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Early Versus Late Conversion From Immediate to Prolonged-Release Tacrolimus After Renal Transplantation: Clinical Effects and Treatment Costs

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Introduction. Prolonged-release tacrolimus (PR-TAC) was associated with improved renal function after transplantation when compared to immediate-release tacrolimus (IR-TAC) although evidence is still scarce. This study aimed to compare clinical outcomes and treatment costs in patients who converted from IR-TAC to PR-TAC during the first year after renal transplantation (RT) (early converters [EC]) or after that period (late converters [LC]). **Methods.** We performed a retrospective study including 79 patients (EC, 39; LC, 41) which were followed up over 60 months. A mixed-effects approach was used to investigate the differences between both groups regarding renal and metabolic outcomes as well as treatment costs. **Results.** The median time from RT to conversion was 3 months for EC and 25 months for LC. For both EC and LC, a significant increase in estimated glomerular filtration rate was observed after conversion (5.2 and 4.9 mL/min per 1.73 m^2, respectively). During the first year after RT, EC presented a higher estimated glomerular filtration rate and inferior tacrolimus trough levels when compared to LC, with higher mean treatment costs associated. However, thereafter, these outcomes were similar between groups over the remaining time. At the end of follow-up, no significant differences were found regarding allograft acute rejection (2.6% and 2.4%), new-onset diabetes (15.7% vs 12.2%) or cardiovascular events (5.2% vs 7.3%). **Conclusions.** There was a significant benefit on renal function after conversion from IR-TAC to PR-TAC. During the first year after RT, EC presented improved renal function, but higher treatment costs. None of these differences persisted at the end of follow-up.

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Calcineurin inhibitors (CNI), such as tacrolimus, represent the mainstay of immunosuppression in solid organ transplantation, particularly in kidney allograft recipients.[1] Tacrolimus is very effective in preventing acute rejection, showing superiority over its counterpart, cyclosporine, in a low-dose regimen.[2] However, the associated renal and metabolic side effects remain a concern.[3] Tacrolimus was initially conceived and used twice daily (immediate-release tacrolimus [IR-TAC], Prograf; Astellas), but a slow-release preparation (prolonged-release tacrolimus [PR-TAC], Advagraf; Astellas),[4] has been commercially available in Europe since 2008. Clinical outcomes including biopsy-proven acute rejection, graft, and patient survival were noninferior to IR-TAC.[4] Moreover, once-daily administration allows better patient compliance,[5] less blood concentration variability and equivalent overall drug exposure.[6] Some authors have shown that kidney graft function may even improve after conversion from IR-TAC to PR-TAC,[7] but definitive data are still scarce. When considering costs, a

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budget-impact model based on patient adherence, estimates of acute rejection, graft, and patient survival showed that PR-TAC involved lower healthcare expense.[5] Considering this, switching from IR-TAC to PR-TAC is considered clinically and economically superior. However, no previous study has addressed the influence of the time of conversion, especially if it should occur before or after the first year of transplantation. Additionally, most of the clinical findings have been derived from probability models and estimated outcomes.

In this cohort study, our aim was to compare patients who underwent renal transplantation (RT) and were switched from IR-TAC to PR-TAC during or after the first year posttransplantation with respect to renal and metabolic outcomes including renal function, allograft rejection or loss, new-onset of diabetes after transplantation (NODAT) and treatment costs.

PATIENTS AND METHODS

Study Population and Outcomes

Between 2007 and 2010, 79 renal patients who underwent RT at the Renal Transplantation Unit of São João Hospital Center were enrolled in this study. The patients' initial immunosuppressive regimen included corticosteroids, mycophenolate mofetil, and IR-TAC (Prograf; Astellas) during the first month after RT. All patients were subsequently switched to PR-TAC (Advagraf; Astellas) after a 1:1 mg dose schema. They were classified as early converter (EC) when this process occurred during the first year posttransplantation or late converter (LC) thereafter. The moment of conversion derived from the fact that the drug only became available at our institution after 2009. After that date, it was up to the assistant nephrologist to decide when to convert. We excluded patients with primary allograft failure, those who converted to PR-TAC during the first month and those who switched to mTOR inhibitors or other CNI.

Study participants were followed up over 5 years. Serum creatinine, tacrolimus trough levels, fasting glucose, total/low-density lipoproteins. cholesterol, and triglycerides were collected 1, 3, 6, 12, 36, and 60 months after RT. The average treatment cost per patient (in 2016 euro [€]) was also estimated considering the dose prescribed and the unitary price of each formulation of tacrolimus provided by the Hospital Procurement Services Department.

Baseline characteristics were considered those collected 1 month after RT. NODAT, impaired fasting glucose (IFG), cardiovascular events, acute rejection, graft loss and death were determined at the end of follow-up (ie, 60 months after RT). Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[8] NODAT and IFG were diagnosed according to the criteria of the American Diabetes Association.[9] Cardiovascular events including myocardial infarction, stroke or transient ischemic attack were collected from each patient's hospital record.

The study was reviewed and approved by the ethics committee of our hospital (no. 229-15).

Statistical Analyses

Continuous variables are presented as mean ± standard deviation or median (interquartile range) and categorical variables as a proportion (%). Patients' baseline characteristics were compared using *t* tests and Mann-Whitney analyses for normally distributed variables and nonparametric variables, respectively. χ^2 tests were used for categorical variables.

Paired *t* tests were applied to compare continuous variables within the same patient before and after conversion to PR-TAC. During the 5-year follow-up, a linear mixed-effect model was used to determine the differences between groups, regarding eGFR, tacrolimus trough level, metabolic parameters and treatment costs. Fixed effects included baseline measurement, month (as a categorical variable with 5 categories), treatment group, and the interaction between month and treatment group. A random intercept by participant was used to model within-participant correlations. Associations regarding eGFR were adjusted for tacrolimus trough levels, recipient's age and delayed graft function. A *P* value less than .05 was considered significant. All statistical analyses were performed using Stata (Version 14.1, 2015; Stata Corp., College Station, Texas Corp., College Station, TX).

RESULTS

Patients' Clinical Characteristics

Of 79 patients included in this study, 38 (48.1%) patients switched from IR-TAC to PR-TAC during the first year after RT (EC) and 41 (51.9%) patients were converted afterward (LC). The median time between RT and conversion was 3 months for EC and 25 months for LC. The differences in baseline characteristics (1 month post-RT) between these 2 groups are displayed in Table 1. Early converters were significantly older (49 ± 11.9 years) than LC (42 ± 10.4 years) (*P* = .018). No difference was found regarding the baseline eGFR or delayed graft function.

Acute Effect of Conversion

For both EC and LC eGFR significantly increased after switching from IR-TAC to PR-TAC. For EC eGFR was 55.3 ± 16.4 mL/min per 1.73 m^2 on the day of conversion and 60.5 ± 16.0 (*P* = .008) on the next visit, whereas for LC, eGFR was 58.5 ± 18.4 and 63.4 ± 20.8 (*P* = .009), respectively (Table 2). This increase in eGFR remained significant after adjustment for tacrolimus trough levels.

TABLE 1.

Baseline (1 month post-RT) clinical characteristics of 79 patients included in the study, grouped by the time of conversion to prolonged-release tacrolimus

	EC (n = 38)	LC (n = 41)	*P*
Sex, n (%)			
Male	20 (52.6%)	24 (58.5%)	.184
Female	18 (47.4%)	17 (41.5%)	
Age: mean ± SD, y	49.2 ± 11.98	41.80 ± 10.38	.018
CKD etiology, n (%)			
Undetermined	13 (34.2%)	12 (29.3%)	.210
Hypertension	7 (18.4%)	5 (12.2%)	
ADPKD	5 (13.15%)	5 (12.2%)	
Other	13 (34.2%)	19 (46.3%)	
Delayed graft function, n (%)	11 (28.9%)	10 (24.4%)	.757
eGFR: mean ± SD, mL/min per 1.73 $m^{2,}$	61.5 ± 18.3	56.2 ± 19.3	.543
TAC dose: mean ± SD, mg	6.7 ± 3.8	7.4 ± 4.0	.223
TAC trough levels, mean ± SD, ng/mL	9.8 ± 2.0	10.4 ± 2.0	.07
Conversion time: median (IQR), mo	3 (1)	25 (14)	<.001

ADPKD, autosomal dominant polycystic disease; CKD, chronic kidney disease; EC, early converter; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LC, late converters; TAC, tacrolimus.

TABLE 2.

Effect of conversion on renal and metabolic parameters for both EC and LC

	EC				LC			
	Before conversion	After conversion	*P*	*P*[a]	Before conversion	After conversion	*P*	*P*[a]
eGFR: mean ± SD, mL/min per 1.73 m^2	55.3 ± 16.4	60.5 ± 16.0	.008	.01	58.5 ± 18.4	63.4 ± 20.8	.009	.02
TAC trough levels: mean ± SD, ng/mL	8.4 ± 2.2	7.5 ± 1.8	.03		8.6 ± 2.1	7.1 ± 1.21	<.001	
Fasting glucose: mean ± SD, mg/dL	89.5 ± 18.9	92.9 ± 29.3	.2	.3	83.5 ± 14.3	82.4 ± 15.3	.5	.5
Total cholesterol: mean ± SD, mg/dL	215.9 ± 53.9	200.0 ± 62.7	.1	.2	208.5 ± 40.5	201.3 ± 33.8	.3	.3
LDL cholesterol: mean ± SD, mg/dL	133.7 ± 34.0	123.7 ± 41.6	.1	.2	126.7 ± 31.4	120.7 ± 24.7	.38	.4

EC, early converters; eGFR, estimated glomerular filtration rate; LC, late converters; LDL, low-density lipoproteins; TAC, tacrolimus.

[a]Adjusted for tacrolimus trough levels.

Evolution of Renal Function

Early converters exhibited a sustained increase in eGFR during follow-up, which was more expressive in the first 12 months after RT (Figure 1A). Late converters also presented a progressive increase, although later, from 12 months onward. This explained the significant difference between both groups during the first year after RT with EC presenting a higher eGFR (67.9 ± 19.4 vs 59.0 ± 18.3; *P* = .002) even after adjustment for tacrolimus trough levels (Table 3). Renal function was similar between both groups at the end of follow-up.

Early converters received a significantly lower dose of tacrolimus during the first year (Figure 1B). The dose of tacrolimus was 3.7 ± 2.4 mg for EC and 5.3 ± 2.8 mg for LC at month 12 (*P* = .02). No significant differences were observed after that.

Similarly, tacrolimus trough levels (Figure 1C) were lower for EC (6.6 ± 1.6 ng/mL) than for LC (8.6 ± 1.9 ng/mL) at month 12. Thereafter, no significant differences were found between the 2 groups.

Glycemic Metabolic Status and Cardiovascular Events

At the end of the follow-up, EC and LC did not differ significantly with regard to IFG (18.4% vs 14.6%; *P* = .65), NODAT (15.7% vs 12.2%; *P* = .64), and cardiovascular events (5.2% vs 7.3%; *P* = .71) (Figure 2).

Acute Rejection, Allograft Loss, and Mortality

During follow-up, acute renal allograft rejection was diagnosed in 1 patient of each group (2.6% for EC and 2.4% for LC group, *P* = .95) (Figure 2). There were no significant differences concerning allograft loss (2.6% and 4.9%, respectively, *P* = .94) or mortality (5.3% and 2.4%, respectively, *P* = .61).

Treatment Costs

During the first 3 months after RT, the estimated daily cost was similar between both groups with a mean cost per patient of 1.82 ± 0.96 € for EC and 2.29 ± 1.05 € for LC (*P* = .07) (Figure 3). Six months after RT we observed a significantly increased cost for EC, 2.89 ± 1.68 €/patient per day compared with LC, 2.01 ± 1.04 €/patient per day (*P* = .008). The groups had similar costs from the first year onward. At the end of follow-up, the mean estimated cost was 2.17 ± 1.21 €/patient per day for EC and 1.80 ± 0.91 €/patient per day for LC (*P* = .1).

DISCUSSION

In this observational study, the conversion from IR-TAC to PR-TAC was associated with an increase in eGFR after RT. Changing the formulation during the first 12 months after transplantation resulted in better short-term renal function. However, renal and metabolic outcomes at the end of follow-up were not affected by the moment of conversion. Although the treatment cost was higher for EC during the first months after conversion, the 2 groups had similar costs after the first year post-RT.

The pathophysiology of CNI-induced nephrotoxicity is a common problem.[10] It is recognized as a 2-step process which includes an acute vasomotor imbalance and a chronic irreversible fibrotic response.[10,11] Increasing CNI plasma levels has been linked to both acute and chronic nephrotoxicities.[12] Our results reinforce the acute effect of CNI levels on renal function as we showed that switching from IR-TAC to PR-TAC was associated with a 13% decrease in trough blood levels and a 10% increase in eGFR. The consequences of changing the tacrolimus formulation have been addressed by some authors with inconsistent findings, from no difference[13]

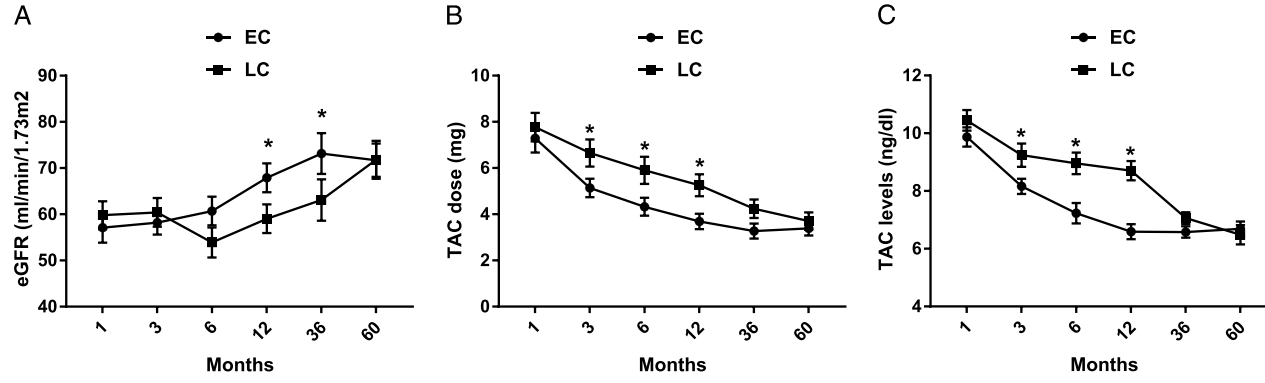

FIGURE 1. Evolution of eGFR (A), tacrolimus dose (B), and trough levels (C) over 5 years of follow-up for EC and LC; *$P < 0.05$.

TABLE 3.

Multivariate analysis to compare the effect of early and late conversion of tacrolimus formulation over time, using a mixed-effect model adjusted for tacrolimus trough levels, recipient age and rate of delayed graft function

	Model 1 crude			Model 2 adjusted		
eGFR, mL/min per 1.73 m^2	Coefficient	95% CI	*P*	Coefficient	95% CI	*P*
EC versus LC						
Month 3	4.81	−1.54 to 11.16	.138	4.58	−1.83 to 10.98	.160
Month 6	3.52	−2.61 to 9.64	.260	3.38	−2.89 to 9.66	.291
Month 12	8.90	2.92 to 14.88	.004	8.77	2.57 to 14.98	.006
Month 36	8.13	1.27 to 14.99	.02	8.81	1.79 to 15.83	.014
Month 60	1.29	−8.02 to 10.6	.786	1.18	−8.36 to 10.72	.809
TAC trough levels per 1 ng/mL				−0.10	−0.87 to 0.68	.808
Age per 1 y				0.01	−0.29 to 0.32	.949
DGF				−6.85	−14.70 to 0.98	.087

EC, early converters; eGFR, estimated glomerular filtration rate; CI, confidence interval; DGF, delayed graft function; LC, late converters; TAC, tacrolimus.

to a slight improvement in renal function.[14] These conclusions were limited by a significant heterogeneity of transplant vintage and low baseline tacrolimus trough levels.[13] In a small crossover trial with healthy volunteers, Zaltzman et al[15] observed that PR-TAC was associated with a lower maximal concentration (Cmax) of tacrolimus and a higher renal plasma flow, but the eGFR was not statistically different. However, in this trial, the target trough levels were higher than in our study (8 to 12 ng/mL) and were similar after conversion.[15] Considering the difference between these findings and our results, we may hypothesize that eGFR is more influenced by trough levels than by Cmax or that a beneficial effect just occurs in a lower range of trough levels. In our study, the lower trough levels obtained after conversion to PR-TAC probably resulted from using a 1:1 mg switching schema, because the 2 formulations are not truly bioequivalent, as previously described.[16] However, even after adjusting for trough levels, eGFR still improved with the conversion to PR-TAC which suggests that other differences in the pharmacokinetic profile beyond trough levels may play a role. The improvement in eGFR was clear in both EC and LC, suggesting that switching to PR-TAC also reduces some acute nephrotoxicity in higher transplant vintages.

We observed that EC presented lower tacrolimus levels and higher eGFR during the first year after RT, but the groups were similar by 5 years, regarding renal and metabolic outcomes. These findings suggest that the moment of conversion was not determinant to long-term renal outcomes. Previous studies have indeed demonstrated a similar efficacy of the 2 formulations by 6 months[17] and 12 months[13,18,19] after transplantation, both in patients who started de novo each of the formulations or who were converted later, but none of them had a follow-up as long as 5 years. These findings reinforce the notion that the pathogenic mechanisms underlying chronic CNI-induced nephrotoxicity are not yet clear and that no "safe" CNI dose has been defined so far.

We did not observe any significant acute or long-term beneficial effects of the conversion on glycemic or lipid parameters. It has been suggested that avoiding high tacrolimus peak levels may minimize its diabetogenic effects[20]; however, data are still scarce and inconsistent.[14,21] In fact, all CNI increase the risk of NODAT,[22] but additional studies addressing the effect of different formulations of tacrolimus are needed.

Economic aspects of each of the tacrolimus formulation are still unexplored due to the complexity of quantifying direct and indirect costs. Arithmetic quantification of the costs showed that EC presented an increase in expenses after conversion from PR-TAC to IR-TAC which reflects the fact that they were taking higher doses at this time. For LC, the conversion was not accompanied by a significant increment in costs, although they tended to reduce as doses decreased. Although early conversion seems more expensive during the first months after RT, EC had lower tacrolimus trough levels

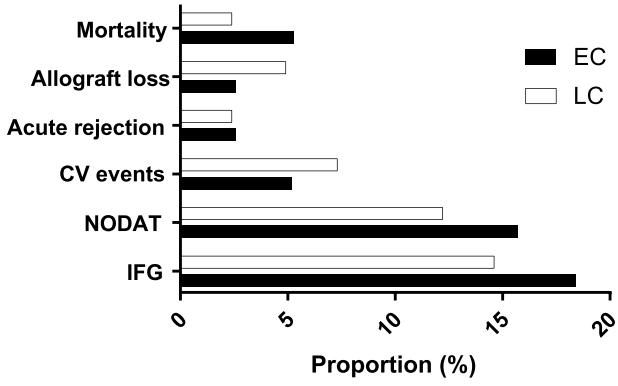

FIGURE 2. Renal and cardiovascular outcomes at the end of follow-up for EC and LC. CV cardiovascular.

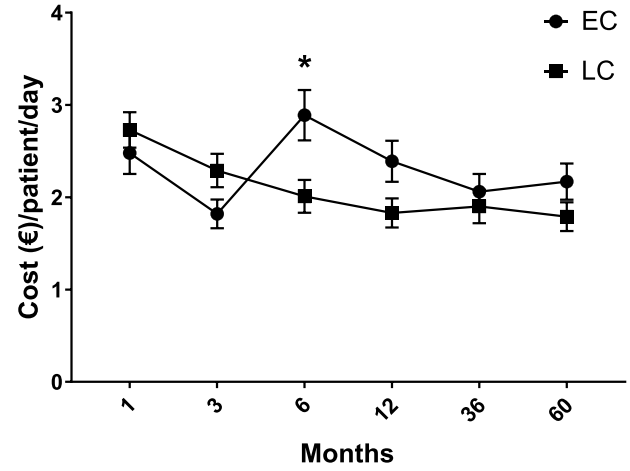

FIGURE 3. Evolution of individual daily costs related to tacrolimus administration over 5 years of follow-up for EC and LC; *$P < .05$.

and better renal function during this period. Muduma el al[5] showed a lower incidence of graft failure at 5 years after switching to PR-TAC with consequent reduced costs. In our study, graft failure or acute rejection was similar for EC and LC. A cost-utility analysis from the same author based on data related to liver transplantation also showed that, despite the higher price, PR-TAC was more cost effective and improved life expectancy and quality-adjusted life-years.[23] We believe that future research on RT should include these general effectiveness measures.

This study provides data regarding the use of different tacrolimus formulations in RT with longer follow-up than previous studies. However, some limitations should be mentioned. It has a retrospective design and uses of records not specifically designed for this study, produced by different clinicians. However, most variables are objective and independent of clinical judgment. Allograft protocol biopsies could have been relevant to identify subclinical changes, such as borderline lesions and grade chronic lesions associated with CNI. Our study did not include a control group who did not convert to PR-TAC because in our Unit all patients were converted to PR-TAC regardless of the allograft vintage. Historical controls would not be used because other immunosuppressants changed throughout time.

Despite these limitations, we conclude that the long-term prognosis does not seem affected by the moment of conversion. Higher direct costs are not negligible for EC during the first year. Additional randomized clinical trials with a longer follow-up and a larger sample would be important to clarify the benefits of conversion on chronic nephrotoxicity induced by CNI and explore the potential associated economic advantages.

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