-T was consistent with that previously described, and the majority of patients expressed a preference for PR-T over IR-T.

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