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Original article

Efficacy and Safety of *de Novo* and Early Use of Extended-release Tacrolimus in Heart Transplantation

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ABSTRACT

Introduction and objectives: The extended-release formulation of tacrolimus (ERT) allows once-daily dosage, thus simplifying the immunosuppressive regimen. This study aimed to describe the safety and efficacy of the *de novo* and early use of ERT in heart transplantation.
Methods: This was an observational, retrospective, multicenter study comparing the safety and efficacy of the *de novo* use of ERT (ERT group [n = 94]), standard-release tacrolimus (SRT group [n = 42]) and early conversion (EC) from SRT to ERT (EC group [n = 44]). Extended-release tacrolimus was used between 2007 and 2012. One-year incidence rates of acute rejection, infection, and cytomegalovirus infection were analyzed. Safety parameters were also evaluated.
Results: There were no significant between-group differences in the daily dose or trough levels of tacrolimus during the first year after transplantation. The rejection incidence rates were 1.05 (95%CI, 0.51-1.54), 1.39 (95%CI, 1.00-1.78), and 1.11 (95%CI, 0.58-1.65) episodes per patient-years in the SRT group, ERT group, and EC group, respectively ($P = .48$). The infection incidence rates were 0.75 (95%CI, 0.60-0.86), 0.62 (95%CI, 0.52-0.71), and 0.55 (95%CI, 0.40-0.68) in the SRT group, ERT group, and EC group, respectively ($P = .46$). Cytomegalovirus infection occurred in 23.8%, 20.2%, and 18.2% of the patients, respectively ($P = .86$). No significant between-group differences were found in laboratory tests or in allograft function. There was 1 death in the SRT group and 2 in the ERT group.
Conclusions: Both *de novo* and early use of ERT seem to have similar safety and efficacy profiles to conventional SRT-based immunosuppression.

Eficacia y seguridad del uso *de novo* y precoz de tacrolimus de liberación prolongada en el trasplante cardiaco

Palabras clave:
Tacrolimus
Trasplante cardiaco
Rechazo
Infección

RESUMEN

Introducción y objetivos: El tacrolimus de liberación prolongada (TLP) permite una dosificación única diaria, lo que simplifica el régimen inmunosupresor. El presente estudio describe la eficacia y la seguridad del uso de TLP *de novo* y precoz para el trasplante cardiaco.
Métodos: Se realizó un estudio observacional, retrospectivo y multicéntrico para comparar el uso *de novo* de TLP (grupo de TLP; n = 94), tacrolimus de liberación estándar (grupo de TLE; n = 42) y la conversión precoz (CP) de TLP a TLE (grupo de CP; n = 44). El TLP se usó entre 2007 y 2012. Se analizaron la tasa de incidencia de rechazo agudo, infección e infección por citomegalovirus al primer año tras el trasplante, así como parámetros de seguridad.
Resultados: Entre los grupos no hubo diferencias significativas en la dosis diaria y las concentraciones séricas de tacrolimus durante el primer año tras el trasplante. La incidencia de rechazo fue de 1,05 (IC95%, 0,51-1,54), 1,39 (IC95%, 1,00-1,78) y 1,11 (IC95%, 0,58-1,65) eventos/pacientes-años en los grupos de TLE, TLP y CP respectivamente (p = 0,48). La incidencia de infección fue de 0,75 (IC95%, 0,60-0,86), 0,62 (IC95%, 0,52-0,71) y 0,55 (IC95%, 0,40-0,68) en los grupos de TLE, TLP y CP respectivamente (p = 0,46). Se produjo infección por citomegalovirus en el 23,8, el 20,2 y el 18,2% respectivamente (p = 0,86). No hubo diferencias significativas entre los grupos en los parámetros de seguridad o la función del injerto. Falleció 1 paciente del grupo de TLE y 2 del grupo de TLP.

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Conclusiones: Parece que el uso *de novo* de TLP o la CP de TLP a TLE tienen similares eficacia y seguridad que el TLE en el trasplante cardiaco.

Abbreviations

CMV: cytomegalovirus
EC: early conversion
ERT: extended-release tacrolimus
SRT: standard-release tacrolimus

INTRODUCTION

Despite the shortage of donors, cardiac transplantation remains the standard of care in selected cases of advanced heart failure.[1] In the last decade, tacrolimus has become the most frequently used calcineurin inhibitor in heart transplantation.[2] Tacrolimus is available worldwide as an immediate-release oral formulation, which is administered twice-daily (standard-release tacrolimus [SRT]). Recently, a prolonged-release oral formulation of tacrolimus (extended-release tacrolimus [ERT]) has been developed, allowing once-daily dosage. Pharmacokinetic evaluation carried out in stable heart recipients[3] has demonstrated that ERT has similar tacrolimus exposure (as assessed by the 24-hour area under the curve, and intrapatient and interpatient variabilities compared with SRT. Moreover, both formulations showed a similar correlation between the 24-hour area under the curve and minimum concentration, which allows the use of serum trough levels for effective monitoring. When using ERT, about one-third of recipients need the tacrolimus dosage to be increased with respect to the previous SRT dosage.[3,4] However, 1 daily dose can result in simplification of the immunosuppression regimen and, consequently, in improved adherence.[5]

So far, several studies have evaluated the safety, efficacy, and tolerability of conversion from SRT to ERT in stable heart transplant recipients.[3–6] In contrast, data on the safety and efficacy of the use of ERT in a *de novo* setting (ie, from the beginning of post-transplant immunosuppression) are limited to studies with a reduced sample size.[7–12] Thus, the purpose of the present study was to investigate the safety and efficacy of the early use of ERT compared with SRT in a multicenter study with a larger sample size.

METHODS

This was an investigator-driven, industry-supported, retrospective, multicenter study conducted on an intention-to-treat basis. The coordination of the 6 participating centers across Spain, the adjudication process, and analyses were performed centrally according to the standards of the Spanish Registry of Heart Transplantation.[13] Data were obtained from the Spanish Registry of Heart Transplantation and from a review of clinical records with the use of a standardized form with predefined variables. The study protocol was approved by the Ethics Committee at the Universitary Hospital Marqués de Valdecilla, Santander, Cantabria, Spain.

Study Patients

We included patients who underwent single heart transplantation before December 31, 2012 and who survived for more than 7 days after the procedure. The participating centers identified all the patients who fulfilled the inclusion criteria and were treated with ERT (Advagraf, Astellas Pharma Europe Ltd, Staines, United Kingdom) within the first 15 days after transplant (ERT group). For comparison, a consecutive series of recipients initially treated with SRT (Prograf, Astellas Pharma Europe Ltd, Staines, United Kingdom) (with similar sample size to the ERT group) was selected. In this sample, 2 subsets of patients were then identified: patients who received SRT throughout the study (SRT group) and those who initially received SRT and routinely converted to ERT within 6 months after transplant because of a center-specific immunosuppressive strategy (early conversion [EC] group). Some study patients have already been partially described in previous reports.[8]

Procedures and Outcomes

Immunosuppression regimes (type of immunosuppressant, daily doses, and trough levels), laboratory and clinical data were recorded monthly during the first 6 months after transplantation and at months 9 and 12 thereafter. The primary outcome parameter was the 1-year rejection incidence rate. The secondary outcome parameters were the 1-year infection incidence rate and safety evaluation (analytic parameters, left ventricular function, drug withdrawal, and mortality).

Rejection surveillance was based on the conventional use of routine endomyocardial biopsy in all but 1 center that carried out clinical-echocardiographic follow-up, with use of biopsy only in selected patients. For the purpose of the present study, acute rejection was defined, as previously reported, as a clinical event (either endomyocardial biopsy findings, an echocardiogram indicating ventricular dysfunction, and/or abnormal hemodynamics) leading to temporary augmentation of immunosuppression consisting of a short course of oral or intravenous high-dose steroids with or without cytolytic therapy.[14] Hemodynamic compromise was defined as 1 or more of the following: left ventricular ejection fraction $\leq$ 30% or a 20% decrease from baseline, a cardiac index < 2.0 L/min/m^2 or a 25% decrease from baseline and/or the need for inotropic agents or ventricular assist device implantation. An infection episode was defined as infection requiring hospital admission or leading to prolongation of an ongoing hospital admission, or when intravenous antimicrobial therapy or a specific therapy (for example, for opportunistic infections) was given. Cytomegalovirus (CMV) infection was defined by the isolation of the CMV virus or the detection of viral proteins or nucleic acid in any body fluid or tissue specimen. Renal function was assessed by means of estimation of the glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration equation.[15] Post-transplant new-onset diabetes was defined as the use of oral antidiabetics and/or insulin in patients without a pretransplant diagnosis of diabetes.

Statistical Analysis

Continuous variables are summarized as mean and standard deviation unless otherwise stated. Categorical variables are expressed as percentages. Differences among the 3 groups for

continuous variables were analyzed by 1-way ANOVA (Welch test) and the Fisher Least Significant Correlation test for post hoc comparisons. Differences for categorical variables were assessed by the chi-square test. No imputation for missing values was performed.

Changes in continuous variables over the study period were analyzed by linear fixed-effect models with repeated measures. Clinical outcomes (rejection, infection, CMV infection) were assessed by their respective cumulative incidence rates. The incidence rate was calculated as the number of episodes during 1 post-transplant year/cumulative patient-years of follow-up. To adjust for differences in baseline group characteristics, Poisson or negative binomial regression, as appropriate, was fitted with the inclusion of the study group and other relevant clinical variables as independent variables. Odds ratios were compared with the SRT group as reference. A P value $< .05$ was considered as significant throughout. The analyses were performed with commercially available SPSS 20.0 and Stata 12 packages.

RESULTS

Patient Characteristics

The study population consisted of 42 patients in the SRT group, 94 patients in the ERT group, and 44 patients in the EC group. The mean time of conversion from SRT to ERT in the EC group was 4.3 ± 1.4 months (range, 1-6 months). The main demographic and clinical characteristics of recipient, donor, and surgical procedures for the 3 study groups are summarized in Table 1. The groups were unbalanced regarding some baseline characteristics. The most marked differences were observed between the EC group and the SRT group. No significant differences were observed between the ERT and SRT groups.

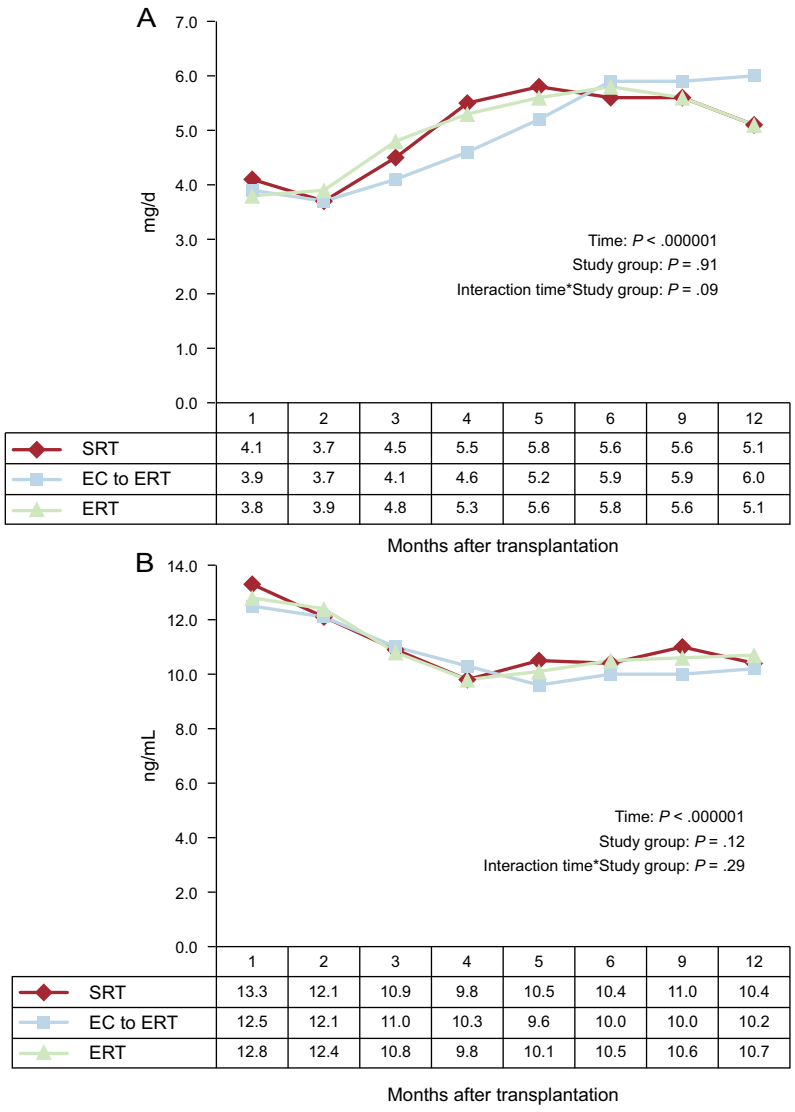
Tacrolimus Dose and Serum Levels

Data regarding the dose and serum levels of tacrolimus are summarized in Figures 1A and 1B, respectively. The mean daily

Table 1
Baseline Characteristics of the Study Groups

	SRT (n = 42)	ERT (n = 94)	EC to ERT (n = 44)
Age, y	52.8 ± 9.6	54.7 ± 10.3	51.6 ± 10.7
Male sex, %	78.6	83.0	70.5
Body mass index, kg/m²	25.5 ± 3.6	25.9 ± 4.3	25.7 ± 3.7
Cardiac primary diagnosis, %			
Ischemic	50.0	46.8	50.0
Dilated	38.1	40.4	36.4
Others	11.9	12.8	13.6
NYHA functional class, %			
III	23.8	8.5	11.4
III-IV	50.0	52.1	47.7
IV	26.2	39.4	40.9
Hypertension, %	40.5	40.4	23.3
Diabetes, %	26.2	21.3	6.8[a,b]
CMV (+), %	78.6	83.0	77.3
*Pulmonary vascular resistance, dyn*s/cm⁵*	192 ± 104	184 ± 112	224 ± 96
Mechanical circulatory support, %	7.1	11.7	20.5[a]
Mechanical ventilation, %	9.5	9.6	9.1
Pretransplant cardiac surgery, %	23.8	32.3	29.5
Pretransplant malignancy, %	2.4	3.2	6.8
Pretransplant infection, %	0.0	5.3	18.2[a,b]
Donor age, y	35.0 ± 12.4	40.5 ± 13.3	43.6 ± 10.2*
Donor male sex, %	26.2	31.9	38.6
Donor body mass index, kg/m²	26.2 ± 4.3	26.3 ± 3.6	26.0 ± 3.7
Donor CMV (+), %	43.9	45.2	66.7[a,b]
Donor cause of death, %			
Head trauma	57.5	43.0	20.5[a]
Stroke	35.0	49.5	68.2
Others	7.5	7.5	11.4
Recipient CMV (−)/donor CMV (+), %	4.8	10.6	18.2[a]
Recipient weight/donor weight	0.97 ± 0.21	0.97 ± 0.16	0.98 ± 0.16
Recipient male/donor female, %	21.7	30.4	17.5
Cold ischemia time, min	201 ± 63	196 ± 57	187 ± 54
Cumulative follow-up (patient-y)	41.1	93.5	44.0

CMV, cytomegalovirus; EC, early conversion; ERT, extended-release tacrolimus; NYHA, New York Heart Association; SRT, standard-release tacrolimus.
[a] $P < .05$ with respect to SRT.
[b] $P < .05$ with respect to ERT.



	1	2	3	4	5	6	9	12
SRT	4.1	3.7	4.5	5.5	5.8	5.6	5.6	5.1
EC to ERT	3.9	3.7	4.1	4.6	5.2	5.9	5.9	6.0
ERT	3.8	3.9	4.8	5.3	5.6	5.8	5.6	5.1

	1	2	3	4	5	6	9	12
SRT	13.3	12.1	10.9	9.8	10.5	10.4	11.0	10.4
EC to ERT	12.5	12.1	11.0	10.3	9.6	10.0	10.0	10.2
ERT	12.8	12.4	10.8	9.8	10.1	10.5	10.6	10.7

Figure 1. A: daily dose of tacrolimus according to study groups (SRT, ERT, EC from SRT to ERT group). Mean values (mg/d) are shown in the table underneath. B: serum through levels of tacrolimus according to the study group (SRT, ERT, EC from SRT to ERT group). Mean values (ng/mL) are shown in the table underneath. EC, early conversion; ERT, extended-release tacrolimus; SRT, standard-release tacrolimus.

dose of tacrolimus significantly increased over the first post-transplant year ($P < .000001$). This was observed irrespective of the study group ($P = .91$) (Figure 1A). An opposing trend was found for tacrolimus trough levels (Figure 1B), which showed a highly significant decrease over the study period ($P < .000001$). Overall, average serum levels did not show significant intergroup differences ($P = .12$).

Concomitant Immunosuppression

In the whole population, induction therapy was used in 152 recipients (84.4%): basiliximab in 148 (82.2%), daclizumab in 2 (1.1%), and OKT3 in 2 (1.1%). There were significant between-group differences in the rate of induction use: 73.8% in the SRT group, 90.4% in the ERT group, and 81.8% in the EC group ($P = .002$). In all patients, concomitant immunosuppression consisted of mycophenolate and prednisone. Changes in the daily doses of MMF and prednisone are summarized in Table 2. The mean daily dose of MMF was similar in the 3 groups throughout the study period ($P = .47$). The mean daily dose of prednisone was significantly higher in the EC group than in the SRT group ($P = .001$) and the ERT group ($P = .009$). Complete prednisone withdrawal rates at 1 year were 42.9%, 40.4%, and 38.6% for the SRT, ERT, and EC groups, respectively ($P = .92$).

Statin therapy rates were lower in the ERT group (75.5%) than in the SRT group (90.2%) and the EC group (93.2%) ($P = .014$).

Rejection

Overall, there were 222 rejection episodes in 83 patients (incidence rate, 1.23 episodes per patient-years; 95% confidence interval [95%CI], 0.97-1.50). We found 43 rejection episodes in 18 SRT group patients, 130 episodes in 47 ERT group patients and 49 episodes in 18 EC group patients. Incidence rates were 1.05 (95%CI, 0.51-1.54), 1.39 (95%CI, 1.00-1.78), and 1.11 (95%CI, 0.58-1.65) episodes per patient-years, respectively ($P = .48$). No between-group comparisons reached statistical significance (Figure 2). Compared with the SRT group, the odds ratios of rejection (adjusted for recipient age and sex, pretransplant diabetes, pretransplant infection, use of mechanical circulatory

Table 2
Concomitant Immunosuppression, Laboratory Data, Blood Pressure and Left Ventricular Function Throughout the Study According to the Study Group

Variable/time after transplantation	SRT group	ERT group	EC group	*P*[a]
MMF dose, g/d				.48
1 mo	1.76 ± 0.46	1.78 ± 0.51	1.71 ± 0.59	
6 mo	1.38 ± 0.75	1.57 ± 0.65	1.46 ± 0.63	
12 mo	1.23 ± 0.71	1.41 ± 0.69	1.42 ± 0.64	
Prednisone dose, mg/d				.003
1 mo	16.1 ± 9.1	18.5 ± 13.0	23.1 ± 13.8[b]	
6 mo	4.7 ± 2.5	5.6 ± 3.3	7.5 ± 5.5[b,c]	
12 mo	2.3 ± 3.0	2.3 ± 2.8	3.6 ± 5.6	
eGFR, mL/min/1.73 m²				.92
1 mo	77.0 ± 28.9	83.0 ± 28.1	78.5 ± 26.4	
6 mo	62.2 ± 29.4	63.6 ± 23.5	65.9 ± 28.3	
12 mo	68.8 ± 28.2	66.1 ± 26.6	67.8 ± 29.5	
Glycated hemoglobin at 12 mo, %				
Diabetics	5.8 ± 0.8	6.5 ± 1.0	5.8 ± 0.8	.08
Nondiabetics	5.0 ± 0.8[c]	5.8 ± 0.4	5.4 ± 0.5[c]	.005
Leucocytes, × 10³				.59
1 mo	9.6 ± 6.3	7.9 ± 2.9	8.1 ± 2.7	
6 mo	6.2 ± 2.3	6.9 ± 4.4	6.5 ± 2.6	
12 mo	5.9 ± 1.8	6.2 ± 2.4	5.8 ± 2.5	
Platelets, × 10³				.66
1 mo	249 ± 102	241 ± 92	249 ± 109	
6 mo	233 ± 87	206 ± 62	203 ± 60	
12 mo	208 ± 68	201 ± 67	202 ± 68	
Hemoglobin, mmol/L				.24
1 mo	6.9 ± 0.9	6.9 ± 0.9	7.0 ± 0.7	
6 mo	7.4 ± 0.9	7.4 ± 0.9	7.8 ± 0.8	
12 mo	7.9 ± 0.8	7.6 ± 0.9	7.8 ± 0.8	
ALT, ukat/L				.46
1 mo	0.56 ± 0.27	0.82 ± 1.00	0.75 ± 0.81	
6 mo	0.41 ± 0.23	0.40 ± 0.24	0.48 ± 0.37	
12 mo	0.43 ± 0.29	0.39 ± 0.26	0.40 ± 0.21	
Bilirrubin, umol/L				.18
1 mo	17.8 ± 18.1	16.8 ± 14.2	14.4 ± 7.7	
6 mo	8.4 ± 4.1	10.8 ± 5.0	9.2 ± 2.9	
12 mo	8.2 ± 3.6	12.5 ± 6.3	10.8 ± 12.1	
LDL cholesterol, mmol/L				.89
1 mo	2.44 ± 0.89	2.29 ± 0.87	2.31 ± 0.89	
6 mo	2.29 ± 0.66	2.37 ± 1.02	2.25 ± 0.61	
12 mo	2.02 ± 0.54	2.43 ± 0.95	2.35 ± 0.68	
Triglycerides, mmol/L				.65
1 mo	1.53 ± 0.63	1.32 ± 0.48	1.39 ± 0.60	
6 mo	1.47 ± 0.57	1.43 ± 0.61	1.63 ± 0.72	
12 mo	1.42 ± 0.55	1.60 ± 0.84	1.63 ± 1.00	
SBP, mmHg				.64
1 mo	133.3 ± 19.3	132.1 ± 21.1	130.7 ± 16.2	
6 mo	129.6 ± 19.9	130.5 ± 15.4	132.3 ± 13.6	
12 mo	138.5 ± 18.5	131.5 ± 16.3	130.0 ± 10.7	
LVEF, %				.30
1 mo	65.8 ± 7.8	65.5 ± 6.9	65.6 ± 6.1	
6 mo	66.9 ± 5.8	64.2 ± 7.8	63.7 ± 7.2	
12 mo	65.8 ± 9.5	64.9 ± 7.1	63.8 ± 6.6	

ALT, alanine aminotransferase; EC, early conversion; eGFR, estimated glomerular filtration rate; ERT, extended-release tacrolimus; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; MMF, mycophenolate mofetil; SBP, systolic blood pressure; SRT, standard-release tacrolimus.
Values are expressed as the mean ± standard deviation.
[a] *P* value for group differences.
[b] $P < .05$ with respect to SRT group.
[c] $P < .05$ with respect to ERT group.

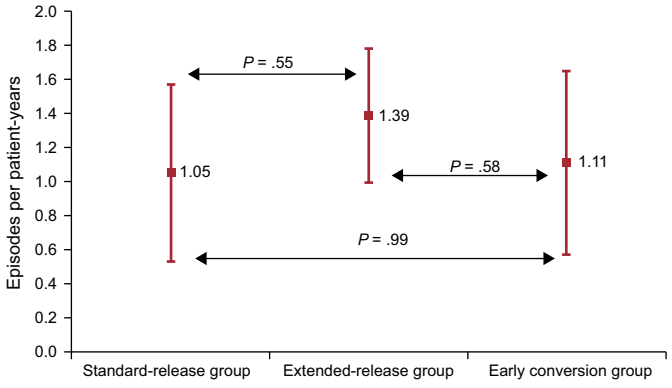


Figure 2. Incidence rate (episodes per patient-years) of rejection according to study groups.

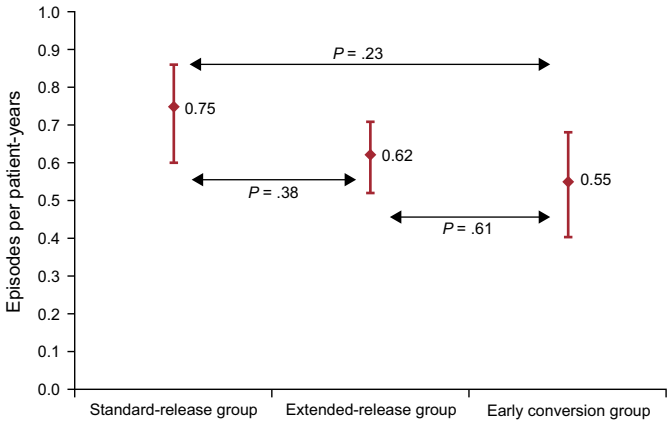


Figure 3. Incidence rate (episodes per patient-years) of infection according to study groups.

support, donor age and sex, donor cause of death, recipient/donor CMV serology mismatch, use of induction therapy, and statin use) were 0.99 (95%CI, 0.56-1.75) for the ERT group ($P = .99$), and 0.85 (95%CI, 0.44-1.65) ($P = .85$) for the EC group, respectively (Table 1 of the supplementary material). A second model was built adding the fact that some study patients had a nonroutine endomyocardial biopsy-based rejection surveillance as a covariate. Odds ratios of rejection in this model were 1.14 (95%CI, 0.63-2.04) for the ERT group ($P = .67$) and 1.05 (95%CI, 0.53-2.12) for EC group ($P = .87$), respectively (Table 2 of the supplementary material).

Hemodynamic compromise was observed in 28 (12.6%) of the rejection episodes, with no significant differences between groups (20.9% for the SRT group, 10.8% for the ERT group, and 10.2% for the EC group; $P = .19$). Cytolytic therapy for rejection treatment was used in 11.6%, 10.0%, and 4.1% for the SRT, ERT, and EC groups, respectively ($P = .37$). There were no rejection-related deaths.

Infections

In the whole population, there were 113 non–CMV-related infective episodes in 73 patients (incidence rate, 0.63 episodes per patient-years; 95%CI, 0.56-0.70). We found 31 infective episodes in 18 SRT group patients, 58 episodes in 37 ERT group patients, and 24 episodes in 18 EC group patients. Incidence rates were 0.75 (95%CI, 0.60-0.86), 0.62 (95%CI, 0.52-0.71), and 0.55 (95%CI, 0.40-0.68) episodes per patient-years, respectively ($P = .46$). No between-group comparisons reached statistical significance (Figure 3). Compared with the SRT group, the odds ratios of infection (adjusted for recipient age and sex, recipient body mass index, previous cardiac surgery, pretransplant diabetes, pretransplant infection, use of mechanical circulatory support, pretransplant mechanical ventilation, recipient/donor CMV serology mismatch, use of induction therapy, use of statins, urgency of the procedure, and cold ischemia time) were 0.83 (95%CI, 0.51-1.34) for the ERT group ($P = .44$) and 0.62 (95%CI, 0.34-1.13) for the EC group ($P = .12$), respectively (Table 3 of the supplementary material).

The causal microorganism and location of infective episodes are summarized in Table 3. There was a trend to higher rates of bacteremia in the ERT and EC groups than in the SRT group. In contrast, a trend to higher rates of viral infections (mainly Herpes Zoster) in the SRT group compared with the SRT group and EC group was observed. There were no infection-related deaths.

Cytomegalovirus infection/disease occurred in 10 recipients (23.8%) of the SRT group, 19 (20.2%) of the ERT group and 8 (18.2%) of the EC group ($P = .86$). Odds ratios (adjusted for recipient age and sex, pretransplant diabetes, pretransplant infection, recipient/donor CMV serology mismatch, use of induction therapy, use of CMV prophylactic therapy, and total 1-year episodes of acute allograft rejection), were 0.77 (95%CI, 0.29-2.03) for the ERT group ($P = .59$) and 0.56 (95%CI, 0.18-1.86) for the EC group ($P = .34$), respectively (Table 4 of the supplementary material).

Safety Parameters

In the whole group, the glomerular filtration rate at 1 month (80.5 ± 27.8 mL/min) declined significantly at 6 months and at

Table 3
Characteristics of Infective Episodes

	Standard-release group	Extended-release group	Early conversion group	*P*
Microorganism, %				.089
Bacteria	27.3	59.5	56.5	
Virus	40.9	24.3	8.7	
Fungi	13.6	5.4	8.7	
Unknown	18.2	10.8	26.1	
Location, %				.085
Bacteremia	9.1	21.6	21.7	
Respiratory	22.7	8.1	43.5	
Surgical wound mediastinitis	13.6	18.9	8.7	
Skin	31.8	27.0	8.7	
Others	22.7	24.3	17.4	

12 months after transplantation (63.8 ± 26.0 and 67.1 ± 27.5 mL/min, respectively; $P < .000001$). There were no significant between-group differences ($P = .92$) (Table 2).

Post-transplant new-onset diabetes was found in 26.0% of recipients, without significant between-group differences (ERT group, 29.7%; EC group, 24.4%; SRT group, 19.4%; $P = .52$). Levels of glycated hemoglobin at 12 months were available in 98 patients (54.4%). Glycated hemoglobin was significantly higher in the ERT group (6.2% ± 0.8%) than in the SRT group (5.3% ± 0.9%; $P = .0002$) and the EC group (5.5% ± 0.6%; $P = .001$). Between-group differences were statistically significant only in nondiabetic patients (Table 2), although average levels of glycated hemoglobin were less than 6% in the 3 groups. These results did not change after adjustment for mean daily dose of prednisone, mean trough levels of tacrolimus, or total number of rejection.

The main laboratory findings, systolic blood pressure and left ventricular ejection fraction during the first year after transplantation are summarized in Table 2. Nonstatistically significant differences were observed between the study groups.

One patient on ERT therapy was converted to SRT 6 months after transplantation due to persistent allograft rejection and the requirement of high ERT dosages to achieve adequate tacrolimus trough levels. No other formulation-related adverse effect led to switching to another therapy group. There were 3 deaths during the first year after transplantation, 1 in the SRT group and 2 in the ERT group.

DISCUSSION

Extended-release tacrolimus, available in Europe since 2007, was designed from a galenic modification of tacrolimus intended to be delivered in a more distant area of the gastrointestinal tract. This modification allows once-daily dosage and presumably better treatment adherence.[5] In chronic, stable heart recipients, the extended-release formulation has proved to be similar to the standard-release preparation in terms of safety and efficacy.[3–6] Although both tacrolimus formulations share a similar pharmacokinetic profile, in this clinical context, the trough levels achieved with the ERT formulation seem to be lower than those obtained with equivalent doses of the SRT formulation, with approximately one third of patients requiring a dose up-titration to maintain drug levels within the therapeutic range.[3,4] The experience with the *de novo* use of ERT in heart transplantation is much more limited. The possible benefits of a simplified immunosuppressive regimen should be balanced against the uncertainties related to the absorption of the new formulation in the specific environment of the acute phase of the transplant. This also includes the possibility of interaction with the multiple medications used in this phase.

In the present multicenter study with the largest population using ERT in the *de novo* setting reported to date, there were no significant differences between the SRT and the ERT formulations regarding mean tacrolimus dose and serum trough levels. Similar findings were observed for EC from SRT to ERT. Only 1 patient (1.06%) on ERT therapy had to be converted to SRT due to persistent allograft rejection and inadequate drug levels, despite increasing doses of ERT. Ghodsizad et al.[9] found lower trough levels of tacrolimus with the use of ERT compared with SRT only in the first 5 days after transplantation, a similar finding to that reported in kidney transplantation.[16] In contrast, Fuchs et al.[10] reported a need for higher doses of ERT compared with SRT to reach similar trough levels for both formulations beyond the first month after transplantation. Similarly, Helmschrott et al.[12] observed lower serum levels of tacrolimus with ERT use than with the use of equivalent doses of SRT. It should be recognized that there is no clear explanation for these discordant results. A possible explanation could be that an eventual failure of adherence can have a more profound impact in once-daily than in twice-daily schemes.

We found that both *de novo* and the early use of ERT had similar incidence rates of allograft rejection, infection, and CMV infection/disease compared with conventional immunosuppression with SRT. These results remained unchanged after adjustment for the main clinical confounders in each endpoint and agree with those previously reported,[7–12] although some authors[9,10] have reported a higher incidence of low-grade rejection in recipients treated with SRT than in those treated with ERT therapy but with no impact on clinical outcome. The results should be interpreted in the context of contemporary immunosuppression, with high rates of antibody induction therapy as well as use of MMF and prednisone. Irrespective of the formulation of tacrolimus selected, corticosteroids were withdrawn in approximately 40% of patients at 1 year. Likewise, the clinical characteristics of the present cohort reflect the current patient profile, particularly in the ERT groups, with a high proportion of diabetes, mechanical circulatory support, and use of marginal donors. This could explain the trend to a higher incidence of bacteremia in the ERT groups compared with the SRT group.

The safety parameters (laboratory, systolic blood pressure, left ventricular ejection fraction) showed no significant differences between the study groups. Of note, as previously reported,[10–12] the time course of renal function did not differ for the ERT and SRT formulations. There was no significant increase in the incidence of new-onset diabetes after transplantation with the use of ERT. This is in accordance with data from a meta-analysis carried out in kidney recipients.[17] However, we observed a mild but significant increase in glycated hemoglobin with the use of ERT compared with SRT, particularly in nondiabetic patients. This agrees with findings from studies in chronic liver transplantation,[18] although the opposite has been reported in stable kidney recipients.[19] In the present study, the increase in glycated hemoglobin was not dependent on the tacrolimus trough levels and cumulative corticosteroid dose. Consequently, this finding raises some concerns with regard to the possibility of a specific diabetogenic effect of ERT that deserves further investigation.

Limitations

The main shortcoming of this study is its retrospective design, which entails definite limitations. However, our results reflect daily clinical practice in a group of transplant programs applying a previously favorable experience with ERT in chronic heart recipients to an earlier post-transplant clinical context. There could also be an era effect, since patients treated with ERT corresponded to a more recent time period. This affected the baseline characteristics of the study groups, which in general terms were more unfavorable in the ERT group than in the SRT group. Furthermore, the sample size could jeopardize the statistical power of some of our analyses. This applies particularly to the analysis of glycated hemoglobin, which was available in only half of the patients.

Our analysis was restricted to the first year after transplantation, the most critical phase regarding the incidence and severity of rejection and infection. However, previous publications have already proven the safety and efficacy of ERT in chronic stable patients after the first year. We could not assess treatment adherence, which is possibly the greatest advantage of the use of ERT compared with SRT. However, adherence could be a less prevalent problem in the acute phase of heart transplantation than in later stages.

A newer formulation of ERT has recently been developed.[20] It seems that this formulation has different pharmacokinetics than

the formulation assessed in our study. Thus, the results of the present study cannot be extrapolated to this new formulation.

CONCLUSIONS

Our results suggest that ERT used in a *de novo* heart transplantation setting, as well as in EC from SRT, seems to have a similar safety and efficacy profile to SRT.

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CONFLICTS OF INTEREST

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WHAT IS KNOWN ABOUT THE TOPIC?

- Tacrolimus is currently the most frequently used calcineurin inhibitor in heart transplantation.
- The use of an extended-release formulation of tacrolimus allows once-daily dosage.
- This formulation has been thoroughly evaluated in the chronic setting of heart transplantation compared with the standard formulation requiring twice-daily dosage.

WHAT DOES THIS STUDY ADD?

- To our knowledge, the present study evaluates the safety and efficacy of *de novo* use and the use in the early phases (within 6 months) of heart transplantation of ERT in the largest series reported to date. The results are compared with those obtained with the use of SRT.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version available at http://dx.doi.org/10.1016/j.rec.2017.03.014.

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