Conversion to Sirolimus in Kidney Transplant Recipients
A single-center Study

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Keywords. kidney transplantation, sirolimus, cyclosporine, nephrotoxicity

Introduction. As an immunosuppressive treatment, cyclosporine carries a significant risk of nephrotoxicity. In this study, we assessed the safety and efficacy of sirolimus conversion in our kidney transplant recipients.

Materials and Methods. Sirolimus conversion in 99 kidney transplant recipients was evaluated. Serum level of creatinine, glomerular filtration rate (GFR), and the occurrence of adverse effects of sirolimus were evaluated at conversion time and 1, 6, 12, 24, and 36 months after conversion.

Results. The major causes of conversion were chronic allograft nephropathy and cyclosporine nephrotoxicity. The median time to conversion and follow-up were 54.7 months and 24 months, respectively. Three patients died during the study period. The acute rejection rate was 4%. In 16.6% of the patients, sirolimus was discontinued because of refractory adverse effects. No significant changes in estimated GFR and incidence of adverse effects were observed between patients with baseline estimated GFR lower or higher than 40 mL/min. Patients with early sirolimus conversion ($\leq$ 6 months after transplant) had improvement of their GFR (59.9 ± 22.3 mL/min to 68.0 ± 15.5 mL/min, P = .02), while kidney recipients with late conversion did not show such an improvement. The difference between GFRs in these two groups reached significant level at 12 months and stayed significant until the end of the follow-up.

Conclusions. This study emphasizes that conversion of cyclosporine to sirolimus could be associated with stable kidney allograft function. However, cyclosporine discontinuation should be considered early when it is indicated.

IJKD 2013;7:309-15
www.ijkd.org

Original Paper

INTRODUCTION

Kidney transplantation is the treatment of choice for most patients with end-stage renal disease (ESRD). Strategies to prolong the allograft survival have become priorities in kidney transplantation. Current standard protocols include 3-drug groups, which consist of calcineurin inhibitors (cyclosporine and tacrolimus), antiproliferative agents (azathioprine and mycophenolic acid), and steroids (prednisolone).[1]

Since the early 1980, calcineurin inhibitors, and at the top of this group, cyclosporine, have been considered as the cornerstone of immunosuppressive treatment in kidney transplant recipients. Cyclosporine has dramatically improved short-term allograft survival, especially by decreasing

the number of acute rejection episodes during the first month after transplantation.[2] However, long-term use of cyclosporine may contribute to an increase in blood pressure, decrease in estimated glomerular filtration rates (GFR), and development of chronic allograft nephropathy.[3,4] Indeed, the effect of cyclosporine on long-term graft survival has been doubted. Based on these observations, identification of strategies of calcineurin inhibitors avoidance or elimination in order to prolong the long-term graft survival and reduce acute rejection rates, has been a subject of many research studies.

Sirolimus is a novel immunosuppressant drug that has been recently used to prevent organ rejection, especially in kidney transplant recipients. Originally described in 1975 as an antibiotic of the macrolide family, the immunological activity of sirolimus was reported in 1977 in a rodent model of autoimmune encephalomyelitis.[5] However, recently its effect on the immune system has generated great interest.[6] This immunosuppressive drug that structurally resembles tacrolimus, binds to the FK binding protein and forms an immunophylin complex that serves as a catalyst and inhibits the mammalian target of rapamycin (mTOR), a key serine- threonine kinase involved in regulation of cell growth and proliferation.[7] Proliferation process in various nonimmune cells such as endothelial cells, hepatocytes, fibroblasts, and smooth muscles could be affected by inhibition of the growth factor-mediated responses. Additionally, it has been shown that mTOR takes part in several protein synthesis pathways that could be involved in oncogenesis.[6]

In an attempt to avoid or eliminate the use of cyclosporine in kidney transplant recipients, the results of several studies showed that early elimination of cyclosporine from a sirolimus-cyclosporine-steroid regimen resulted in significantly better kidney allograft function and blood pressure, with a growing advantage in graft survival when compared with a continuous sirolimus-cyclosporine-steroid regimen.[8,9] Therefore, in a retrospective study, we evaluated the renal outcome in patients with different baseline GFRs who underwent sirolimus conversion in our center.

MATERIALS AND METHODS

Patients

In a retrospective study, all the patients who had a kidney transplant and underwent sirolimus conversion in the transplant center of Dr Shariati Hospital, from 2005 to 2009, were included. The date 2005 was selected because sirolimus has been available since 2005 in Iran. The patients who had the following characteristics had been chosen to be included in sirolimus conversion program: proteinuria less than 1g/d, serum creatinine level less than 2.0 mg/dL, and stable kidney allograft function for the last 2 weeks. All of the patients were recipients of living unrelated donors. The study protocol was compatible with the Declaration of Helsinki and approved by the ethics committee of Tehran University of Medical Sciences.

Treatment Strategy

In the majority of the patients (93.6%), the preconversion immunosuppressive therapy consisted of cyclosporine, prednisolone, and mycophenolate mofetil. The rest of the patients were on cyclosporine, prednisolone, and azathioprine. In patients who were converted to sirolimus therapy, sirolimus, 2 mg/d, was started within 24 hours after discontinuation of cyclosporine. Then, the mycophenolate mofetil dose was adjusted to 1500 mg/d while the dose of corticosteroid remained unchanged. The blood trough level of sirolimus was maintained at 4 ng/mL to 8 ng/mL.

Patient Monitoring and Endpoints

The overall safety of the sirolimus conversion was evaluated by measuring of acute rejection episodes, graft and patient survival, and drug adverse effects. Follow-up visits, according to local practice, were performed monthly in the 1st year and then every 2 months. A blood sample was taken at baseline and 1, 6, 12, 24, and 36 months postconversion for measurement of the laboratory parameters, including kidney function (serum creatinine; for calculation of GFR according to the Modification of Diet in Renal Disease formula), proteinuria (24-hour urine collection), hemoglobin, and lipid profile.

Adverse events were recorded at each visit. Hematological and metabolic complications were categorized based on the following definitions: hemoglobin level less than 10 g/dL as anemia, platelet count less than 100×10^9/L as thrombocytopenia, leukocyte count less than 4×10^9/L as leukopenia, triglyceride level greater than 150 mg/dL as hypertriglyceridemia, total

cholesterol level greater than 200 mg/dL and low-density lipoprotein cholesterol level greater than > 130 mg/dL as hypercholesterolemia, and urine protein level greater than 300 mg/24 h as proteinuria. In those patients who were under treatment for hyperlipidemia, a 30% change in any lipid markers (triglyceride, cholesterol, or low-density lipoprotein cholesterol) was considered as dyslipidemia.

Statistical Analysis

All calculations were performed using the SPSS software (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, Ill, USA). Normal distribution was tested as needed. Continuous (quantitative) variables were reported as mean ± standard deviation. Continuous data was compared by the independent *t* test between the two constructed groups (baseline GFR < 40 mL/min/1.73 m^2 versus ≥ 40 mL/min/1.73 m^2 and early versus late conversion), and qualitative data were compare by the chi-square test or Fisher exact test, as appropriate. The paired *t* test was used to assess the changes in estimated GFRs at different times in comparison to the baseline measurement. A *P* value less than .05 was considered significant.

RESULTS

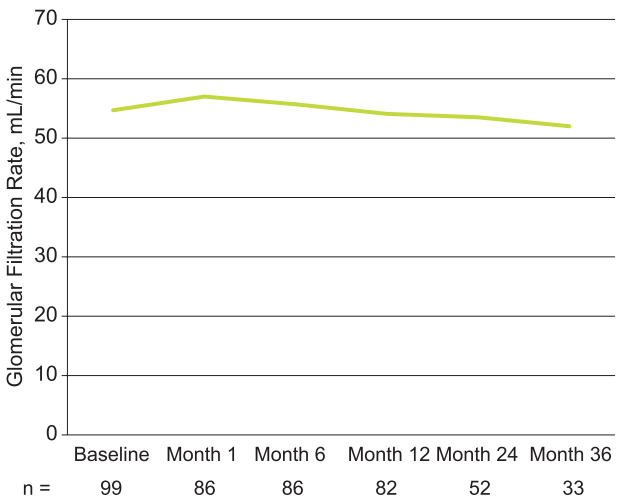
A total of 99 kidney transplant recipients who underwent sirolimus conversion were enrolled in this study. Table 1 demonstrates the baseline characteristics of the patients. In 88 recipients (88.9%), preconversion kidney biopsy had been performed. The mean age of patients was 44.0 ± 14.1 years and men consisted about two-thirds (67.7%) of the participants. The median duration of follow-up was 24 months (range, 1 to 36 months). Three deaths occurred during the follow-up period and 6 patients developed the ESRD.

The median time from transplantation to conversion was 54.7 months (range, 0.6 to 243.1 months). The major causes for conversion according to the clinical and pathological findings of allograft biopsies were chronic allograft dysfunction in 55 patients (62.5%) and cyclosporine nephrotoxicity in 18 (20.5%; Table 1). The estimated GFR at baseline and the end of study period (after 36 months) was 54.7 mL/min and 52 mL/min, respectively, which showed no significant change (*P* = .24; Figure). The most common side effects following sirolimus conversion included anemia (n = 9; 9%), thrombocytopenia (n = 1; 1%), anemia and thrombocytopenia (n = 1; 1%), pancytopenia (n = 1; 1%), hyperlipidemia (n = 24; 24.2%), and oral aphthae (n = 14; 14.1%). However, in most of the patients, the side effects were controlled. In

Table 1. Baseline Characteristics and Kidney Biopsy Results of Patients With Sirolimus Conversion

Characteristic	Values
Mean age, y	44.0 ± 14.1
Sex	
Male	67 (67.7)
Female	32 (32.3)
Median time from transplant to conversion (range), mo	54.7 (0.6 to 243.1)
Cause of ESRD	
Hypertension	4 (4.3)
Diabetes	5 (5.3)
Chronic Glomerulonephritis	11 (11.7)
ADPKD	6 (6.4)
Others	3 (3.2)
Unknown	65 (69.2)
Baseline kidney biopsy results	
IFTA/CAD	55 (62.5)
Mild	30 (34.1)
Moderate	15 (17.0)
Severe	10 (11.4)
IFTA/CNI toxicity	18 (20.5)
IFTA (CAD and CNI toxicity)	15 (17.0)
C4d positive	4 (4.5)
Mean estimated GFR, mL/min	54.7 ± 15.2

*Values in parentheses are percentages except for the reports of median values. ESRD indicates end-stage renal disease; IFTA/CAD, interstitial fibrosis tubular atrophy/chronic allograft dysfunction score; CNI, calcineurin inhibitors; ADPKD, autosomal dominant polycystic kidney disease; and GFR, glomerular filtration rate.



Kidney functions over a 36-month follow-up in sirolimus-converted patients.

16 patients (16.2%), sirolimus was discontinued because of refractory peripheral edema (n = 1; 1%), severe lymphedema (n = 2; 2%), severe hyperlipidemia (n = 1; 1%), proteinuria greater than 1 g/d (n = 5; 5%), pneumonitis (n = 1; 1%), allograft edema (2 patients; 2%), and biopsy-confirmed acute rejection (n = 4; 4%). Renal biopsy was performed in 4 of 5 patients with proteinuria (> 1g/d) and showed focal segmental glomerulosclerosis in 2 patients, membranous glomerulonephritis in 1, and immunoglobulin A nephropathy in 1 patient.

To compare the outcome of sirolimus conversion in patients with different levels of kidney function, the subjects were divided into 2 groups based on their baseline GFR (GFR ≤ 40 mL/min versus GFR > 40 mL/min; Table 2). The difference in GFR at baseline was still present at the end of the follow-up period (27.7 ± 10.28 mL/min versus 54.4 ± 18.45 mL/min; *P* = .02). No significant differences in adverse outcomes and causes of sirolimus discontinuation were observed between the two groups after the follow-up period (*P* = .47; Table 3).

The patients were divided into early (within 6 months after transplant) and late (after 6 months of transplant) conversion groups (Table 4). At baseline, the two groups showed no significant differences in their GFR (59.9 ± 22.3 mL/min in the early-converted versus 54.5 ± 14.4 mL/min in the late-converted group, *P* = .49); however, from month 12, the changes in GFR between the two groups reached the significant level (71.1 ± 20.3 mL/min versus 52.2 ± 16.1 mL/min, *P* = .001) and remained significant at the end of the study (68.0 ± 15.5 mL/min versus 48.4 ± 18.6 mL/min, *P* = .02). At baseline, 50% of the patients in the early-converted group showed interstitial fibrosis and tubular atrophy on kidney biopsy specimens, in comparison with 62.5% of those in the late-converted group (*P* = .67).

Table 2. Patients Characteristic by Glomerular Filtration Rate at Baseline

Parameter	Baseline Glomerular Filtration Rate		*P*
	≤ 40 mL/min (n = 15)	> 40 mL/min (n = 84)	
Mean age, y	48.9 ± 16.3	43.2 ± 13.6	.16
Sex			
Male	9	65	
Female	6	19	.23
Median time from transplant to conversion (range), mo	6.1 ± 4.2	5.2 ± 4.1	.42
Baseline kidney biopsy results	15 (100)	68 (81.0)	
IFTA/CAD	10 (66.6)	41(48.8)	.49
Mild	5 (33.3)	24 (35.0)	
Moderate	2 (13.3)	12 (17.6)	
Severe	3 (20.0)	5 (7.3)	
IFTA/CNI toxicity	2 (13.3)	15 (22.0)	.79
IFTA (CAD and CNI toxicity)	3 (20.0)	12 (17.6)	.69
C4d positive	0	4 (5.8)	> .99
Mean estimated GFR, mL/min	33.1 ± 6.0	58.6 ± 12.9	.001

*Values in parentheses are percentages. IFTA/CAD indicates interstitial fibrosis tubular atrophy/chronic allograft dysfunction score and CNI, calcineurin inhibitors.

Table 3. Causes of Sirolimus Discontinuation by Glomerular Filtration Rate at Baseline

Cause of Sirolimus Discontinuation	Baseline Glomerular Filtration Rate		Total
	≤ 40 mL/min (n = 15)	> 40 mL/min (n = 84)	
Proteinuria	1	4	5
Acute rejection	1	3	4
Lymph edema	1	1	2
Allograft edema	0	2	2
Peripheral edema	0	1	1
Hyperlipidemia	0	1	1
Pneumonitis	0	1	1
Total	3	13	16

Table 4. Glomerular Filtration Rate (GFR) in Kidney Transplant Recipients With Early (≤ 6 Months) and late (> 6 Months) Sirolimus Conversion*

GFR	Conversion to Sirolimus		*P*
	Early (n = 11)	Late (n = 88)	
Baseline	59.9 ± 22.3 (44.9 to 74.9)	54.5 ± 14.4 (51.4 to 57.5)	.49
Month 1	64.7 ± 18.2 (52.5 to 76.9)	56.7 ± 17.1 (53.1 to 60.3)	.20
Month 6	66.0 ± 20.6 (52.2 to 79.8)	55.1 ± 16.8 (51.5 to 58.7)	.08
Month 12	71.1 ± 20.3 (57.5 to 84.7)	52.2 ± 16.1 (48.8 to 55.6)	.001
Month 24	72.8 ± 18.6 (60.3 to 85.3)	51.1 ± 16.9 (47.5 to 54.7)	.003
Month 36	68.0 ± 15.5 (57.6 to 78.4)	48.4 ± 18.6 (44.5 to 52.3)	.02

*Values in parentheses are 95% confidence intervals.

DISCUSSION

Chronic administration of calcineurin inhibitors (either cyclosporine or tacrolimus) is associated with chronic nephrotoxicity which can lead to progressive graft loss. Lowering the dose of calcineurin inhibitors may improve kidney function in selected patients. However, calcineurin inhibitor nephrotoxicity is progressive over time as long as the exposure is maintained. Therefore, using the alternative regimen with the aim of improving the long-term allograft survival is the major objective of kidney transplantation. In our study, we documented that sirolimus conversion from a regimen that includes cyclosporine stabilizes graft function with low rejection rate in kidney transplant recipients and no important changes in the overall GFR during a 36-month follow-up.

In accordance with our results, several randomized and nonrandomized studies have evaluated the safety and efficacy of conversion from calcineurin inhibitors based regimen to sirolimus in renal transplant patients,[10-14] and they found the stabilization of kidney function in sirolimus-included regimen. A randomized clinical study performed by Nafar and colleagues in Iran showed that patients who received sirolimus from the baseline compared to patients who were on cyclosporine had better graft and patient survival.[15] In a recent randomized control trial, the efficacy of using everolimus (as a member of mTOR inhibitor family) in de novo kidney transplant patients was evaluated and improvement of kidney function over a 12-months period was observed.[16] In a systematic review performed by Mulay and coworkers,[17] 5 randomized trials (1040 kidney transplant patients) and 25 nonrandomized studies (977 kidney transplant patients) involving conversion from a calcineurin inhibitor to sirolimus were analyzed. The conclusion was that in nonrandomized clinical trials, improvement or stabilization of kidney function in 66% of subjects, increase in creatinine clearance with mean of 5.7 ml/min, and acute rejection rates between 3% and 10% were evident. In our study, we had an acceptable acute rejection rate 4%, with no change in creatinine clearance in abrupt conversion protocol.

The use of sirolimus can be significantly limited by a high incidence of side effects such as proteinuria, edema, infertility, and hyperlipidemia,[18-22] and the associated side effects have been reported to count for 20% to 40% of sirolimus discontinuation cases in kidney transplant patients.[17,23] In our study, we found 16.6% sirolimus discontinuation because of adverse events.

Two of our patients developed severe swelling of the transplanted kidney with severe interstitial edema on renal biopsy specimens. In these two patients, sirolimus was discontinued. We assumed that allograft edema was due to localized renal lymphatic obstruction. In 1 patient, this was reversed when sirolimus was discontinued after 3 months; however, in another patient, because of late referral, the problem stayed in spite of discontinuation of sirolimus.

In a recent large prospective randomized clinical trial, performed on 555 patients undergoing sirolimus conversion, superior kidney function was observed among patients with a baseline GFR higher than 40 mL/min.[10] In our study, the majority of the patients (85%) had an estimated GFR higher than 40 mL/min at the time of conversion, but the final GFR and incidence of adverse effects were not significantly different from the small group with a GFR of 40 mL/min and lower. One reason that we did not see the difference between two groups might be caused by small number of individuals in the latter group (n = 11).

Another finding of this study was that

early conversion to calcineurin inhibitor-free immunosuppressive regimen in kidney transplant patients might have benefits in comparison to late initiation of calcineurin inhibitor-free regimen, since the improvement in GFR was better in this group compared to patients in whom cyclosporine therapy was converted to sirolimus at a later time. Chronic use of calcineurin inhibitors leads to arteriolopathy, tubular atrophy, interstitial fibrosis, glomerular sclerosis, and irreversible decreased kidney function.[24] Therefore, early recognition of kidney function worsening is of particular importance, since it may prevent further deterioration. In accordance with these findings, several studies reported that a right-time conversion to mTOR inhibitors (including sirolimus) could result in a better improvement in kidney function in heart, liver, and kidney transplant recipients.[25-27]

One of the shortcomings in our study was the lack of a control group for further comparison between patients who might have remained on calcineurin inhibitor-based immunosuppression. On the other hand, the majority of patients were referred very late for sirolimus conversion. This causes us to have a small number of patients in the early conversion group, which we should consider as one of the other limitations of the study. Absence of postconversion kidney biopsy to compare the histopathological changes after conversion is another limitation of our study.

CONCLUSIONS

Our study adds to the body of evidence that emphasizes sirolimus conversion in patients with kidney allograft dysfunction as a safe and effective treatment. However, the drug discontinuation should be considered early when it is indicated. The selection of patients and optimization of time of conversion needs further evaluation.

FINANCIAL SUPPORT

This research work was supported by a research grant from Tehran University of Medical Sciences. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

CONFLICT OF INTEREST

None declared.

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Received July 2012
Revised January 2013
Accepted February 2013