Early Switch to Mammalian Target of Rapamycin Inhibitors Is a Sustainable Treatment Approach in Renal Transplant Recipients: 7-Year Results

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ABSTRACT

Objective. The aim of this study was to investigate the safety and sustainability of mammalian target of rapamycin inhibitor (m-TORi)-based treatment protocols in renal transplant patients.

Methods. We retrospectively evaluated a total of 206 patients who were switched to low-dose calcineurin inhibitors (CNI) + m-TORi or mycophenolate mofetil (MMF) + m-TORi treatment protocols in the first 3 months of renal transplantation between January 2010 and August 2011 in our center. Demographic and laboratory features of the patients were recorded.

Results. Of the patients included in the study, 89 (43.2%) were female and 117 (56.8%) were male. The mean age was 41.9 ± 13.8 years. Panel reactive antibody was negative in 95% of the recipients. One hundred thirty-four (65%) patients received anti-thymocyte globulin induction therapy. Initially, 108 patients were treated with cyclosporine and 98 (47.6%) were treated with tacrolimus-based regimens. One hundred thirty-five patients (65.5%) were switched to low-dose CNI + m-TORi and 71 patients (34.5%) were switched to MMF + m-TORi. The mean switching time was 3 months. At the end of the study, 161 patients (78.2%) were still continuing the m-TORi treatment protocol and 45 patients (21.8%) could not continue for various reasons (11.4% proteinuria, 5.5% edema, 2.9% acute rejection, 1% acne + oral aphthae, 1% neuropathy). The biopsy-proven acute rejection rate was 4.5% (n = 9). The mean duration of sustainability of m-TORi treatment protocol was 84.15 ± 6.79 months. Mean serum creatinine of patients who were still continuing m-TORi was 1.42 ± 1.09 mg/dL.

Conclusion. Switching to m-TORi in the early posttransplant period is a safe and sustainable treatment approach.

TODAY, steroids, calcineurin inhibitors (CNIs), and antimetabolites continue to form the cornerstones of immunosuppressive therapy in renal transplantation [1]. CNIs (eg, cyclosporine and tacrolimus) are commonly used in renal transplant recipients. Tacrolimus-based regimens in particular are still considered to be the best protocols in preventing acute rejection. However, adverse outcomes on long-term graft survival are reported due to the nephrotoxicity of CNI [2]. Permanent damage such as arteriolar hyalinosis, interstitial fibrosis, tubular atrophy, and microcalcification have been indicated in almost all patients after 10 years of CNI use, which is an important cause of long-term graft failure or graft loss [3]. In addition, new-onset diabetes mellitus after transplantation,

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0041-1345/19
https://doi.org/10.1016/j.transproceed.2019.01.098

hypertension, and dyslipidemia lead to increased morbidity and cardiovascular mortality rates in recipients [4,5].

Because of these long-term bad outcomes, researchers have been encouraged to explore the blockade of some costimulation pathways to generate efficient and non-nephrotoxic immunosuppressive treatment protocols via complete cessation or tapering doses of CNI [6,7]. The biggest challenge with immunosuppression therapy is to maintain the balance of immunosuppression need in order to prevent any rejection episode whilst keeping the check on the toxicities. Studies performed on the withdrawal of CNI have found increases in the incidence of acute rejection episodes but less deterioration in histopathologic findings. However, these findings did not reflect graft or patient survival [8]. In the renal transplant community, conversion strategies to low-dose CNI or antimetabolites combined with mammalian target of rapamycin inhibitors (m-TORi) in the early posttransplant period was approved. These strategies are still debatable because of adverse effects such as higher rates of acute rejection, or more frequent drug withdrawal due to various side effects.

The aim of this study was to evaluate the safety and sustainability of m-TORi based immunosuppressive regimens and causes of their discontinuation in renal transplant recipients.

MATERIALS AND METHODS

Patients who underwent renal transplantation in our center between January 2010 and August 2011 were retrospectively assessed. Written informed consent was obtained from all patients before enrollment. Low-immunological-risk renal recipients who were switched from CNI + mycophenolate mofetil (MMF) to low-dose CNI + m-TORi or MMF + m-TORi in the first 3 months of transplantation were included in the study. The exclusion criteria were <18 years of age and having moderate or high immunologic risk. Demographic data (age, gender, dialysis modality, duration of dialysis, etc), laboratory results, side-effects related to m-TORi treatment, cause of drug dropout, biopsy-proven acute rejection (BPAR), graft dysfunction, and graft loss were recorded.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 22.0 (IBM, Armonk, NY, United States). Results were given as mean ± standard deviation, median (25th-75th percentile), and percentage (%). The Kolmogorov-Smirnov test was used to determine whether variables had a normal distribution. The Student t-test was used to compare between-group differences of numerical variables with normal distribution, while the Mann-Whitney U test was used to compare between-groups differences of numerical variables not showing normal distribution. The χ^2 test was used to assess categorical variables. Independent predictors affecting the sustainability of treatment were examined using logistic regression analysis. Differences were considered to be significant when the P value was <.05.

RESULTS

A total of 206 patients were included in the study. One hundred and ninety-seven patients (95.6%) underwent living donor transplantation, while 9 patients (4.4%) underwent deceased donor renal transplantation. Eighty-nine (43.2%) of the patients were female and 117 (56.8%) were male. Their mean age was 41.9 ± 13.8 years. The median duration of dialysis was 36 months (range 12–94; 12.6% preemptive, 78.4% hemodialysis, 9% peritoneal dialysis). Ninety-five percent of patients had negative panel reactive antibody. With regard to mismatches, 2.4% had 0, 3.4% had 1, 11.7% had 2, 27.2% had 3, 20.4% had 4, 22.8% had 5, and 12.1% had 6. One hundred thirty-four patients (65%) received anti-thymocyte globulin (ATG) induction therapy and a mean cumulative dose of 450 mg was administered. All patients were given 1 g methylprednisolone for induction and tapered down to a maintenance dose of 5 mg at the end of the first month; 52.4% were given cyclosporine and 47.6% were given tacrolimus-based regimens as initial immunosuppressive therapy. Later 65.5% of the patients were switched to low-dose CNI + m-TORi and 34.5% of patients were switched to MMF + m-TORi treatment. The mean switching time to m-TORi was 2.2 ± 0.4 months. Everolimus was the preferred m-TORi in all patients. The demographic and laboratory features of the patients are summarized in Table 1.

Table 1. Demographic and Laboratory Features of the Patients

Variable	Value
Number of participants	206
Mean age (y)	41.9 ± 13.8
Sex (F/M) (%)	43.2/56.8
Median duration of dialysis (mo)	36 (12–94)
Donor type (living/cadaveric) (%)	95.6/4.4
PRA (negative/positive) (%)	95/5
Mean HLA mismatch	3.7 ± 1.4
Dialysis type (preemptive /hemodialysis/peritoneal dialysis) (%)	12.6/78.4/9
ATG induction therapy (%)	65
Mean switching time to m-TORi (mo)	2.2 ± 0.4
Sustainability of m-TORi therapy (mo)	84.15 ± 6.79

Abbreviations: ATG, anti-thymocyte globulin; F, female; M, male; m-TORi, mammalian target of rapamycin inhibitor; PRA, panel reactive antibody.

At the end of the study, 78.2% of the cases were still continuing the m-TORi treatment protocol while 21.8% could not continue due to various reasons (11.4% proteinuria, 5.5% edema, 2.9% acute rejection, 1% acne + oral aphthae, and 1% peripheral neuropathy). BPAR was recorded in 9 (4.5%) of the cases. The mean duration of the continuation of m-TORi treatment protocol was 84.15 ± 6.79 months. The mean serum creatinine of recipients who were still continuing m-TORi was 1.42 ± 1.09 mg/dL. Eight patients diagnosed with acute rejection were in the CNI + m-TORi group while 1 patient was in the MMF + m-TORi group ($P = .16$). In addition, 66.7% of the patients who had acute rejection had not received ATG induction therapy, while 33.3% of them had ($P = .068$).

There was no significant difference between m-TORi continuing group and m-TORi dropout group in terms of sex, body mass index, duration of dialysis, number of HLA

mismatches, and ATG induction therapy. The mean age of the patients in the m-TORi dropout group was significantly higher ($P = .03$) (Table 2).

An age ≥50 years was negative predictor and preemptive transplantation was positive predictor factor for dropout of m-TORi ($P < .05$) (Table 3). The mean serum creatinine levels remained stable in the m-TORi continuing and m-TORi dropout groups for 84 months ($P > .05$) (Fig 1).

No graft or patient loss occurred in the study group.

DISCUSSION

Recent studies on the minimization or cessation of CNI and adding m-TORi to immunosuppressive therapy revealed significant positive outcomes. They have shown that low-dose CNI and early conversion to m-TORi therapy is effective and safe for long-term graft function [9–11]. The m-TOR pathway plays an important role in a number of common renal diseases including polycystic kidney disease, acute kidney injury, and diabetic nephropathy. m-TORi has been shown to improve renal graft dysfunction by reducing glomerular hypertrophy, proinflammatory and profibrotic cytokine production, interstitial inflammation, and fibroblast production, and by inhibiting epithelial-to-mesenchymal transition [12]. They also reduce angiogenesis, which may prevent or reduce the incidence of some malignancies in solid organ transplantation [13]. They differ mainly in pharmacokinetic characteristics and have variable inter/intra-individual pharmacokinetics. The narrow therapeutic window of these drugs makes therapeutic drug monitoring fundamental to avert acute rejection or side effects. They are metabolized by cytochrome-3A4/5 and cytochrome-2C8 enzymes and are substrates for P-glycoprotein. Some physicians do not prefer m-TORi because of the multiplicity of side effects and the difficulty of sustaining it for long time. Their most common adverse effects are thrombocytopenia, leukopenia, anemia, dyslipidemia, proteinuria, aphthous stomatitis, acne, diarrhea, and, although rare, interstitial pneumonitis is well documented. These side effects usually develop due to high drug concentrations. If the drug trough levels are closely monitored, these side effects can be significantly reduced or manageable [14].

Table 2. Comparison of Demographic and Clinical Features Between m-TORi Continuing and m-TORi Dropout Groups

	mTORi Continuing Group n = 161	m-TORi Dropout Group n = 45	*P* Value
Mean age (y)	40.9 ± 13.9	45.8 ± 12.8	.036
Sex (M/F) (%)	54.7/45.3	64.4/35.6	.241
BMI (kg/m^2)	24.0 (21.0–27.0)	25.0 (22.0–27.5)	.490
Duration of dialysis (mo)	36.0 (12.0–94.7)	35.5 (9.0–102.0)	.926
Number of HLA mismatches	4.0 (3.0–5.0)	4.0 (3.0–5.0)	.163
ATG induction (%)	62.7	73.3	.187

Abbreviations: ATG, anti-thymocyte globulin; BMI, body mass index; F, female; M, male; m-TORi, mammalian target of rapamycin inhibitor.

Table 3. Predictive Factors for m-TORi Dropout

Predictive Factors	Hazard Ratio	*P* Value
Age ≥50	2.2 (1.08–4.47)	.020
Preemptive transplantation	0.12 (0.02–0.91)	.041

Abbreviation: m-TORi, mammalian target of rapamycin inhibitor.

In this study, we showed that early conversion to low-dose CNI + m-TORi or CNI withdrawal (m-TORi + MMF) were sustainable treatment approaches to preserve long-term graft function. At the end of the study, 78.2% of the patients were still continuing m-TORi treatment protocols. Similarly, the ZEUS study (a 5-year, multicenter, randomized study) showed that conversion to m-TORi therapy after 4.5 months of renal transplantation was better in terms of improvement of graft function compared to remaining on CNI treatment, but worse results were obtained with regard to the number of acute rejection episodes [15]. The mean estimated glomerular filtration rate difference between the 2 groups was calculated as 8.2 mL/min/1.73 m^2 (95% confidence interval [CI] 4.3, 12.1; $P < .001$) in favor of m-TORi. The cumulative incidence of BPAR postrandomization was 13.6% with everolimus vs 7.5% with cyclosporine ($P = .095$); the majority of rejected patients experienced for low-grade rejection. The majority of the study population were also deceased donor renal transplantations (everolimus group, 74.8%; cyclosporine group, 73.4%). The increase in acute rejection rates was not statistically significant between the 2 groups. These results did not affect graft survival or patient survival. In our study, serum creatinine levels of the patients remained stable for 7 years. We also found that BPAR rates were only 4.5%. Eight patients who were diagnosed with BPAR were in the CNI + m-TORi group and 1 patient was in the MMF + m-TORi group ($P = .16$). In addition, 66.7% of those who had acute rejection had not received ATG induction, while 33.3% of them had received ATG induction therapy ($P = .068$).

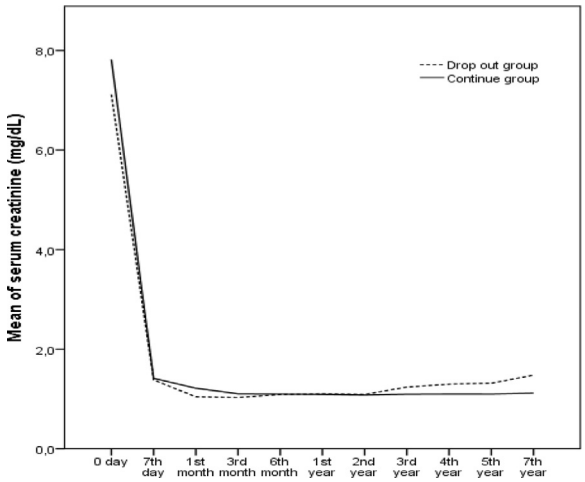

Fig 1. Mean serum creatinine of patients in m-TORi continuing and m-TORi dropout groups during 7-year follow-up.

One of the factors that affect the sustainability of m-TORi drugs in renal transplantation is whether to start de novo or to choose late (post-transplant 6–12 months) conversion. Some studies revealed a high discontinuation rate of m-TORi due to adverse effects, especially when it is used in de novo recipients. m-TORi was discontinued for 28% of patients (95% CI, 0%–59%) in the randomized trials and 17% (95% CI 12%–22%) in the nonrandomized trials. Increased proteinuria was the most common serious side effect leading to discontinuation [16]. In the recent multicenter prospective TRANSFORM study it was shown that de novo m-TORi treatment was successful in low- and moderate-immunologic risk patients in terms of efficacy and protection of graft function 1 year following renal transplantation. Moreover, the incidence of cytomegalovirus and BK virus infections were less frequent (cytomegalovirus: 3.6% vs 13.3% and BK 4.3% vs 8.0%) [17]. In the CONVERT study with a 3-year follow-up period, conversion to m-TORi 6–12 months after renal transplantation yielded excellent results for both graft and patient survival. Furthermore, proteinuria progression and BPAR rates were not significantly increased. Drug dropout rates because of side effects were significantly higher in the m-TORi group compared to the CNI group within the first year (15.7% vs 9.5% respectively, $P = .013$), but this result changed in favor of m-TORi in the second year of follow-up (25.8% vs 20.0%, $P = .07$) [18]. In our study, the predictive factors for m-TORi dropout were determined as ≥ 50 years of age as a negative predictor and preemptive transplantation as a positive predictor factor. In addition, mean serum creatinine levels were stable for 84 months. A relative increase in serum creatinine levels was observed in the m-TORi dropout group at the end of the follow-up period, but this was not statistically significant ($P > .05$).

CONCLUSIONS

Early conversion to m-TORi therapy within the first 3 months of renal transplantation is a safe and sustainable treatment approach to preserve long-term graft function in patients with low immunological risk. Side effects related to m-TORi therapy may be significantly reduced via close monitorization of drug trough levels.

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