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Conversion from immediate-release tacrolimus to prolonged-release tacrolimus in stable heart transplant patients: a retrospective study

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Abstract

Background

Lifelong adherence with post-transplant immunosuppression is challenging, with nonadherence associated with greater acute rejection (AR) risk.

Methods

This retrospective study evaluated conversion from immediate-release tacrolimus (IRT) to prolonged-release tacrolimus (PRT), between January 2008 and December 2012 in stable adult heart transplant recipients. Cumulative incidence rate (IR) of AR and infection pre- and postconversion, safety, tacrolimus dose and trough levels, concomitant immunosuppression, and PRT discontinuation were analyzed (intention-to-treat population).

Results

Overall, 467 patients (mean age, 59.3 [SD, 13.3] years) converted to PRT at 5.1 (SD, 4.9) years post transplant and were followed for 3.4 (SD, 1.5) years. During the 6 months post conversion, 5 patients (1.1%; 95% CI, 0.35%–2.48%) had an AR episode and IR was 2.2/100 patient-years (95% CI, 0.91–5.26). Incidence of rejection preconversion varied by time from transplant to conversion. Infection IR was similar post- and preconversion (9.2/100 patient-years [95% CI, 7.4–11.3] vs 10.6/100 patient-years [95% CI, 8.8–12.3], respectively; P = .20). Safety variables remained similar post conversion. The IR of mortality/graft loss was 2.3/100 patient-years (95% CI, 1.7–3.1).

Conclusions

Conversion from IRT to PRT in heart transplant recipients in Spain was associated with no new safety concerns and appropriate immunosuppressive effectiveness.

Tacrolimus is a well-established immunosuppressive agent for the prevention and treatment of allograft rejection. Two oral capsule formulations are currently available. Prolonged-release tacrolimus (PRT), available in Spain since 2007, is a once-daily formulation introduced as an alternative to twice-daily, immediate-release tacrolimus (IRT). Previous studies have indicated that the area under the concentration–time curve of tacrolimus is approximately 10% lower following conversion from IRT to PRT in kidney, liver, and heart recipients [1], [2], [3], and dose adjustments may be required post conversion to achieve similar tacrolimus trough levels [4], [5], [6]. Simplifying transplant immunosuppressive regimens is desirable, as patient adherence to a lifelong treatment remains challenging. This may be because of complex treatment regimens with multiple tablets and different frequencies of administration in addition to adverse events (AEs). Nonadherence in transplant patients is especially important in the long term, where unsatisfactory outcomes are observed [7], [8], [9], [10]. Indeed, nonadherence is increasingly recognized as an important and scarcely reported cause of late acute rejection (AR), chronic rejection, and graft loss [8], [10], [11], [12], [13], [14], [15], [16], [17]. Recent studies of converting solid organ transplant recipients to PRT [18], [19], [20], [21] suggest that once-daily dosing improves adherence vs twice-daily dosing [18], [19], [20], [21], [22].

While many heart recipients in Spain have converted to PRT, the outcomes and safety of this conversion have not been evaluated. This retrospective observational study explored the conversion from IRT to PRT in the largest series of stable heart transplant patients to date, with the primary aim to analyze AR episodes and infections, which are associated with tacrolimus under- and overimmunosuppression, respectively [23]. A secondary aim was to explore the dose and trough levels of tacrolimus, and tolerability and safety after the conversion.

Patients and Methods

This multicenter, observational, retrospective study was carried out in 14 centers in Spain. The study was conducted according to the Declaration of Helsinki and was approved by the ethics committee of the University Hospital Marqués de Valdecilla (Santander, Spain). All current regulations for noninterventional studies, patient and data protection, and the specific policy of each center or administrative region were applied. All patients provided written informed consent for their data to be used.

Patients and Procedures

Adult patients (older than 18 years at the time of conversion) who had undergone heart transplant, received ≥6 months of continued treatment with IRT (Prograf®, Astellas Pharma Ltd, Chertsey, United Kingdom), and who underwent conversion to PRT (Advagraf®, Astellas Pharma Europe BV, Leiden, Netherlands) between January 2008 and December 2012 were eligible to participate in the study. Patients were followed up until June 2013; all study visits took place at the participating centers. All data were collected retrospectively from the centers' registries in an electronic case report form. Data collection was performed by the investigator or the person delegated to act on their behalf. The procedures used for assuring data quality were consistent with those reported for the Spanish Heart Transplantation Registry [24].

Tacrolimus daily dose and serum trough levels, concomitant immunosuppression, concomitant medication, laboratory evaluation, and graft function were recorded at 6 months preconversion, at the time of conversion, and at 1, 6, 12, 24, 36, and 48 months post conversion. Occurrence of AR and infections was recorded from 2 years preconversion to the end of follow-up. Incidence and reasons for PRT discontinuation were recorded over the follow-up period.

Variables and Endpoints

No common strategy or specific protocol for rejection surveillance following PRT conversion was used across participating centers. The primary endpoint was the cumulative incidence rate (IR) of AR at 6 months post conversion from IRT to PRT, defined as any episode of rejection determined by clinical suspicion, echocardiogram, or biopsy that caused an intensification of immunosuppressive treatment. AR episodes separated by ≥15 days after the treatment of the preceding event were considered independent, in line with recommendations from the Spanish Heart Transplant Groups Consensus Conference [25].

Secondary variables, including the incidence of biopsy-confirmed AR and infection, were compared before and after conversion from IRT to PRT. Infection was defined as any episode requiring intravenous antibiotic therapy, hospital admission, or specific therapy for opportunistic infections (eg, tuberculosis). Safety analyses included the incidence of diabetes, and renal dysfunction–as renal dysfunction has been associated with the use of calcineurin inhibitors [26] and post-transplant diabetes mellitus has been reported in patients receiving tacrolimus-based immunosuppression [27], [28]. Renal dysfunction was defined as a 25% increase in serum creatinine at 2 consecutive determinations, in line with current consensus for the decrease in estimated glomerular filtration rate used to define chronic renal disease [29]. It was considered that an increase of <25% may be due to physiological variations in serum creatinine levels. At the end of the follow-up period, patient and graft survival, and biopsy-confirmed AR, were also analyzed.

Statistical Procedures

No formal sample size calculation was performed. Continuous variables are summarized as mean (SD). Categorical variables are described as percentages.

Differences in pre- and postconversion occurrence of AR and infection were assessed by comparing their respective IRs (number of episodes per 100 patient-years on treatment) and by comparing the IR ratio using the preconversion period as reference. Because the incidence of rejection is influenced by the time elapsed since transplant, differences between pre- and postconversion periods were analyzed in the whole study group and separately in 3 patient subsets according to time from transplant to conversion (<2, 2–4, and ≥4 years).

Significance level was established at $P < .05$, with no adjustment for multiplicity. The statistical package SPSS 17.0 (SPSS Inc., Chicago, Illinois) was used.

Results

Overall, 467 heart recipients met eligibility criteria and were included in the study, and none were lost to follow-up; demographic and clinical characteristics are summarized in Table 1. The mean time from transplant to conversion was 5.1 (SD, 4.9) years. Conversion from IRT to PRT was carried out <2 years post transplant in 119 patients (25.5%), between 2 and 4 years in 82 patients (17.6%), and ≥4 years after transplant in 266 patients (57.0%). Patients were followed up after conversion for a mean of 3.4 (SD, 1.5) years.

Table 1. Patient Baseline and Preconversion Characteristics, Time of Conversion, and Donor Characteristics (N = 467)

Characteristic	
Age, mean (SD), y	59.3 (13.3)
Sex, male/female, %	68.5/31.5
Primary diagnosis of cardiopathy, %	
Dilated	71.7
Ischemic	7.7
Others	20.6
Weight at baseline, mean (SD), kg	70.1 (14.5)
CMV serology positive, %	79.0
Hypertension (n = 454), %	60.4
Diabetes (n = 454), %	29.1
Cerebrovascular accident, %	8.1
Malignant neoplasm (n = 32), %	
Cutaneous	56.3
Lymphoproliferative	12.5
Solid organ	34.4
History of heart failure, %	7.7
Cardiac allograft vasculopathy, %	11.6
Cardiac rhythm (conversion visit) (n = 463), %	
Sinus rhythm	96.1
Atrial fibrillation	0.6
Pacemaker	1.7
Other	1.5
Time from transplant to conversion, mean (SD), y	5.1 (4.9)
Conversion time post transplant, No. (%)	
<2 y	119 (25.5)
2–4 y	82 (17.6)
≥4 y	266 (57.0)
Donor age (n = 466), mean (SD), y	34.7 (12.8)
Donor sex, male/female (n = 467), %	65.7/34.3

Abbrevation: CMV, cytomegalovirus.

Tacrolimus Daily Dose and Serum Trough Levels

The mean doses of IRT immediately preconversion and the initial dose of PRT at conversion were 3.84 (SD, 2.54) mg/d and 3.97 (SD, 2.57) mg/d, respectively (P = .27). Compared with preconversion values on IRT, mean PRT daily dose remained steady after 2 years had elapsed post conversion (Fig 1A). Mean tacrolimus trough level (preconversion) with IRT (8.93 [SD, 3.49] ng/mL) declined 1 month after conversion to PRT (7.86 [SD, 2.86] ng/mL), and was 7.70 (SD, 2.91) ng/mL and 6.95 (SD, 2.53) ng/mL at months 6 and 48, respectively (Fig 1B). During the 48-month follow-up period, serum levels of PRT decreased significantly vs preconversion levels (P < .01).

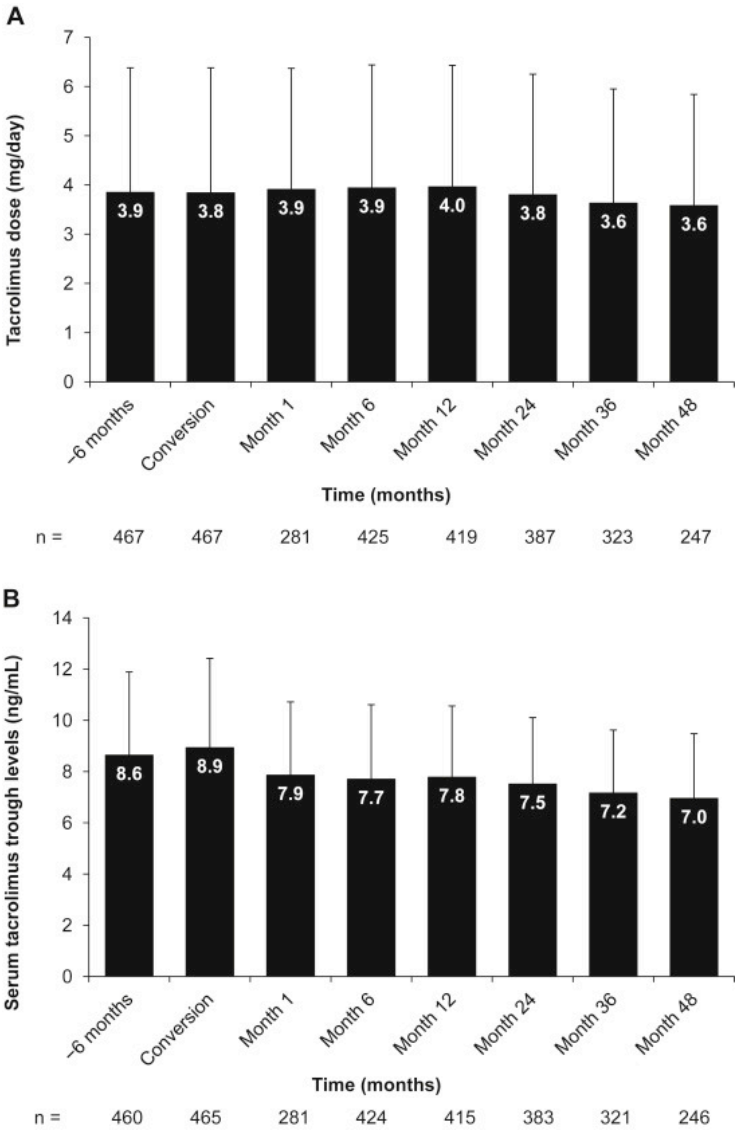

Fig 1. **(A)** Mean (SD) daily dose and **(B)** mean (SD) serum trough levels of tacrolimus over the study period for all patients. Conversion was at time point 0.

Concomitant Immunosuppression

Concomitant immunosuppression use is summarized in Table 2. The proportion of patients using mycophenolate mofetil and prednisone decreased between month 1 and month 48 post conversion. Use of mammalian target of rapamycin inhibitors (largely everolimus and not sirolimus) increased approximately 2-fold during follow-up.

Table 2. Concomitant Immunosuppression Use in All Patients Defined According to Time From Conversion to Prolonged-Release Tacrolimus

Immunosuppressive Agent, %	Conversion Visit*	6 Mo (n = 432)	12 Mo (n = 434)	24 Mo (n = 401)	36 Mo (n = 341)	48 Mo (n = 261)
MMF	76.6	73.4	71.0	69.0	67.3	65.9
Mycophenolic acid	7.0	7.7	8.3	8.0	9.1	10.7
Prednisone	58.6	56.2	54.1	51.1	50.7	49.4
Azathioprine	5.4	5.1	5.1	5.0	5.3	4.6
Sirolimus	1.1	1.2	1.1	1.2	1.2	0.8
Everolimus	6.4	7.9	10.2	11.7	12.9	13.5

Information on immunosuppressive agent use in all patients was not available; therefore, denominators vary (n).
Abbreviation: MMF, mycophenolate mofetil.
*Because of missing data, n is: MMF, n = 461; mycophenolic acid, n = 444; prednisone, n = 454; azathioprine, n = 441; sirolimus, n = 438; everolimus, n = 437.

Rejection and Infection

During the 6 months post conversion, 5 patients (1.1%; 95% CI, 0.35%–2.48%) had an AR episode. The time-adjusted IR of AR 6 months after conversion was 2.19 (95% CI, 0.91–5.26) AR events per 100 patient-years, with a cumulative follow-up of 228.35 patient-years.

In the 2 years before conversion (837.68 patient-years), there were 68 episodes of rejection in 48 patients. Thus, 10.3% of patients had at least 1 rejection episode preconversion, with most (79.2%) of these patients experiencing 1 event.

In the 2 years post conversion, with a cumulative follow-up of 891.56 patient-years, there were 18 rejection episodes. Fifteen patients (3.2%) presented with at least 1 rejection episode; 12 of these patients had 1 rejection episode, and 3 patients had 2 rejections. The 2-year preconversion rejection IR was 8.1 per 100 patient-years (95% CI, 6.4–10.3), and was 2.0 per 100 patient-years (95% CI, 1.3–3.2) in the 2-year postconversion period ($P < .0001$) (Fig 2A). Therefore, the IR ratio of rejection (2 years post conversion:2 years preconversion) was 0.25 (95% CI, 0.14–0.42). This overall decrease was largely due to the decline in rejection IR among patients converted <4 years post transplant, with no significant changes in those patients converted beyond 4 years post transplant (Fig 2B).

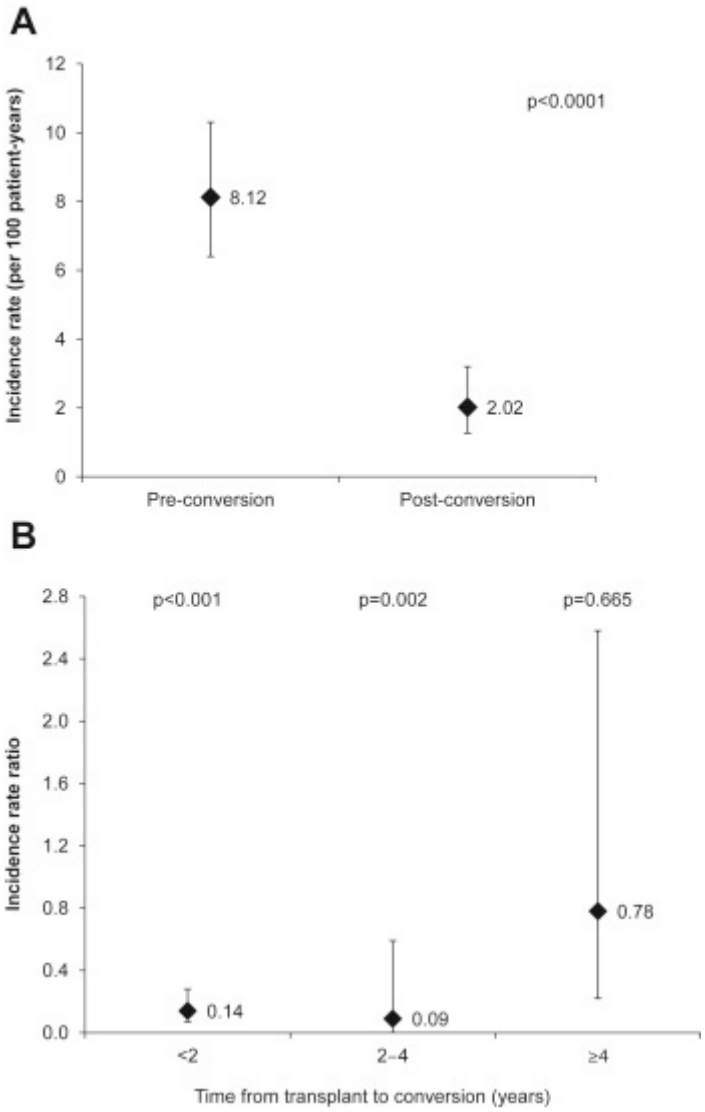

Fig 2. **(A)** Pre- and postconversion incidence rates of rejection for all patients and **(B)** incidence rate ratio (post- to preconversion) of rejection split by time from transplant to conversion from immediate- to prolonged-release tacrolimus (<2, 2–4, and ≥4 years). Bars represent the upper and lower limits of the CI. IRT, immediate-release tacrolimus

In the 2 years before conversion, 16 (23.5%), 50 (73.5%), and 15 (22.1%) rejection episodes were diagnosed based on clinical suspicion, biopsy, and echocardiogram, respectively (rejections could be diagnosed by more than 1 method). In the 2 years post conversion, of the 18 rejection episodes, 16 (88.9%), 15 (83.3%), and 11 (61.1%) were diagnosed based on clinical suspicion, biopsy, and echocardiogram, respectively. Compared with the 2-year preconversion period, the 2-year postconversion period showed a trend toward a higher likelihood of a rejection diagnosis being made by biopsy (73.5% vs 83.3%), a higher proportion of rejection episodes with hemodynamic compromise (10.3% [n = 7] vs 25.0% [n = 4]), and a higher proportion of cytolytic therapy usage (4.4% [n = 3] vs 11.1% [n = 2]).

Overall, there were 99 infection episodes in 82 patients in the 2 years preconversion (infection rate 17.6%; IR, 10.6 per 100 patient-years; 95% CI, 8.8–12.3) and 82 infections in 67 patients in the 2-year postconversion period (IR, 9.2 per 100 patient-years; 95% CI, 7.4–11.3). The difference between the postconversion and preconversion IR was not statistically significant (IR ratio, 0.87; 95% CI, 0.64–1.17; $P = .17$) (Fig 3). During the pre- and postconversion periods, most infection episodes required hospitalization (82.8% vs 80.7%, respectively).

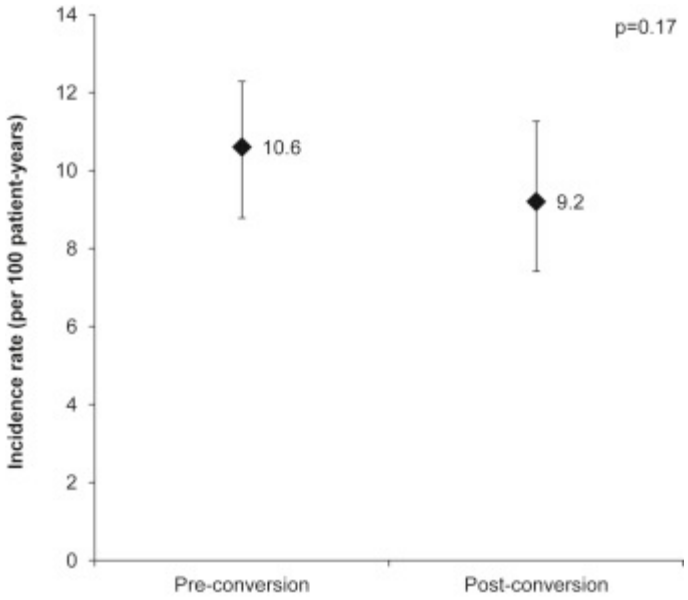

Fig 3. Pre- and postconversion incidence rates of infection for all patients. Bars represent the upper and lower limits of the CI. IRT, immediate-release tacrolimus.

Safety Evaluation

Key safety findings among patients converted to PRT are summarized in Table 3. There were increases in leukocytes, hemoglobin, total cholesterol, low-density lipoprotein cholesterol, body weight, systolic and diastolic blood pressure, and the prevalence of nonsinus rhythm during follow-up. Cardiac and renal function, assessed by left ventricular ejection fraction and serum creatinine levels, respectively, remained stable, and there was a decrease in glomerular filtration rate. The trends in safety parameters were not considered clinically relevant. Between month 1 and month 24 post conversion, 6.5% of patients experienced renal dysfunction. The proportion of patients with diabetes in the preconversion period and 48 months post conversion was similar (29.1% and 31.5%, respectively).

PRT was discontinued in 33 patients (7.1%), who could have more than 1 reason for discontinuation; in approximately half of cases (n = 15, 3.2% of the total study population), AEs were the reason for treatment discontinuation. Other reasons for discontinuation included implementation of a calcineurin inhibitor-free regimen because of malignancy (8 patients, 1.7%), patients' refusal to take PRT (5 patients; 1.1%), inadequate tacrolimus serum trough levels (2 patients; 0.4%), renal failure (2 patients; 0.4%), AR (1 patient; 0.2%), and physician's refusal to administer PRT (1 patient; 0.2%).

There were 34 deaths (7.3%) by the end of follow-up. Causes of death were malignancy (10 patients; 2.1%), graft vascular disease (6 patients; 1.3%), sudden death (6 patients; 1.3%), AR (4 patients; 0.9%), infection (1 patient; 0.2%), and "other" (7 patients; 1.5%). The IR of mortality/graft loss was 2.3 per 100 patient-years (95% CI, 1.7–3.1).

Table 3. Safety Parameters in Patients Converted to Prolonged-Release Tacrolimus (N = 467)

Parameter	Preconversion	6 Mo	12 Mo	24 Mo	36 Mo	48 Mo
Leukocytes, × 10^3	7.2 (2.3)	7.4 (2.1)	7.5 (2.2)	7.4 (2.4)	7.4 (2.2)	7.3 (2.1)
Hemoglobin, g/dL	13.4 (1.8)	13.6 (1.7)	13.7 (1.7)	13.7 (1.7)	13.7 (1.8)	13.8 (1.7)
Platelets, × 10^3	211.5 (67.7)	209.2 (61.9)	211.0 (61.9)	205.7 (61.8)	207.2 (64.8)	208.4 (67.8)
Fasting glycemia, mg/dL	106.4 (38.9)	107.4 (41.3)	107.7 (37.1)	106.61 (33.1)	106.5 (31.4)	107.1 (37.3)
Insulin therapy, %	18.0	18.8	18.9	17.2	18.8	18.8
Serum creatinine, mg/dL	1.28 (0.61)	1.26 (0.62)	1.24 (0.62)	1.27 (0.61)	1.27 (0.52)	1.27 (0.56)
GFR, mL/min/1.73 m^2	71.9 (25.2)	66.4 (23.8)	67.5 (23.6)	73.3 (26.2)	65.9 (25.1)	65.7 (24.6)
Total cholesterol, mg/dL	168.4 (35.2)	172.4 (34.6)	174.4 (35.5)	175.3 (35.9)	173.6 (35.7)	173.3 (34.2)
HDL cholesterol, mg/dL	52.4 (15.6)	52.4 (15.6)	53.6 (15.2)	55.1 (15.9)	53.6 (15.5)	54.6 (17.2)
LDL cholesterol, mg/dL	91.0 (28.5)	94.7 (28.5)	94.6 (26.8)	94.3 (28.9)	95.2 (26.3)	94.7 (25.8)
Triglycerides, mg/dL	131.1 (82.2)	128.2 (82.2)	133.4 (95.1)	129.3 (69.3)	126.2 (64.2)	125.8 (63.6)
AST, U/L	23.5 (15.7)	23.5 (15.7)	22.7 (16.9)	21.9 (13.8)	23.4 (18.2)	22.9 (16.6)
ALT, U/L	23.1 (18.6)	23.1 (18.6)	21.3 (14.9)	21.2 (14.4)	22.2 (18.6)	22.7 (17.7)
Weight, kg	74.7 (15.9)	74.7 (16.0)	75.6 (16.4)	76.3 (16.4)	76.2 (16.5)	76.3 (16.3)
Systolic blood pressure, mm Hg	128.7 (16.7)	128.7 (16.7)	129.7 (16.5)	132.1 (16.4)	132.0 (18.4)	133.0 (17.4)
Diastolic blood pressure, mm Hg	81.1 (10.7)	81.1 (10.7)	81.9 (10.6)	83.7 (11.9)	83.3 (11.8)	83.9 (11.9)
Heart rate, bpm	88.8 (13.9)	88.8 (13.9)	88.0 (13.5)	87.9 (14.0)	88.6 (13.9)	88.2 (13.3)
Nonsinus rhythm, %	3.9	3.9	5.5	5.0	6.2	7.7
Left ventricle ejection fraction, %	63.8	64.6	64.8	64.8	64.1	64.45

Data are mean (SD) unless otherwise stated.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; bpm, beats per minute; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Discussion

To date, a small number of studies have explored the use of PRT immunosuppression in heart transplant recipients. As these studies were small [5] or focused on pharmacokinetics and drug dosage [1], [4], data on the characteristics and results of tacrolimus conversion in cardiac recipients have not been described. Our results from this large multicenter study suggested that the rate of infection remained similar before and after conversion from IRT to PRT. The incidence of AR was lower during the 48 months of follow-up post conversion from IRT to PRT compared with the rates within 2 years preconversion. However, the time since transplant was not accounted for in analyses of the overall cohort. Therefore, comparisons of rejection IR between pre- and post conversion should be interpreted with caution. Indeed, after stratifying our results by time between transplant and conversion, the decrease in rejection IR was largely due to the decline in rejection IR among patients converted <4 years post transplant, with no significant changes in those patients converted beyond 4 years post transplant. As such, the reduction in rejection rates post conversion may be due to greater time elapsed since transplant than to a true positive effect of the conversion. Additionally, it is likely that the frequency of routine biopsy surveillance was lower post- vs preconversion, and that postconversion rejection episodes were diagnosed on the basis of clinical suspicion and were confirmed by biopsy findings. Indeed, the frequency of diagnosis of rejection episodes based on clinical suspicion was substantially higher post conversion (88.9%) vs preconversion (23.5%). Interestingly, compared with the 2-year preconversion period, during all study follow-up there was a higher proportion of rejection episodes with hemodynamic compromise, although the cause for this is unclear.

In our study, the PRT daily dose used at conversion was only 0.13 mg higher than that used for IRT. Mean tacrolimus trough levels are approximately 10% lower immediately post conversion from IRT to PRT on a 1mg:1mg total daily dose basis [1], [2], [3], and the reduction in trough levels may be greater in individual patients [2]. However, the maintenance of target tacrolimus levels is manageable via trough level monitoring and dose adjustment [30]. Studies have shown that approximately 10% of kidney and liver transplant patients converted from IRT to PRT on a 1mg:1mg total daily dose basis may require tacrolimus dose adjustment [31], [32]. In heart transplant patients, after conversion from IRT to PRT on day 8, Alloway et al reported an increase of approximately 10% in tacrolimus dose by day 35 to achieve tacrolimus trough levels within the range of 5 to 15 ng/mL [2]. Marzoa-Rivas et al report that a 25% increase in daily dose may be required to achieve the appropriate trough levels immediately after conversion from IRT to PRT in heart transplant recipients [4]. Accordingly, in a recent study of heart transplant patients receiving de novo PRT or IRT, a significantly higher daily dose of PRT was required to provide similar trough levels to IRT [6]. In our study, the trough level achieved with a mean IRT dose of 3.84 mg/d was higher than that achieved with a similar dose of PRT, which is consistent with other reports. However, the levels determined during the 48 months of follow-up, with the steady dose reduction, were within target [30].

The tacrolimus trough levels achieved with PRT in our study were sufficient (with concomitant immunosuppressive agents) to avoid AR. We did not observe the previously reported substantial progressive reduction in serum tacrolimus trough levels in patients receiving PRT de novo [5], [6]. Our results are more consistent with those of van Hooff et al, who found that tacrolimus trough concentrations were generally maintained at a stable level during 4 years of follow-up in heart transplant patients who converted to PRT, while doses were slightly reduced [33]. In our study, doses and serum trough levels maintained almost parallel curves during follow-up, which suggests good adherence to PRT.

Biochemical parameters indicate a comparable safety profile between IRT and PRT in our study, which is consistent with other reports showing similar renal function, blood cell counts, liver function tests [1], [3], [4], [6], [18], [34], left ventricular function [6], and glycemia [4] between the formulations. Although there were changes in several parameters, including blood cell counts, lipid levels, body weight, and blood pressure, these trends were not considered to be clinically relevant. Regarding comorbidities and the safety of conversion to PRT in our study, follow-up data did not reveal substantial changes over time between the formulations or compared with baseline. For instance, serum glucose levels and the proportion of patients with insulin-dependent diabetes remained similar throughout the study.

Conversion from IRT to PRT was generally well tolerated, as shown by the low dropout rate. There were 33 patients who discontinued PRT, with AEs the cause in approximately half of cases. The incidence of AEs with PRT administration in a 4-year period is high, according to previous trials [33], but this aspect was not closely monitored in our study. Van Hooff et al found that the incidence of AEs decreased over the 4-year follow-up, with infections, metabolic and nutrition disorders, and neoplasms being the most commonly-reported events among heart transplant recipients [33]. Of note, in this study, most infections (>80%) required hospitalization. This may be related to the challenge of tracking milder infections, for which patients may see their family physician or which may not be well documented in outpatient notes.

There were some limitations to the study analyses. For example, observations were not independent, and only patients that converted were analyzed. It is likely that only patients with clinically stable tacrolimus dose and trough levels were converted, and, therefore, results may not apply to less clinically stable patients. Furthermore, competing risks (death and graft loss) and time since transplant may not have been sufficiently controlled. As such, there may be bias in the analyses herein, which could affect interpretation of the data. Additionally, comparing the overall IR for AR pre- vs post conversion could be affected by decreases in the risk of AR with time post transplant. There were also no controls for the different factors that may have contributed to the incidence of AR, such as nonadherence with immunosuppressive medication and concomitant immunosuppressive use. However, as concomitant immunosuppressive use was generally similar pre- and post conversion, it is unlikely to have strongly impacted the incidence of AR. The retrospective nature of the study also makes it difficult to explain the trend toward a higher likelihood of a rejection diagnosis being made by biopsy and the increase in rejection with hemodynamic compromise post vs preconversion to PRT, and patterns in cytolytic therapy usage. There was also a delay between study completion and manuscript preparation; however, the data remain relevant.

Conclusions

In summary, this study provides valuable information about tacrolimus dosing, trough levels, and clinical effectiveness associated with the conversion of stable heart transplant recipients from IRT to PRT in clinical practice. The long-term experience reported here suggests that conversion from IRT to PRT in stable heart transplant recipients is accompanied by appropriate immunosuppressive effectiveness, adequate tolerability, and no new safety concerns. Moreover, PRT offers a more convenient dosing regimen that may have an impact on adherence, possibly influencing effectiveness, since enhanced adherence may yield improvements in long-term graft survival.

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Data Statement

Access to anonymized individual participant level data will not be provided for this trial as it meets 1 or more of the exceptions described on www.clinicalstudydatarequest.com under "Sponsor Specific Details for Astellas."

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