High Rate of Discontinuation of a Mammalian Target of Rapamycin Inhibitor-based Regime During Long-term Follow-up of Cardiac Transplant Recipients

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Abstract

In heart transplant recipients receiving mammalian target of rapamycin inhibitors, we observed a discontinuation rate of 38% due to adverse effects after a median follow-up of 3.8 years. Immunosuppressants with better tolerability are needed. **(Trends in Transplant. 2013;7:92-6)**

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Key words

Heart transplant. Mammalian target of rapamycin inhibitor. Adverse effect.

Introduction

Mammalian target of rapamycin (m-TOR) inhibitors have well demonstrated immunosuppressive effects and their use in heart transplantation has been promoted in protocols of minimization or withdrawal of calcineurin inhibitors (CNI) in the context of renal insufficiency, cardiac allograft vasculopathy (CAV) and post-transplant malignancies[1]. However the use of m-TOR inhibitors is not free of adverse effects and discontinuation of m-TOR inhibitors ranges from 13 to 18% in randomized clinical trials[2-4]. A recent large, multicenter, observational study showed a discontinuation rate of 16% in the first year and 4% per year thereafter[5]. We aimed to assess long-term safety and tolerability of an m-TOR inhibitor-based regime in heart transplant recipients.

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Methods

We prospectively followed 96 heart transplant recipients converted from a CNI to an m-TOR inhibitor-based immunosuppressive regime from 2001 to 2010 in our hospital. We collected reasons for conversion, adverse events, and the main reason that led to discontinuation. Trough levels of m-TOR inhibitors were determined at one and three months and every six months thereafter and the average of all determinations was analyzed.

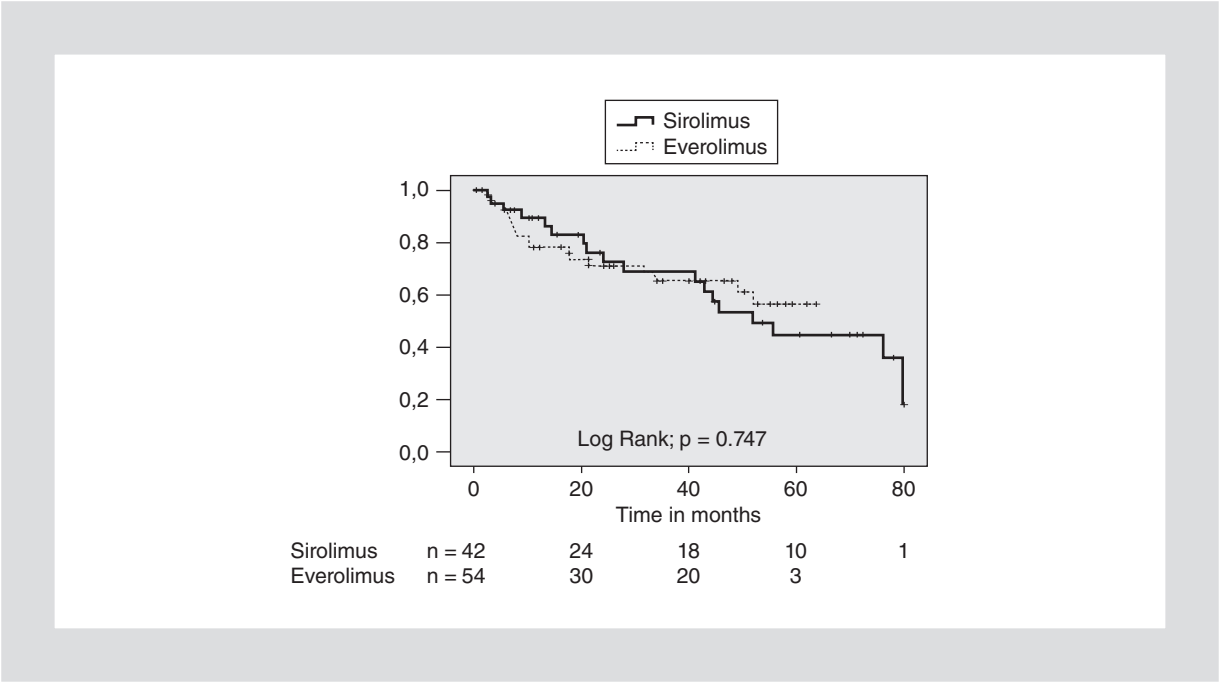

Figure 1. *Cumulative probability of discontinuation of the mammalian target of rapamycin inhibitor censored for death.*

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or as median and interquartile range (IQR) if not normally distributed. We calculated the cumulative probability of discontinuation censored for death using Kaplan-Meier curves. The log-rank test was used to compare differences between groups. To identify predictors of m-TOR inhibitor discontinuation, we performed univariate Cox proportional hazard analysis. Comparisons between creatinine clearance (CrCl) pre- and post-conversion were analyzed with the Wilcoxon signed Rank test for related samples. The influence of m-TOR inhibitor discontinuation on death during follow-up was assessed by a Cox proportional hazard model. The model was adjusted for age, sex, hypertension, diabetes mellitus, CrCl, left ventricular ejection fraction, cancer, CAV, time from heart transplantation to conversion, and strategy (CNI withdrawal vs. minimization). Significance was set at $p < 0.05$ (2 tailed).

Results

Baseline characteristics of the population

Mean age was 62 ± 8 years and 86% were male. Seventy-five (78%) were hypertensive and 31 (32%) diabetic. Pre-heart transplant cardiomyopathy was mainly ischemic (n = 55; 57%) and conversion was performed a mean of 6.3 ± 4 years post-transplantation. Pre-conversion CNIs (n = 94) were cyclosporine (CsA) in 44 cases (46%) and tacrolimus (TAC) in 50 (52%). Median CrCl was 52 ml/min (IQR: 35-64). Mycophenolate mofetil was used in 86 (90%), azathioprine in 10 (10%), statins in 91 (95%), and prednisone in 86 (90%). Reasons for conversion were: CNI toxicity (n = 43; 45%), CAV (n = 15; 16%), cancer (n = 15; 16%), CNI toxicity plus CAV (n = 16; 17%) and CNI toxicity plus cancer (n = 7; 7%). The 22 cancer cases involved six skin and 16 non-skin tumors (six lung ones). The reasons for CNI toxicity were nephrotoxicity in 58 and neurotoxicity in seven.

Table 1. Predictors of mammalian target of rapamycin inhibitor discontinuation due to adverse events: Univariate analysis

Variable	Hazard ratio (95% CI)	p-value
Reasons for m-TOR inh use:		
Graft vasculopathy	0.79 (0.54-1.18)	0.251
Renal failure	0.84 (0.43-1.64)	0.611
Malignancy	0.75 (0.31-1.83)	0.530
Creatinine clearance	1.01 (0.99-1.02)	0.350
Time from HT to m-TOR inh use	1.01 (0.99-1.01)	0.682
Minimization vs. withdrawal	0.953 (0.41-2.19)	0.909
Azathioprine vs. MMF	1.045 (0.32-3.42)	0.942
Statin	0.339 (0.10-1.11)	0.074
Trough levels:		
Sirolimus	1.26 (1.04-1.54)	0.021
Everolimus	1.23 (0.93-1.61)	0.137

m-TOR inh : mammalian target of rapamycin inhibitor; HT: heart transplant; MMF: mycophenolate mofetil.

Calcineurin inhibitors were withdrawn in 77 patients (80%) and minimized in 19 (20%). Everolimus was used in 54 cases (56%) and sirolimus in 42 (44%) and their median trough levels during follow-up were 5.3 ng/ml (IQR: 4.7-6.7) and 6.6 ng/ml (IQR: 5.9-8.8), respectively.

Mammalian target of rapamycin inhibitor discontinuation

During a median follow-up of 3.8 years (IQR: 1.5-5.0), m-TOR inhibitor discontinuation was common (n = 36; 38%). The actuarial rate of m-TOR inhibitor discontinuation was 16% at one year, 23% at two years, and an additional 4% per year thereafter. Figure 1 shows the cumulative probability of m-TOR inhibitor discontinuation censored for death according to treatment either with sirolimus or everolimus. The reasons for discontinuation were: peripheral edemas or serositis (n = 24), pneumonitis (n = 7), infections (n = 2), oral ulcers (n = 1), fever of unknown origin (n = 1), and diminished leucocytes and platelets (n = 1). At the end of follow-up, 28 subjects (29%) were receiving tacrolimus, and 20 (21%) CsA.

Table 1 shows that the only predictor of m-TOR inhibitor discontinuation was the average trough level for patients on sirolimus (p = 0.021).

Impact of mammalian target of rapamycin inhibitor discontinuation on clinical outcomes

Among the 58 patients converted because of nephrotoxicity, CrCl improved at the end of follow-up compared to baseline, but this improvement was only significant in those who did not discontinue m-TOR inhibitor treatment (Fig. 2).

During follow-up, 15 patients (16%) developed at least one episode of ≥ grade 2 cellular rejection and seven (7%) “new” cancers. There were 43 deaths (45%) during follow-up due to: cancer (n = 17), CAV (n = 13), infections (n = 4), sudden death (n = 3), rejection (n = 2), stroke (n = 2), renal failure (n = 1), and pneumonitis (n = 1). Discontinuation of m-TOR inhibitors was associated with increased survival during follow-up (Fig. 3). Multivariate analysis showed that m-TOR

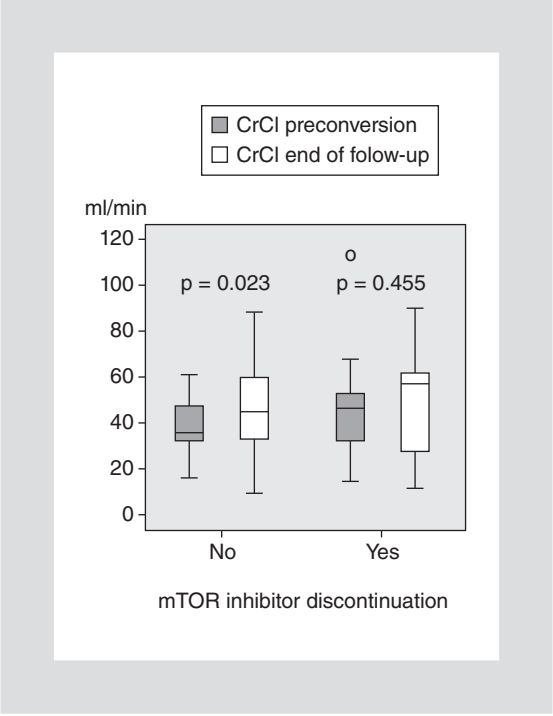

Figure 2. *Evolution of creatinine clearance (CrCl) in heart transplant recipients converted to a mammalian target of rapamycin (m-TOR) inhibitor regimen because of calcineurin inhibitor nephrotoxicity according to the discontinuation of the m-TOR inhibitor during follow-up.*

discontinuation (HR: 0.45; 95% CI: 0.22-0.91; p = 0.026) and hypertension (HR: 0.48; 95% CI: 0.24-0.95; p = 0.036) predicted better survival.

Discussion

The main findings of our study of heart transplant patients converted from a CNI to an m-TOR inhibitor-based regimen are:

– After a median follow-up of 3.8 years, 38% of patients had to discontinue m-TOR inhibitors due to adverse effects.

– The only predictor of m-TOR inhibitor discontinuation was the mean trough level of m-TOR inhibitors.

– m-TOR inhibitor discontinuation was associated with worsening renal function but increased survival.

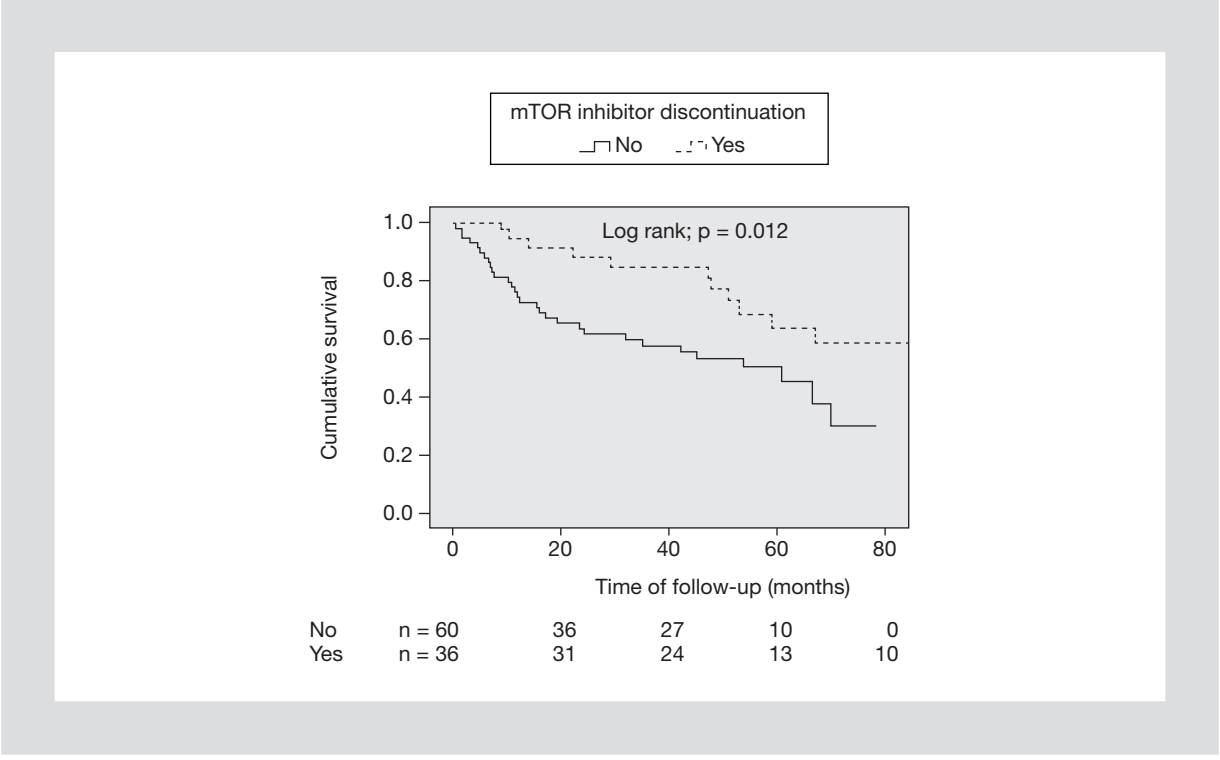

Figure 3. *Cumulative probability of survival according to the discontinuation of the mammalian target of rapamycin (mTOR) inhibitor.*

The discontinuation rate of m-TOR inhibitors in our study is slightly higher than in the study by Gonzalez-Vilchez, et al.[5] and confirms that adverse effects due to m-TOR inhibitors are a relevant clinical problem that extends beyond the first year of treatment. This information is important, as some adverse effects such as pneumonitis can be fatal[6].

Non-controlled comparisons have suggested a better risk profile for everolimus than for sirolimus[7] and a poor relationship between m-TOR inhibitor serum levels and their discontinuation[2,3,5]. One study[4] found that patients with pneumonitis tended to have higher trough levels. In our series we found that the only predictors of m-TOR inhibitor discontinuation were the trough levels of sirolimus, and there was a trend also for everolimus. However, we did not find any difference in the discontinuation rate between everolimus and sirolimus.

The impact of m-TOR inhibitor discontinuation on renal function is similar to previous reports[5,7]. A surprising finding is that m-TOR inhibitor discontinuation was associated with better survival after adjusting for confounders. This finding has to be interpreted with caution, given the limitations of a single-center study, limited number of patients, and that the discontinuation of m-TOR inhibitors was not protocolized. The study by González-Vílchez, et al.[5] did not show any difference in survival among patients who discontinued the m-TOR inhibitor regimen. An explanation for our findings could be: (i) More than 50% of our patients had either cancer or CAV and treatment with m-TOR inhibitors cannot reverse their poor outcomes; (ii) our high incidence of pneumonitis implies a better outcome in those who discontinued the m-TOR inhibitor regimen.

We conclude that heart transplant recipients receiving an m-TOR inhibitor-based regimen have a high discontinuation rate during long-term treatment due to adverse events. Immunosuppressants with better tolerability are needed.

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