Everolimus With Reduced Cyclosporine Versus MMF With Standard Cyclosporine in De Novo Heart Transplant Recipients

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Background. Pharmacokinetic modeling supports trough monitoring of everolimus, but prospective data comparing this approach versus mycophenolate mofetil (MMF) in de novo cardiac transplant recipients are currently unavailable.

Methods. In a 12-month multicenter open-label study, cardiac transplant patients received everolimus (trough level 3–8 ng/mL) with reduced cyclosporine A (CsA) or MMF (3 g/day) with standard CsA, both with corticosteroids±induction therapy.

Results. In total, 176 patients were randomized (everolimus 92, MMF 84). Mean creatinine clearance was 72.5±27.9 and 76.8±32.1 mL/min at baseline, 65.4±24.7 and 72.2±26.2 mL/min at month 6, and 68.7±27.7 and 71.8±29.8 mL/min at month 12 with everolimus and MMF, respectively. The primary endpoint was not met since calculated CrCl at month 6 posttransplant was 6.9 mL/min lower with everolimus, exceeding the predefined margin of 6 mL/min. However, by month 12 the between-group difference had narrowed versus baseline (3.1 mL/min). All efficacy endpoints were noninferior for everolimus versus MMF. The 12-month incidence of biopsy-proven acute rejection International Heart and Lung Transplantation grade more than or equal to 3A was 21 of 92 (22.8%) with everolimus and 25 of 84 (29.8%) with MMF. Adverse events were consistent with class effects including less-frequent cytomegalovirus infection with everolimus (4 [4.4%]) than MMF (14 [16.9%], $P=0.01$).

Conclusion. Concentration-controlled everolimus with reduced CsA results in similar renal function and equivalent efficacy compared with MMF with standard CsA at 12 months after cardiac transplantation.

Keywords: Everolimus, Cyclosporine, MMF, Renal function, Cardiac transplantation, PSI, mTOR.

(*Transplantation* 2009;88: 115–122)

Calcineurin inhibitors (CNIs) effectively decrease the rate of acute rejection after cardiac transplantation and remain the cornerstone of immunosuppressive regimen. However, nephrotoxicity caused by CNIs impacts adversely on both short- and long-term morbidity and, together with new-onset diabetes and hypertension leads to an increased risk for cardiac allograft vasculopathy (*1*, *2*). Accordingly, there is intense interest in immunosuppressive strategies that can reduce long-term CNI exposure after cardiac transplantation.

The proliferation signal inhibitor everolimus offers the potential to reduce CNI exposure without loss of efficacy. In a randomized trial of 634 cardiac transplant recipients, everolimus administered at a fixed dose with standard cyclosporine A (CsA) and corticosteroids showed superior efficacy to azathioprine but was associated with a dose-related decrease in renal function versus the azathioprine cohort (*3*) attributed to everolimus potentiating the nephrotoxicity of CsA. More recently, in a randomized trial in de novo cardiac transplant recipients, concentration-controlled everolimus with reduced CsA from month 2 onward showed similar efficacy to everolimus

This work was supported by Novartis Pharma AG, Basel, Switzerland.
HL, JA, MV, LA, GG, MM, MF, and UL have received honoraria and travel grants from Novartis; HL, JA, LA and UL have received research grants from Novartis; and HL is a member of a Novartis Advisory Board. SV has no conflicts of interest to declare.
JMH and KCM are employees of Novartis.

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Received 21 January 2009. Revision requested 5 February 2009.
Accepted 25 March 2009.
Copyright © 2009 by Lippincott Williams & Wilkins
ISSN 0041-1337/09/8801-115
DOI: 10.1097/TP.0b013e3181aacd22

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with a standard CsA regimen, and there was a trend toward improved renal function in the reduced CsA cohort (*4*). In renal transplantation, concentration-controlled everolimus with reduced CsA has also been shown to preserve efficacy, while maintaining stable renal function (*5–7*). The synergistic action of everolimus and CsA thus seems to support the clinical strategy of reducing CsA without loss of immunosuppressive potency (*8*).

To date, only observational data are available to compare everolimus with mycophenolate mofetil (MMF) in cardiac transplantation (*9*). Here, we present the results of a multicenter, 12-month, randomized trial in which de novo heart transplant recipients were randomized to concentration-controlled everolimus with reduced CsA or to MMF with standard CsA, both in combination with corticosteroids, with or without induction therapy. The aim of the study was to compare renal function in the two treatment groups at month 6 after cardiac transplantation.

MATERIALS AND METHODS

Study Design

This was a 12-month multicenter, randomized, open-label study of renal function and efficacy in adult de novo heart transplant recipients. Patients were randomized 1:1 within 72 hr of transplantation to either (a) concentration-controlled everolimus with targeting of reduced CsA or (b) MMF with standard CsA, in combination with corticosteroids, with or without induction therapy. Randomization was performed using a validated system of blinded treatment allocation cards. Written informed consent was obtained from all patients and the study was conducted in accordance with the International Conference on Harmonization Harmonized Tripartite Guidelines for Good Clinical Practice and the ethical principles laid down in the Declaration of Helsinki after approved by the Institutional Review Board at each center.

Patients

Patients aged 18 to 65 years who received a primary heart transplant and who had a functioning graft at randomization with a calculated creatinine clearance greater than or equal to 50 mL/min at screening were eligible to take part in the study. Creatinine clearance was calculated by the Cockcroft-Gault equation (*10*), that is

$$\text{Creatinine clearance (ml/min)} = (140 - \text{age in years}) \times \text{weight in kg}/(72 \times \text{serum creatinine in mg/dL})(\textit{males})$$

$$\text{Creatinine clearance (ml/min)} = 0.85 \times (140 - \text{age in years}) \times \text{weight in kg}/(72 \times \text{serum creatinine in mg/dL})(\textit{females})$$

Exclusion criteria included multiorgan transplantation; induction therapy other than per local practice; donor age more than 60 years or a donor with known coronary or heart disease; cold ischemic time more than 6 hr; panel reactive antibodies more than 20%; platelet count less than 50,000/mm^3, absolute neutrophil count less than 1500/mm^3 or white blood cell count less than 4000/mm^3 at baseline; severe hypercholesterolemia (>9 mmol/L); or hypertriglyceridemia (>8.5 mmol/L).

Immunosuppression and Concomitant Medication

Patients randomized to everolimus (Certican, Novartis, Basel, Switzerland) received an initial dose of 0.75 mg two times per day within 72 hr of transplantation, subsequently adjusted to a target trough level of 3 to 8 ng/mL. For patients randomized to MMF (Cellcept, Roche, Basel, Switzerland), the dose was 1500 mg two times per day and usage was according to approved labeling. MMF was also initiated within 72 hr posttransplant. All patients received CsA microemulsion (Neoral, Novartis, Basel, Switzerland), initiated within 48 hr after reperfusion at a dose of 12 mg/kg per day or according to local practice in centers using induction therapy, and adjusted to target-prespecified CsA trough (C_0) levels. In the everolimus group, the C_0 target was 200 to 350 ng/mL during month 1, 150 to 250 ng/mL during month 2, 100 to 200 ng/mL during months 3 to 4, 75 to 150 ng/mL during months 5 to 6, and 50 to 100 ng/mL during months 7 to 12. In the MMF arm, C_0 target was 200 to 350 ng/mL during months 1 to 2, 200 to 300 ng/mL during months 3 to 4, 150 to 250 ng/mL during months 5 to 6, and 100 to 250 ng/mL during month 7 to 12. CsA levels measured locally (by antibody-based methods, high-performance liquid chromatography, or liquid chromatography mass spectroscopy) were used to adjust dosing and are reported here. CsA trough and C_2 levels were also measured centrally. Oral prednisone (or methylprednisolone equivalent) was initiated once oral dosing was tolerated at 0.5 to 1.0 mg/kg per day, tapered to greater than or equal to 0.1 mg/kg per day by month 6 and 0.1 to 0.05 mg/kg per day during months 6 to 12. Induction therapy was according to center practice.

Endomyocardial biopsies were to be performed by protocol at prespecified visits. Patients with suspected acute rejection were required to undergo an endomyocardial biopsy within 48 hr (and echocardiography, if deemed clinically relevant). Antirejection therapy was protocol-specified according to histologic severity and presence or absence of hemodynamic compromise. In patients experiencing a second rejection episode graded greater than or equal to 3A, or any second rejection episode associated with hemodynamic compromise, cessation of CsA or introduction of another agent was permitted, in which case study medication was discontinued. Histologic severity was graded according to the International Heart and Lung Transplantation (ISHLT) criteria established in 1990 (*11*), which were in routine clinical use at time the study was initiated.

Cytomegalovirus (CMV) infection is defined by the occurrence of positive antigenemia or polymerase chain reaction or seroconversion without signs or symptoms. CMV prophylaxis for more than or equal to 30 days was mandatory for D+/R− cases and was recommended after antibody treatment of acute rejection. Treatment with gancyclovir, CMV hyperimmune globulin, valgancyclovir, or valacyclovir was permitted according to center practice. All patients received *Pneumocystis carinii* pneumonia prophylaxis according to local protocol. Statin therapy was administered to all patients regardless of the presence or absence of elevated total or low-density lipoprotein cholesterol at baseline, initiated within the first 2 weeks posttransplant.

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Study Variables

The primary variable was renal function, as measured by calculated creatinine clearance (Cockcroft-Gault) at month 6 posttransplant. The main secondary variable was the incidence of biopsy-proven acute rejection (BPAR) of ISHLT grade greater than or equal to 3A at 6 months posttransplant. Other variables included the incidence of a composite efficacy failure endpoint (defined as BPAR grade ≥3A, acute rejection episodes associated with hemodynamic compromise, graft loss/retransplant, death, or loss to follow-up) and its component elements, serum creatinine, and the incidence of adverse events and infections.

Evaluation

Day 1 of the study was defined as the first day study medication was administered. The baseline period was defined as the 7 days leading up to the first dose of study medication. Baseline creatinine clearance was measured within the first 48 hr posttransplant, before the first dose of study medication. Study visits took place during the baseline period, days 1 and 4, weeks 1, 2, and 3, and months 1, 2, 3, 4, 5, 6, 9, and 12. Vital signs, hematological parameters and blood chemistry were recorded at each visit.

Statistical Analysis

The primary endpoint analysis was based on a noninferiority null hypothesis, that is renal function, as measured by creatinine clearance (Cockcroft-Gault), was similar in the everolimus- and MMF-treatment arms. The noninferiority margin was 6 mL/min, based on previous clinical experience (*3*), that is the everolimus arm would be noninferior to MMF if the creatinine clearance was not more than 6 mL/min lower than that in MMF-treated patients using a one-sided *t* test (0.025 level). In addition, the 95% confidence interval (CI) for the difference between the two treatments was calculated (*z* test); everolimus was considered noninferior if the lower bound of the confidence interval was greater than −6. Analysis of the main secondary variable (BPAR episodes ISHLT grade ≥3A at 6 and 12 months) was also based on a noninferiority null hypothesis, with a noninferiority margin of 10%. The composite efficacy failure endpoint and its components were analyzed similarly. Chi-square test was used for between-group comparisons of categorical data and Wilcoxon rank sum test for numerical data.

A power of 80% and a one-sided significance level of 0.025, assuming 10% dropout, led to a sample size of 88 patients per arm to test creatinine clearance with a noninferiority margin of 6 mL/min, based on the assumption that renal function was balanced at baseline and that the mean creatinine clearance at 6 months posttransplant would be 66 mL/min in the everolimus arm and 63 mL/min in the MMF arm, with an SD of 20 mL/min. With this sample size, the power for assessing noninferiority of BPAR with everolimus versus MMF ranged from 96% (assuming a difference in incidence of 17%) to 84% (assuming a difference of 11%).

The intent-to-treat (ITT) population consisted of all patients who were randomized after transplantation. The safety population consisted of all patients in the ITT population who received at least one dose of study drug and had at least one postbaseline safety assessment.

RESULTS

Study Population

Of 212 patients screened, 176 met the inclusion and exclusion criteria and were randomized (92 to everolimus and 84 to MMF) and formed the ITT population. The first patient visit took place in December 2004, with the last patient visit in May 2007. Two patients, one in each group, were randomized but died without taking study medication (acute graft failure and mediastinitis) and were therefore not included in the safety population. One hundred fifty-five patients completed the study on treatment (Fig. 1). Demographics and baseline characteristics of the study population

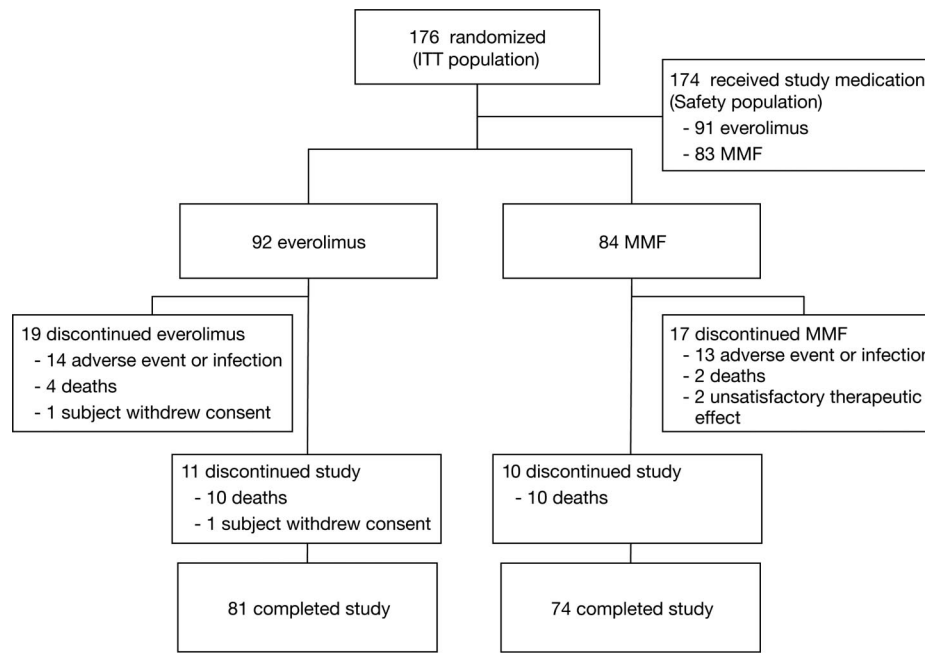

FIGURE 1. Patient disposition.

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were similar between treatment groups, other than a higher rate of pretransplant diabetes in the MMF cohort, which approached statistical significance ($P=0.055$, Table 1). The proportion of patients for whom protocol biopsies were performed at the prespecified time points varied over time (2–38%) but no consistent difference was observed between treatment groups.

TABLE 1. Patient demographics and baseline characteristics (ITT population)

	Everolimus (n=92)	MMF (n=84)
Recipient age (yr)	50.6±10.6	51.9±11.4
Male recipient	71 (77.2%)	71 (84.5%)
Recipient race		
White	90 (97.8%)	81 (96.4%)
Black	0	1 (1.2%)
Asian	0	1 (1.2%)
Other	2 (2.2%)	1 (1.2%)
End-stage disease leading to transplantation		
Idiopathic cardiomyopathy	37 (40.2%)	26 (31.0%)
Coronary artery disease	26 (28.3%)	35 (41.7%)
Valvular heart disease	7 (7.6%)	1 (1.2%)
Myocarditis	3 (3.3%)	4 (4.8%)
Postpartum cardiomyopathy	1 (1.1%)	3 (3.6%)
Viral cardiomyopathy	2 (2.2%)	1 (1.2%)
Congenital heart disease	2 (2.2%)	0
Other	13 (14.1%)	14 (16.7%)
Unknown origin	1 (1.1%)	0
History of diabetes	17 (18.5%)	27 (32.1%)
Panel reactive antibodies (%)		
0	80 (87.0%)	74 (88.1%)
1–10	2 (2.2%)	2 (2.4%)
11–20	1 (1.1%)	0
>20	2 (2.2%)[a]	1 (1.2%)[a]
Unknown	7 (7.6%)	7 (8.3%)
Donor age (yr)	37.3±13.4	37.5±12.7
Donor race		
White	67 (72.8%)	67 (79.8%)
Black	0	0
Asian	0	0
Other	2 (2.2%)	0
Unknown	23 (25.0%)	17 (20.2%)
Cold ischemia time (hr)	3.0±1.1	2.8±1.0
CMV status		
R+/D+	25 (27.2%)	27 (32.1%)
R+/D−	25 (27.2%)	27 (32.1%)
R−/D+	8 (8.7%)	12 (14.3%)
R−/D −	23 (25.0%)	9 (10.7%)
Missing	11 (12.0%)	9 (10.7%)

Continuous variables are shown as mean±SD. All differences were nonsignificant.

[a] Included against protocol.

CMV, cytomegalovirus; ITT, intent-to-treat.

Immunosuppression

Duration of exposure to study medication was similar for everolimus and MMF (mean±SD, 308.3±118 and 309.8±117 days, respectively). The mean everolimus trough level was within target range at all time points after day 4 (Table 2), with minimal adjustments to the initial dose. At months 1, 6, and 12, the mean everolimus trough levels were 5.7, 4.6, and 4.1 ng/mL, respectively. Overall, 85% of subjects remained within the target window through month 12. The mean dose of MMF decreased to month 6 then plateaued (Table 2). Although the proportion of patients who required discontinuation of study medication was almost the same for both arms (20.7% vs. 20.2% for everolimus and MMF, respectively), the proportion of patients with study drug dose adjustments or interruption was 54.2% for subjects in the MMF group, versus a lower rate of 34.1% in the everolimus group.

In the everolimus cohort, the mean CsA trough levels were within target during month 1, but were toward the upper end or above target range thereafter, with 40% to 50% of patients above target during months 3 to 12. For MMF-treated patients, the mean CsA trough level reached target range by day 8 and remained within target range subsequently. At month 6, the mean CsA trough level was 157±61 and 219±83 ng/mL and at month 12 it was 110±50 and 180±55 ng/mL in the everolimus and MMF groups, respectively ($P<0.001$ between groups at each time point). CsA C_2 values were available in approximately two thirds of patients. The mean CsA C_2 level at months 1, 6, and 12 in the everolimus and MMF cohorts was 885±385 and 899±310 ng/mL, 577±241 and 772±285 ng/mL, and 447±227 and 641±272 ng/mL, respectively.

Almost all patients (99% in each group) received antibody induction therapy. The type of antibody induction used was similar between groups. Antithymocyte antibodies were used most frequently (68.4%), with 25.9% of patients receiving anti-interleukin-2 receptor antibody induction. Corticosteroid dose was similar in both treatment groups (Table 2).

Renal Function

The mean calculated creatinine clearance (Cockcroft-Gault) at baseline was 4.31 mL/min lower in the everolimus group (72.5±27.9 mL/min) than the MMF group (76.8±32.1 mL/min, ns) (Fig. 2). Calculated creatinine clearance at month 6 posttransplant was 65.4±24.7 mL/min with everolimus and 72.2±26.2 mL/min with MMF, a difference of −6.9 mL/min, with the 95% CI including the margin of 6 mL/min (95% CI −14.9 to 1.2). At 12 months, creatinine clearance was 68.7±27.7 mL/min with everolimus and 71.8±29.8 mL/min in the MMF group, a narrowing of the between-group difference from baseline to −3.1 mL/min. To accommodate the difference in baseline creatinine clearances, the within-subject difference between baseline and month 12 was evaluated for each group. For month 12, the everolimus group had a mean within-subject difference of 6.1 mL/min and the MMF group had a mean within-subject difference of 4.3 mL/min ($P=0.693$), indicating no difference in the change of renal function between groups over 12 months.

When the primary analysis was repeated including only those patients without major protocol violations who remained on their randomized study treatment throughout the

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TABLE 2. Immunosuppression (safety population)

	Everolimus (n=91)			MMF (n=83)		
	Month 1	Month 6	Month 12	Month 1	Month 6	Month 12
Everolimus dose (mg/d)	1.23±0.54	1.21±0.52	1.20±0.49	—	—	—
Everolimus trough level (ng/mL)	5.7±5.0	4.6±1.8	4.1±1.8	—	—	—
MMF dose (g/d)	—	—	—	2.45±0.77	2.25±0.75	2.27±0.81
CsA dose (mg/kg/d)	3.54±1.41	2.57±1.01	2.11±0.81	4.29±1.39	3.57±1.17	3.23±1.04
CsA trough level (ng/mL)	245±99	157±61	110±50	308±96	219±83	180±55
Corticosteroid dose (median, range) (mg/d)	0.88±2.06 (0.27, 0.04–16.3)	0.17±0.20 (0.14, 0.04–1.56)	0.13±0.14 (0.11, 0.02–1.12)	0.56±0.83 (0.26, 0.07–4.19)	0.22±0.36 (0.14, 0.00–2.22)	0.34±1.71 (0.10, 0.00–13.59)

Continuous variables are shown as mean±SD unless otherwise stated.
MMF, mycophenolate mofetil; CsA, cyclosporine A.

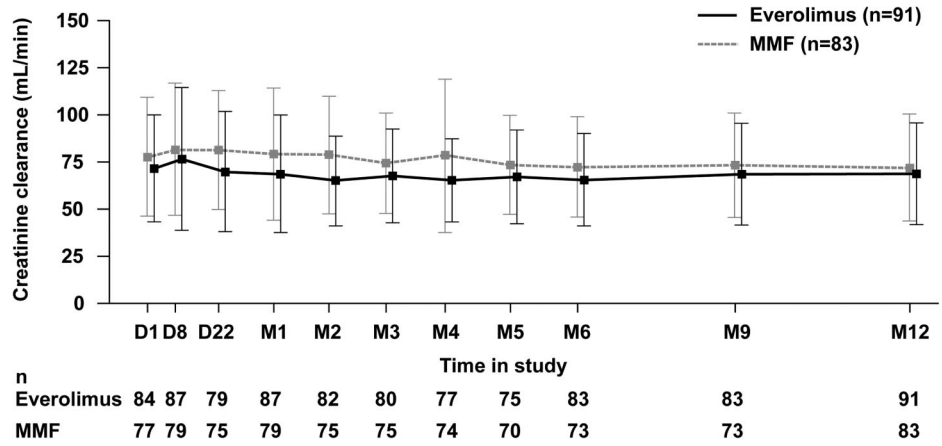

FIGURE 2. Creatinine clearance (Cockcroft-Gault) to month 12 (safety population). Values shown are mean±SD.

TABLE 3. Efficacy endpoints at month 12 (ITT population)

	Everolimus (n=92)	MMF (n=84)	Difference (95% CI)
BPAR ISHLT grade ≥3A	21 (22.8%)	25 (29.8%)	−6.9 (−19.9 to 6.1)
BPAR ISHLT grade ≥3A, acute rejection with hemodynamic compromise, death, graft loss, or lost to follow-up	30 (32.6%)	35 (41.7%)	−9.1 (−23.5 to 5.2)
Acute rejection with hemodynamic compromise	2 (2.2%)	1 (1.2%)	1.0 (−2.8 to 4.8)
Death or graft loss/retransplantation	10 (10.9%)	10 (11.9%)	−1.0 (−10.4 to 8.4)
BPAR treated with antibody	5 (5.4%)	2 (2.4%)	3.1 (−2.62 to 8.7)

ISHLT, International Society for Heart and Lung Transplantation; ITT, intent-to-treat.

study (everolimus 72, MMF 62), the between-group difference was smaller. Mean creatinine clearance in the everolimus and MMF groups was 76.0±28.3 and 79.8±31.6 mL/min at baseline, 67.8±25.1 and 74.6±26.1 mL/min at month 6, and 70.9±28.4 and 74.0±30.4 mL/min at month 12. At month 6, the between-group difference was −3.1 mL/min (95% CI −13.7 to 7.1).

From baseline to month 6, creatinine clearance decreased by more than 6 mL/min in 43 of 83 everolimus patients and 30 of 72 MMF patients for whom glomerular filtration rate values were available at month 6 (51.8% vs. 41.7%, ns). The proportion of patients with an increase in serum creatinine of more than 26.5 μmol/L (>0.3 mg/dL) from baseline to month 6 was also similar between groups (33 of 83 everolimus [39.8%], 21 of 72 MMF [29.2%], ns).

Mean serum creatinine values in the everolimus and MMF groups were 125±59 and 115±46 μmol/L at baseline, 137±64 and 119±37 μmol/L at month 6, and 142±112 and 125±39 μmol/L at month 12, respectively.

Dialysis was required after transplantation in 18 of 91 everolimus patients and 11 of 83 MMF patients ([19.8% vs. 13.3%]; ns); two of the everolimus patients required ongoing dialysis.

Efficacy

All efficacy endpoints (including BPAR ISHLT grade ≥3A, death, graft loss, and the composite) were statistically noninferior in the everolimus cohort compared with the MMF arm at 12 months, based on the prespecified noninferiority margin of 10% (Table 3). The noninferiority of BPAR

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ISHLT grade greater than 3A at month 6 (19.6% in the everolimus group and 27.4%in the MMF group; $P=0.003$ for noninferiority) was preserved till 12 months (22.8% in the everolimus group and 29.8% in the MMF group; $P=0.005$ for noninferiority). Furthermore, 10 of 25 (40.0%) patients in the MMF cohort versus 7 of 21 (33.3%) recipients in the everolimus group with BPAR greater than or equal to 3A experienced recurrence of any grade of rejection. Recurrent rejection of grade greater than or equal to 3A was rare. Additionally, 62.0% of everolimus patients experienced recurrent BPAR of any ISHLT grade versus 79.8% of MMF patients ($P=0.013$, Fisher's exact test).

For patients who averaged everolimus trough exposure of 3 to 8 ng/mL, the incidence of BPAR greater than or equal to 3A was 21.3% (16 of 75), versus MMF 29.8% (25 of 84). Of the five patients in the everolimus group who required antibody therapy for BPAR, three had an everolimus trough concentration below 3 ng/mL in the few days before the event.

Safety

Table 4 summarizes the most frequent adverse events reported during the 12-month trial. Leukopenia occurred significantly less frequently among everolimus-treated patients (16.5% vs. 30.1% with MMF, $P=0.047$). Fifty-nine patients in each group experienced infection (64.8% everolimus, 71.1% MMF). CMV prophlyaxis was administered to 49 of 91 everolimus patients (54.4%, mean duration 116 days) and 56 of 83 MMF patients (67.5%, mean duration 132 days), but there were significantly fewer cases of CMV infection in the everolimus group (n=4, 4.4%) versus MMF (n=14, 16.9%, $P=0.011$). Acute renal failure was reported in eight everolimus patients and four MMF patients. CsA dose was reduced or interrupted because of acute renal failure in three everolimus-treated patients and one MMF patient, and for renal impairment in one patient in each group. Pericardial effusion occurred in 32 everolimus-treated patients (35.2%) and 21 MMF-treated patients (25.3%, n.s.); pleural effusions occurred in 22 everolimus patients (24.2%) and 11 MMF patients (13.3%, n.s.). The incidence of cardiac tamponade was comparable with five (5.5%) and four (4.8%) cases in patients receiving everolimus and MMF, respectively. Moreover, two of the five cases of cardiac tamponade that occurred in the everolimus cohort were caused by iatrogenic myocardial perforation during biopsy. Importantly, the use of CMV prophylaxis was similar with everolimus (19 of 91, 20.8%) and MMF (20 of 83, 24.0%). The adverse event rate of postoperative wound infections was similar between groups (everolimus 6 [6.6%] vs. MMF 7 [8.6%]). Fourteen everolimus patients and 18 MMF patients were hospitalized for major adverse cardiac events (acute myocardial infarction, congestive heart failure, percutaneous coronary intervention, coronary artery bypass graft, automatic implanted cardiac defibrillator, or cerebral or peripheral vascular accident).

The rate of death or graft loss with retransplantation was similar in both treatment arms (Table 3). There were nine deaths in each treatment group in the safety population. Among everolimus-treated patients, death was caused by cardiac tamponade (after myocardial perforation during endomyocardial biopsy procedure), multiorgan failure, pulmonary sepsis, septic shock, retroperitoneal infection, hemorrhagic shock, respiratory distress, lymphoma, and unspecified causes, all in one case each. In the MMF group, death was caused by septic shock in three cases, and by complications of transplant surgery, cerebral infarction, renal failure, paralytic ileus, peritonitis, and unspecified causes in one case each.

Statin therapy was prescribed for 93.4% and 85.5% of everolimus and MMF patients, respectively. Among patients remaining on everolimus or MMF, the mean level of total cholesterol was 5.9±1.4 and 5.0±1.0 mmol/L at month 6 ($P<0.001$) and 5.5±1.3 and 5.0±1.3 mmol/L ($P=0.002$) at month 12, respectively. For triglycerides, the mean level was 2.2±1.4 and 1.7±0.6 mmol/L at month 6 ($P=0.011$) among patients remaining on everolimus or MMF, respectively, and 2.3±1.5 and 1.7±0.8 mmol/L at month 12 ($P=0.001$).

TABLE 4. Adverse events occurring in >20% of patients and infections (safety population)

	Everolimus (n=91)	MMF (n=83)
Any adverse or infection	91 (100.0%)	83 (100.0%)
Hypertension	44 (48.4%)	35 (42.2%)
Peripheral edema	36 (39.6%)	29 (34.9%)
Pericardial effusion	32 (35.3%)	21 (25.3%)
Anemia	28 (30.8%)	26 (31.3%)
Leukopenia	15 (16.5%)[a]	25 (30.1%)[a]
Pyrexia	22 (24.2%)	14 (16.9%)
Pleural effusion	22 (24.2%)	11 (13.3%)
Diarrhea	15 (16.5%)	20 (24.1%)
Nausea	14 (15.4%)	20 (24.1%)
Any infection	59 (64.8%)	59 (71.1%)
Bacterial	29 (31.9%)	33 (39.8%)
Fungal	9 (9.9%)	2 (2.4%)
Viral	16 (17.6%)	21 (25.3%)
Cytomegalovirus	4 (4.4%)[b]	14 (16.9%)[b]
Other	11 (12.1%)	13 (15.7%)

[a] $P=0.047$ (Fisher exact test [two-sided]).
[b] $P=0.011$(Fisher exact test [two-sided]).
MMF, mycophenolate mofetil.

DISCUSSION

This randomized, multicenter trial indicates that concentration-controlled everolimus targeting reduced CsA results in comparable renal function to MMF with standard CsA at 12 months after cardiac transplantation. However, the primary endpoint was not met since calculated CrCl at month 6 posttransplant was 6.9 mL/min lower with everolimus, exceeding the predefined margin of 6 mL/min. The everolimus regimen was associated with noninferior rates of BPAR grade greater than or equal to 3A and lower rates of recurrent BPAR compared with MMF, and showed a manageable safety profile.

Previous experience with everolimus in cardiac transplantation revealed that everolimus is an effective immunosuppressant. However, fixed doses of everolimus in combination with conventional levels of CsA translated into an impairment of renal function in the pivotal trial by Eisen et al. (*3*). Pharmacokinetic modeling of data from this experience in cardiac transplantation, consistent with data from renal transplantation trials using fixed doses of everolimus, indicated that re-

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ducing CsA in conjunction with maintaining a trough level of everolimus above 3 ng/mL should improve renal safety and preserve efficacy. The present study is the first direct comparative trial in de novo cardiac transplantation to examine this strategy versus MMF. Although the noninferiority margin for creatinine clearance was not statistically excluded, renal function and the change in renal function through month 12 were clinically comparable between the groups. Simple randomization did not balance renal function at baseline, which was an assumption made to demonstrate statistical noninferiority. Indeed, it was surprising that since an appropriate randomization procedure was used, the two treatment groups were imbalanced in size, baseline renal function, and a trend to a higher proportion of patients with diabetes in the MMF cohort. In addition, the achieved CsA trough level for the everolimus group was higher than targeted. However, as CsA trough level continued to be reduced by 12 months to a mean level of 110 ng/mL (signifying >35% reduction vs. MMF), the difference in renal function observed at baseline narrowed to 3.1 mL/min. Importantly, this observation was not a result of missing renal function data because only patients in the everolimus group who died did not contribute to this analysis. Single imputation as well as multiple imputation for these missing renal function values revealed results consistent with the analyses limited to subjects with complete renal function data. However, we recognize that while renal performance at 1 year is a useful yardstick for future kidney function, long-term data are required.

All efficacy endpoints showed noninferiority for everolimus with reduced CsA versus MMF with standard CsA according to the predefined 10% noninferiority margin. Indeed, the incidence of BPAR grade greater than or equal to 3A at 12 months was approximately 7% lower in the everolimus cohort. Furthermore, based on protocol biopsies, the recurrence rate of BPAR of any grade by 12 months was approximately 20% lower in the everolimus group. The clinical significance of this observation remains to be defined, although recurrence of BPAR has been associated with foreshortened allograft survival possibly because it may be a risk factor for cardiac allograft vasculopathy (*12*).

The safety profiles of both everolimus and MMF were consistent with those reported previously, and a similar proportion of patients in each group discontinued study medication because of adverse events. As anticipated, leukopenia and gastrointestinal side effects were more common with MMF, and lipid abnormalities occurred more frequently with everolimus. Although the absolute incidence of pericardial effusion was 12% higher with everolimus, the occurrence of cardiac tamponade was similar in both treatment groups. The overall incidence of infection was similar in both treatment arms, although the rate of CMV was significantly lower in the everolimus group despite comparable use of CMV prophylaxis in each cohort. In conclusion, concentration-controlled everolimus within this regimen preserves efficacy and has a similar impact on renal function to MMF at 12 months after cardiac transplantation. Safety profiles were as expected, with a significantly lower incidence of CMV infection in the everolimus arm. Future trials exploring a lower de novo and maintenance CsA exposure range in everolimus-treated cardiac transplant recipients are warranted.

APPENDIX

THE RAD 2411 STUDY INVESTIGATORS

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ACKNOWLEDGMENTS

The authors are indebted to the staff of the centers involved in this work, to the clinical trial team for their expert collaboration and to the patients who participated in the study. They also thank S. Korom for assistance in examining individual patient data on wound healing events.

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