A Prospective, Observational Study of Conversion From Immediate- to Prolonged-Release Tacrolimus in Renal Transplant Recipients in France: The OPALE Study

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
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Background: Potential benefits of once-daily, prolonged-release tacrolimus over the immediate-release formulation include improved adherence to immunosuppressives post transplantation. An observational study was performed to characterize real-world practice surrounding conversion from immediate- to prolonged-release tacrolimus in kidney transplant recipients.

Material/Methods: We performed a prospective, observational study of renal transplant recipients converted from immediate- to prolonged-release tacrolimus capsules. Conversion took place at the baseline visit, within the first 6 months of transplantation (early conversion group) or between 6 and 12 months of transplantation (late conversion group). Data collection was performed at routine follow-up at 6 and 12 months. Endpoints included conversion ratio from immediate- to prolonged-release tacrolimus, reasons for conversion, additional visits due to conversion, safety, and tolerability.

Results: The analysis population comprised 591 patients. Baseline characteristics were similar between the 2 groups. The mean conversion ratio of the daily dose of tacrolimus was 0.98±0.17 in the early group and 0.99±0.09 in the late group. Time from conversion (mean ±SD) to first measurement of trough tacrolimus blood concentration was 12.1±11.6 and 27.6±26.7 days in the early and late groups, respectively. The highest number of additional visits required was 6 in the early conversion group, in 3 patients (0.7%), and 3 in the late conversion group, in 2 patients (1.6%). Conversion from immediate- to prolonged-release tacrolimus was associated with a very low rate of graft rejection.

Conclusions: Favorable clinical outcomes and safety profiles were observed with conversion from immediate- to prolonged-release tacrolimus over 1 year following renal transplantation, with no marked differences between the early and late conversion groups.

Clinical trial registration link: *https://clinicaltrials.gov/ct2/show/NCT02147938*

MeSH Keywords: **Kidney Transplantation • Observational Study • Tacrolimus**

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Background

Renal transplantation requires lifelong immunosuppressive therapy [1], which is most commonly implemented using several agents with complementary mechanisms of action [1,2]. Such an immunotherapy regimen often comprises a calcineurin inhibitor (CNI), an antiproliferative agent (e.g., mycophenolate mofetil or mycophenolic acid), and corticosteroids [1,2]. Tacrolimus is the most frequently used CNI; it is currently prescribed in over 80% of renal transplant recipients and this proportion continues to rise [3,4]. The efficacy and tolerability profile of tacrolimus following renal transplantation is well established [5]. However, non-adherence to immunosuppressive treatment is common and a major cause of renal transplant failure [6]; therefore, any measures to improve adherence could provide a substantial clinical benefit.

Oral tacrolimus is available as traditional twice-daily immediate-release capsules and granules, and as once-daily prolonged-release capsules. The prolonged-release formulation was approved in 2007 in many countries [5], including France. The pharmacokinetic profiles of both formulations are comparable. For example, in a phase II study comparing the pharmacokinetics of tacrolimus in *de novo* kidney transplant patients [7], the mean AUC_{0-24} of tacrolimus on day 1 was approximately 30% lower for prolonged-release versus immediate-release tacrolimus, but was comparable by day 4. There was also a good correlation between AUC_{0-24} and C_{min} for both formulations [7]. The efficacy and safety of both formulations is well established [5,8–11], but the prolonged-release formulation has the advantage of once-daily administration. A study comparing adherence to immediate- and prolonged-release tacrolimus in 219 stable kidney transplant recipients found significantly greater adherence in the group receiving prolonged-release tacrolimus (88% *vs.* 79% with immediate-release tacrolimus, p=0.0009) [12]. Furthermore, a multicenter, prospective, observational, 12-month study following conversion from immediate- to prolonged-release tacrolimus in renal transplant recipients reported that almost all patients (99%) preferred the prolonged-release formulation because of less frequent dosing (66%) and improved adherence (34%) [13]. Kidney function remained stable following conversion, rejection rates were low, and a good tolerability profile was reported [13].

Prolonged-release tacrolimus is frequently used in routine daily practice in French renal transplantation centers [3], although the factors influencing this decision have not been well delineated. At present, publications describing the conversion from immediate- to prolonged-release tacrolimus among renal transplant recipients tend to describe very early (<14 days) [14] or very late (>1 year) [15–18] post-transplantation conversion. As published data regarding conversion within the first year post transplantation are lacking, this observational study was undertaken to characterize the real-world practice surrounding such conversion in a cohort of French kidney transplant recipients.

Material and Methods

Study design and patients

OPALE was a prospective, observational study of renal transplant recipients, converted from immediate-release tacrolimus capsules (Prograf®, Astellas Pharma, Ltd, Chertsey, UK) [19] to prolonged-release tacrolimus capsules (Advagraf®, Astellas Pharma Europe BV, Netherlands) [20] at 28 participating centers in France. The first patient was included on 19 June 2014, and the last on 23 March 2016. The last study visit took place on 15 May 2017. The study was conducted in accordance with the relevant ethical standards, approved by the local advisory committee (CCTIRS), and authorized by the French National Commission for Data Processing and Privacy (CNIL) (authorisation DR-2014-204). All participants provided informed consent and were free to withdraw from the study at any point.

Patients were eligible for the study if they were aged ≥18 years, had undergone renal transplantation within 13 months before enrolment, and their treating physician had decided to convert them from immediate- to prolonged-release tacrolimus according to usual medical practice at a previously scheduled consultation. Patients were excluded from the trial if they were participating in any other interventional clinical trials at the time of inclusion into the study.

Treatment

Individual tacrolimus dosing and patient care during conversion from immediate- to prolonged-release tacrolimus was at the discretion of the treating physician. The patients were split into 2 groups based on the time between transplantation and conversion: early conversion (within the first 6 months post transplantation) or late conversion (originally defined as between 6 and 12 months post transplantation, although the analysis included patients undergoing conversion up to 13 months post transplantation).

Endpoints

The primary endpoint was an evaluation of the modalities of conversion, using: (1) the conversion ratio of the daily dose of tacrolimus (immediate-release: prolonged-release; expressed as=1 or ≠1, and <1 or >1); (2) time from conversion to first assay of trough tacrolimus blood concentration (C_0) post conversion; and (3) the number of additional visits considered by physicians to be due to the conversion (if any). The secondary endpoints
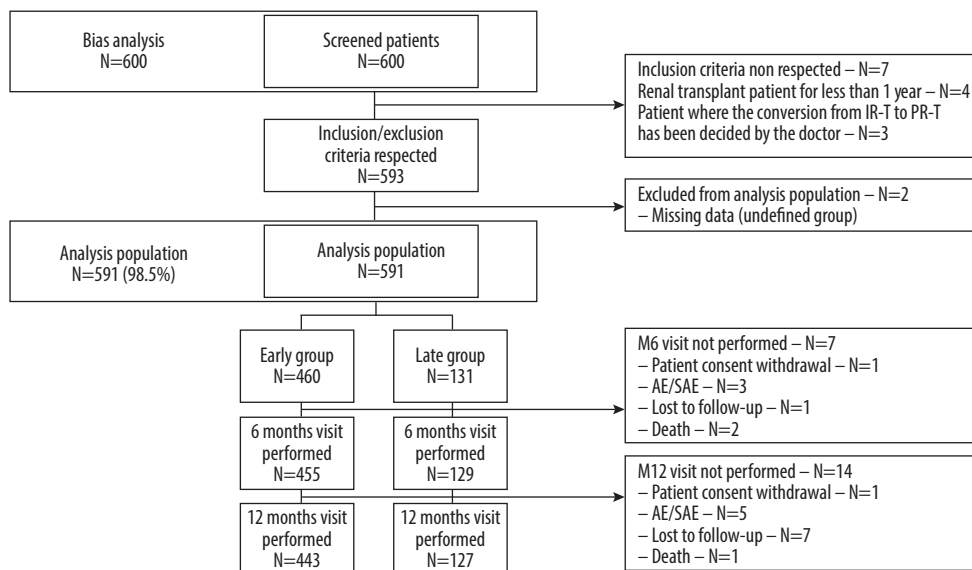
Figure 1. Patient flow chart (all screened patients).

of the study included the reasons for conversion; quality of life; adherence to treatment; patient and graft survival, and complications; renal function and comorbidities; and concomitant treatment. Safety and tolerability were also assessed.

Assessments

At the initial visit, the patient was informed about the study, provided consent, and baseline data were then collected. Follow-up visits were scheduled at 6 and 12 months, in accordance with current practice. Treatment details were collected, as well as the time to first assay of trough tacrolimus blood concentration (C_0) post conversion (i.e., the number of days between the conversion date and the date of the first determination of C_0 post conversion) and the number of additional visits considered by physicians to be due to the conversion (expressed as percentage of patients with and without additional visits). Reasons for conversion from immediate- to prolonged-release tacrolimus, concomitant immunosuppressive therapy, incidence of biopsy-confirmed acute rejections (BCAR), and patient and graft survival 1 year post conversion, were also recorded.

For patients in the late group only, adherence to treatment was assessed at baseline and 12 months using the Morisky questionnaire (where scores of 8, 6–8, and <6 indicated full, moderate, and low adherence, respectively [21]). Quality of life was also assessed at baseline and 12 months using the EQ5D-5L questionnaire [22] for this group. Adverse events (AE) and serious adverse events (SAE) were recorded throughout the study period, and their relationship to treatment assigned by

the treating physician. Renal function and fasting blood sugar were also assessed.

Statistical analysis

As this was a descriptive study, calculation of required sample size was not performed. It was estimated that 600 patients could be enrolled over the period of 1 year based on the 2013 report of the Agence de la Biomédecine [3] and an unpublished post-marketing study on prolonged-release tacrolimus conducted in France. The analysis population consisted of all patients meeting the study inclusion criteria. This was split, as described above, into 2 subgroups of interest: early conversion (within the first 6 months post transplantation) and late conversion (between 6 and 13 months post transplantation).

The type I error rate was defined as α=0.05 and applies to the final analysis reported here. No multiplicity adjustment for the alpha level (e.g., Bonferroni correction) was planned. Descriptive analyses were performed. Missing data were edited for each of the analysis criteria, and a non-response bias analysis was performed.

Results

Patient characteristics

Of the 600 patients screened, 7 did not meet inclusion criteria and a further 2 were excluded from the analysis because of missing data. The remaining 591 patients were included in

Table 1. Demographic characteristics at baseline (analysis population).

	Early conversion (N=460)	Late conversion (N=131)	Total (N=591)
Age (years), mean (±SD)	51.9 (±14.0)	49.6 (±14.7)	51.4 (±14.2)
Gender, n male (%)	294 (63.9)	87 (66.4)	381 (64.5)
Ethnic origin, n (%)			
Caucasian	384 (84.0)	113 (86.9)	497 (84.7)
African	53 (11.6)	11 (8.5)	64 (10.9)
Asian	8 (1.8)	1 (0.8)	9 (1.5)
Other	12 (2.6)	5 (3.8)	17 (2.9)
BMI (kg/m^2), mean (±SD)	25.1 (±4.4)	25.3 (±4.3)	25.2 (±4.3)
BMI WHO classification at inclusion, n (%)			
Underweight (<18.5)	19 (4.2)	5 (3.9)	24 (4.1)
Normal range (18.5–25)	217 (47.7)	59 (46.1)	276 (47.3)
Overweight (25–30)	155 (34.1)	45 (35.2)	200 (34.3)
Obese (≥30)	64 (14.1)	19 (14.8)	83 (14.2)
Diabetes	129 (28.0)	25 (19.1)	154 (26.1)
Systolic BP (mmHg), mean (±SD)	137.5 (±16.2)	134.9 (±16.1)	136.9 (±16.2)
Diastolic BP (mmHg), mean (±SD)	79.2 (±11.2)	78.2 (±9.6)	79.0 (±10.8)
Age at transplantation (years), mean (±SD)	51.7 (±14.0)	48.9 (±14.7)	51.1 (±14.2)

BP – blood pressure; BMI – body mass index; SD – standard deviation; WHO – World Health Organization.

the analysis population: 460 patients in the early group and 131 patients in the late group (Figure 1).

Patient demographics are presented in Table 1. Mean±SD age at transplantation was 51.1±14.2 years, and graft origin was living donor in 20.1% (17.8% of the early group and 28.2% of the late group). The main initial diagnosis was glomerulopathy, including IgA nephropathy (24.2% of patients). Before conversion to prolonged-release tacrolimus, 15 patients (2.5%) had a graft rejection post transplantation. Twenty-six patients (4.4%) withdrew from the study prematurely: 5 deaths, 9 lost to follow-up, 2 patient consent withdrawals, and 10 due to AE/SAE. The mean ±SD time to premature withdrawal was 176.2±98.6 days.

Conversion from immediate- to prolonged-release tacrolimus

The average conversion ratio of the daily dose of tacrolimus was 0.98±0.17 in the early group and 0.99±0.09 in the late group. Overall, over half of the patients (early group: 49.3%; late group: 67.9%) had a conversion ratio equal to 1 (Table 2). The mean±SD conversion ratio was 0.83±0.11 when the ratio was <1, and 1.22±0.17 when the ratio was >1. The doses of immediate- and prolonged-release tacrolimus at time of conversion in the early and late groups are presented in Figure 2.

The mean ±SD time from conversion to the first tacrolimus C_0 was 12.1±11.6 days in the early group and 27.6±26.7 days in the late group. The median (IQR) time from conversion to the first tacrolimus C_0 was 7.0 (4.0; 17.0) days in the early group and 21.0 (12.5; 35.0) days in the late group. Most patients (>94%) did not need additional visits due to the conversion (Table 2). The highest number of additional visits required was 6 in the early conversion group, in 3 patients (0.7%), and 3 in the late conversion group, in 2 patients (1.6%).

Reasons for conversion

The main reasons for conversion from immediate- to prolonged-release tacrolimus were physician's decision (42.6%; 41.1% in early group and 48.1% in late group), followed by center practice (27.6%; 32.6% in early group and 9.9% in late group), and number of intakes (21.8%; 20.4% in early group and 26.7% in late group) (Table 3).

Quality of life and adherence

Quality of life and adherence were assessed in the late conversion group only. Quality of life was maintained following conversion: the mean EQ5D-5L score was 0.8735±0.1906 at inclusion and 0.8814±0.2095 at 1 year post conversion. An overview of the evolution of EQ5D-5L scores over 1 year post conversion is presented in Figure 3.

Table 2. Conversion ratio of the daily dose of tacrolimus and number of additional visits over the first year post conversion (analysis population).

		Early conversion (N=460)	Late conversion (N=131)	Total (N=591)	P value
Conversion ratio, mean (±SD)		0.98 (±0.17)	0.99 (±0.09)	0.98 (±0.15)	P=0.239*
Number of patients (%) [95% CI]					
Conversion ratio=1		227 (49.3) [44.7; 54.0]	89 (67.9) [59.2; 75.8]	316 (53.5) [49.4; 57.5]	P<0.001#
Conversion ratio <1 or >1		233 (50.7) [46.0; 55.3]	42 (32.1) [24.2; 40.8]	275 (46.5) [42.5; 50.6]	
Number of additional visits considered by the physician to be due to the conversion (%) [95% CI]	0	436 (95.8) [93.6; 97.5]	115 (89.1) [82.5; 93.9]	551 (94.3) [92.2; 96.1]	
	1	5 (1.1) [0.4; 2.5]	6 (4.7) [1.7; 9.8]	11 (1.9) [0.9; 3.3]	
	2	3 (0.7) [0.1; 1.9]	6 (4.7) [1.7; 9.8]	9 (1.5) [0.7; 2.9]	
	3	5 (1.1) [0.4; 2.5]	2 (1.6) [0.2; 5.5]	7 (1.2) [0.5; 2.5]	
	4	1 (0.2) [0.0; 1.2]	0 (0.0) [0.0; 2.8]	1 (0.2) [0.0; 1.0]	
	5	2 (0.4) [0.1; 1.6]	0 (0.0) [0.0; 2.8]	2 (0.3) [0.0; 1.2]	
	6	3 (0.7) [0.1; 1.9]	0 (0.0) [0.0; 2.8]	3 (0.5) [0.1; 1.5]	
At least one additional visit considered by the physician to be due to the conversion		19 (4.2) [2.5; 6.4]	14 (10.9) [6.1; 17.5]	33 (5.7) [3.9; 7.8]	

CI – confidence interval; SD – standard deviation. * Wilcoxon test; # Chi-square test.
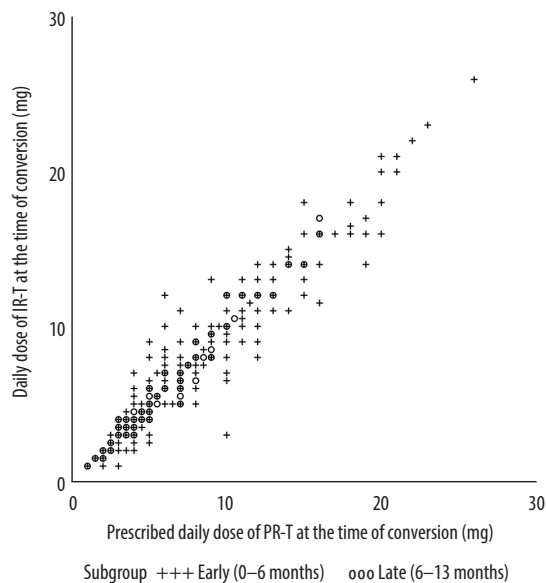

Figure 2. Doses of immediate- and prolonged-release tacrolimus at time of conversion in the early and late groups (analysis population).

Adherence was rated as medium or high by most patients (97.4% and 99% at conversion and 1 year, respectively, late conversion group). Of the 96 patients with available Morisky scores at 1 year post conversion, 14 (14.6%) had an improvement and 14 (14.6%) had a deterioration. The evolution of Morisky scores over this period is presented in Table 4.

Survival, complications, renal function, and comorbidities

Of the 591 patients comprising the analysis set, 19 (3.3%) experienced a graft rejection during the 6 months following conversion, with an additional 7 (1.2%) in the subsequent 6 months. One graft loss was reported at 6 months and an additional 2 at 12 months. There were 2 patient deaths at 6 months (0.3%): 1 with early conversion (0.2%) and 1 with late conversion (0.8%). There were an additional 3 deaths at 12 months (0.5%), all of which occurred in the early conversion group (0.7%). All 5 patient deaths were assessed as being unrelated to treatment. Causes of death included septic shock, melanoma, myocardial ischemia, hyperparathyroidism, and 1 death due to unknown cause. A detailed breakdown of graft rejection, graft loss, and patient death are detailed in Table 5.

Table 3. Reasons for the conversion (analysis population).

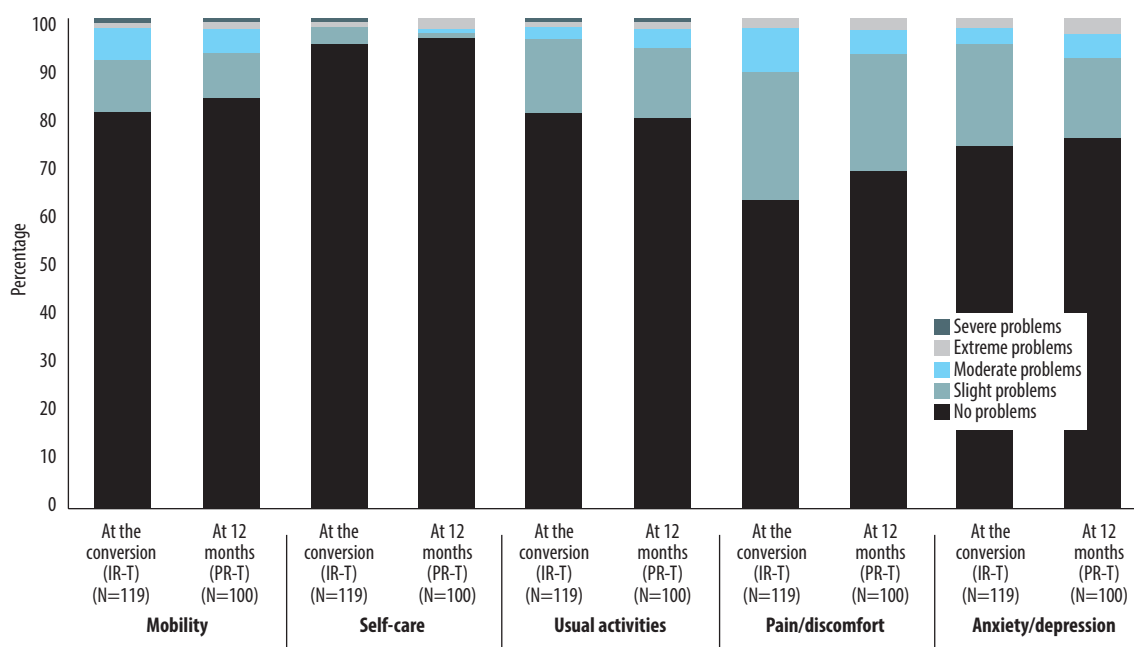|	Early conversion (N=460)		Late conversion (N=131)		Total (N=591)	
Number of capsules, n (%)	17	(3.7)	15	(11.5)	32	(5.4)
Number of intakes, n (%)	94	(20.4)	35	(26.7)	129	(21.8)
Poor compliance, n (%)	6	(1.3)	2	(1.5)	8	(1.4)
Center practice, n (%)	150	(32.6)	13	(9.9)	163	(27.6)
Investigator's decision, n (%)	189	(41.1)	63	(48.1)	252	(42.6)
Patient's request, n (%)	4	(0.9)	3	(2.3)	7	(1.2)

Figure 3. EQ5D-5L evolution at 1-year post conversion (late conversion group, analysis population).

At 6 months, 64 patients (11%) had been prescribed concomitant medication for either diabetes, hypertension, or lipid-lowering, while 210 patients (36.0%) had their previous concomitant medication for these conditions modified. Between 6 and 12 months, a further 30 patients (5.3%) had been prescribed concomitant medication for these conditions, and 165 patients (28.9%) had had their previous concomitant medication modified.

Immunosuppressive treatment regimens

A total of 30.5% of the late group and 60.0% of the early group had changes in concomitant immunosuppressant therapy by either adjunction or by dose modification. Changes in non-tacrolimus immunosuppressive treatments at 6 and 12 months are presented in Table 6.

Safety and tolerability

Adverse events were reported in 366 patients (61.9%). A higher proportion of patients with at least 1 adverse event was reported with early conversion (65.4%) compared with late conversion (49.6%). The most frequently reported adverse events included infections and infestations (29.4%), gastrointestinal disorders (15.7%), blood and lymphatic system disorders (13.9%), and renal and urinary disorders (11.8%). At least 1 serious adverse event was reported in 164 patients (27.7%), and 92 patients (15.6%) had at least 1 adverse event related to tacrolimus. A total of 4.1% of patients (n=24) experienced a serious adverse event that was thought to be related to tacrolimus.

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Table 4. Adherence to treatment: Evolution of Morisky score from conversion to 1-year post conversion (late conversion group*).

Morisky score classification at conversion	Morisky score classification at 1-year post conversion			
	Low	Medium	High	Total
Low	1 (1.0)	1 (1.0)	1 (1.0)	3 (3.1)
Medium	0 (0.0)	13 (13.5)	12 (12.5)	25 (26.0)
High	0 (0.0)	14 (14.6)	54 (56.3)	68 (70.8)
Total	1 (1.0)	28 (29.2)	67 (69.8)	96 (100.0)

Adherence was measured using the Morisky questionnaire. * Patients with Morisky score available at conversion and at 1-year post conversion. Data are n (%).

Table 5. Post-conversion adverse events during follow-up (analysis population).

	Month 6 visit			Month 12 visit		
	Early (N=460)	Late (N=131)	Total (N=591)	Early (N=460)	Late (N=131)	Total (N=591)
Graft rejection since last visit, n (%)	16 (3.5)	3 (2.3)	19 (3.3)	5 (1.1)	2 (1.6)	7 (1.2)
Biopsy proven graft rejection, n (%)	16 (100.0)	3 (100.0)	19 (100.0)	5 (100.0)	1 (50.0)	6 (85.7)
Time from transplantation to BCAR (months), mean (±SD)	3.8 (±1.8)	13.5 (±3.1)	5.3 (±4.1)	10.1 (±2.6)	16.3 (±NA)	11.2 (±3.5)
Time from conversion to BCAR (months), mean (±SD)	2.6 (±1.5)	3.1 (±2.1)	2.7 (±1.6)	5.7 (±4.3)	9.2 (±NA)	6.3 (±4.1)
Graft loss, n (%)	0 (0.0)	1 (33.3)	1 (5.3)	1 (20.0)	1 (50.0)	2 (28.6)
Post-transplantation graft rejection, n (%)*	2 (12.5)	1 (33.3)	3 (15.8)	0 (0.0)	0 (0.0)	0 (0.0)
Graft rejection at 6 months, n (%)				2 (40.0)	0 (0.0)	2 (28.6)
AEs since last visit, n (%)	208 (45.7)	40 (31.0)	248 (42.5)	150 (33.9)	36 (28.3)	186 (32.6)
Patient death, n (%)	1 (0.2)	1 (0.8)	2 (0.3)	3 (0.7)	0 (0.0)	3 (0.5)
Time from conversion to death (days), mean (±SD)	37.0 (±NA)	63.0 (±NA)	50.0 (±18.4)	280.3 (±57.7)	NA	280.3 (±57.7)
Time from transplantation to death (months), mean (±SD)	4.0 (±NA)	9.9 (±NA)	7.0 (±4.2)	11.4 (±1.7)	NA	11.4 (±1.7)

AE – adverse event; BCAR – biopsy-confirmed acute rejection; SD – standard deviation; NA – not applicable. * Number of graft rejections between transplantation and inclusion (i.e. conversion).

Table 6. Introduction or dose modification of non-tacrolimus immunosuppressive treatments at 6 and 12 months.

Introduction/modification of medication since last visit, n (%)	Early conversion N=460	Late conversion N=131	Total N=591
Month 6 visit			
Yes	233 (51.3)	30 (23.3)	263 (45.1)
No	221 (48.7)	99 (76.7)	320 (54.9)
Month 12 visit			
Yes	146 (33.0)	19 (15.0)	165 (28.9)
No	297 (67.0)	108 (85.0)	405 (71.1)

Table 7. Laboratory results (analysis population).

Mean (±SD)	At inclusion	Month 6 visit	Month 12 visit
Early conversion group (N=460)			
Creatininemia (µM)	152.9 (±102.4)	131.0 (±41.8)	130.4 (±44.9)
eGFR (mL/min)	49.9 (±19.6)	53.0 (±16.9)	53.6 (±17.7)
Uremia (mmol/mL)	10.55 (±5.89)	9.11 (±3.55)	9.58 (±4.15)
FPG (g/L)	1.12 (±0.49)	1.10 (±0.35)	1.12 (±0.41)
Proteinuria (mg/24 h)	349.6 (±506.8)	195.2 (±313.0)	184.7 (±328.6)
Creatininuria (mmol/24 h)	10.3 (±4.2)	11.8 (±6.3)	11.8 (±6.0)
Late conversion group (N=131)			
Creatininemia (µM)	136.6 (±51.6)	143.6 (±70.4)	144.4 (±72.9)
eGFR (mL/min)	54.4 (±20.3)	52.9 (±20.5)	52.9 (±22.1)
Uremia (mmol/mlL)	9.47 (±4.36)	9.95 (±5.34)	10.08 (±5.44)
FPG (g/L)	1.01 (±0.22)	1.01 (±0.18)	1.08 (±0.50)
Proteinuria (mg/24 h)	161.5 (±261.6)	181.0 (±423.7)	141.9 (±293.7)
Creatininuria (mmol/24 h)	12.0 (±5.6)	9.9 (±3.3)	11.8 (±4.9)
Full analysis group (N=591)			
Creatininemia (µM)	149.3 (±93.8)	133.8 (±49.7)	133.6 (±52.7)
eGFR (mL/min)	50.9 (±19.8)	53.0 (±17.7)	53.4 (±18.7)
Uremia (mmol/mlL)	10.32 (±5.61)	9.29 (±4.02)	9.69 (±4.47)
FPG (g/L)	1.09 (±0.45)	1.08 (±0.32)	1.11 (±0.43)
Proteinuria (mg/24 h)	307.9 (±470.2)	192.0 (±340.0)	174.3 (±320.6)
Creatininuria (mmol/24 h)	10.6 (±4.6)	11.4 (±5.8)	11.8 (±5.8)

FPG – fasting plasma glucose; eGFR – estimated glomerular filtration rate by MDRD (modification of diet in renal disease);
SD – standard deviation.

Laboratory results

Laboratory results (including renal function and fasting blood glucose) remained stable between inclusion and follow-up (Table 7).

Discussion

This prospective, observational study sought to describe the real-world experience of converting from immediate- to prolonged-release tacrolimus in a cohort of renal transplant recipients in France over the first year following transplantation. More than half of the patient cohort had a conversion ratio equal to 1, as specified in the Advagraf Summary of Product Characteristics [20], and the conversion ratio in the remaining patients was close to 1 in both the early and late groups. The mean time from conversion to the first tacrolimus C_0 was 12.1±11.6 days in the early group and 27.6±26.7 days in the late group. The median (IQR) time from conversion to the first tacrolimus C_0 was 7.0 (4.0; 17.0) days in the early group and 21.0 (12.5; 35.0) days in the late group. Most patients (>94%) did not require additional visits due to the conversion. Renal and glycemic function remained stable, and rates of graft rejection were very low. Adherence was rated as medium or high in almost all patients (late conversion group), and quality of life was excellent both pre and post conversion.

The findings reported here, particularly the conversion ratio of the daily dose of tacrolimus, are consistent with previously published data. In an open-label, phase 3b study of conversion from immediate- to prolonged-release tacrolimus at a median of 3.9 years following renal transplantation, 40.9% of patients required no dose adjustment to maintain recommended tacrolimus trough levels [18]. Where dose adjustment was required, 1 change was sufficient and the mean change in daily dose was relatively small: 0.6–0.7 mg/day [18]. Late conversion studies (median of 3.9 and 5.4 years post renal transplant) have shown

that compared with baseline, mean tacrolimus trough levels tend to fall slightly following conversion from immediate- to prolonged-release tacrolimus, but stabilize thereafter [16,18]. Lauzurica et al. reported that median trough levels fell from 6.7 ng/mL at day 1 to 6.0 ng/mL at week 1, stabilizing to between 5.8 and 6.7 ng/ml for the remainder of the study [18].

The low percentage of patients requiring additional visits suggests a lack of specific concern from the treating physicians and a favorable safety and tolerability profile. Fewer patients required additional visits in the early versus the late group (4.2% vs. 10.9%, respectively). This difference may be due, at least in part, to the shorter standard follow-up times during the early and late periods post transplantation.

As treatment adherence and quality of life may be affected by the complexity of the early period post transplantation, these parameters were assessed in the late conversion group only. It should be noted that 25% of the late group did not provide a Morisky self-evaluation, yet of patients with scores available at 1-year post conversion, adherence improved in 14.6% and worsened in 14.6%. However, adherence at conversion was already rated as high by 69.3% of patients, meaning that further improvements post conversion may have been modest, possibly explaining why a substantial improvement in adherence with conversion was not observed. Quality of life, as assessed by the EQ5D-5L questionnaire, was excellent, both at baseline (mean score, 0.874±0.19) and at 1 year post conversion (0.881±0.21).

At 1-year post conversion, rates of graft rejection, graft loss, and death were very low. As well as the high rate of adherence reported by the late group, the low rates of adverse graft outcomes and death may also, in part, be due to selection bias. A total of 42.6% of patients were converted based on the physician's decision, which may have made it more likely that stable patients or those at low immunological risk were converted. The second most common reason for conversion was center practice, which was applied to 32.6% and 9.9% of the early and late groups, respectively. Other studies of early and late conversion from immediate- to prolonged-release tacrolimus in renal transplant recipients also showed favorable outcomes, including low rates of rejection, minimal change in graft function, and high rates of patient and graft survival [14,16,18]. As NODAT and hyperglycemia are common post transplantation [23,24], it is important to note that renal and glycemic function remained stable during the 1 year of follow-up in our study. This is also consistent with other studies [14,16,18]. The tolerability profile was consistent with previous reports of prolonged-release tacrolimus in renal transplant recipients [14,16,18], and no new safety signals were detected.

The present study has a number of limitations. The observational nature of the study raises the possibility that the study population was not selected randomly, and therefore may not be representative of the renal transplant patient population in France. For instance, the low rate of graft rejection may suggest that selection was biased towards patients with low immunological risk. Furthermore, time from conversion to first assay of trough tacrolimus blood concentration (C_0) was a primary endpoint; however, while time of the first C_0 assessed at the hospital was recorded, it is likely that this measurement had already been taken prior to this in many patients and was not available in the patient data source. Time to reach steady-state tacrolimus trough levels and intra-patient variability (IPV) of C_0 values had originally been cited as secondary variables; however, data collection was impaired by limitations regarding C_0 collection and the definition of steady-state by the protocol. Consequently, these variables are not reported here. In addition, quality of life and adherence data were both collected via questionnaire; therefore, the data may be subject to recall bias. A further limitation is the lack of a comparator arm comprising patients who did not convert to prolonged-release tacrolimus. However, despite its observational nature, the real-world findings of the study complement the carefully controlled conditions dictated by randomized controlled trials, which can only provide an incomplete picture of clinical practice.

Conclusions

This observational, non-interventional study provides real-world experience with conversion from immediate- to prolonged-release tacrolimus over 1 year following renal transplantation. The conversion ratio of daily dose from immediate- to prolonged-release tacrolimus was very close to 1 in both the early and late groups. The decision to convert was mainly taken by the physician or in keeping with center practice, and conversions were associated with few additional visits. Conversion from immediate- to prolonged-release tacrolimus was associated with a very low rate of graft rejection and no new safety signals were detected. These findings from France support the effectiveness of prolonged-release tacrolimus in preventing transplant rejection and maintaining renal and glycemic function.

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Disclosures

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