

Sirolimus versus Calcineurin Inhibitor-based Immunosuppressive Therapy in Kidney Transplantation

A 4-year Follow-up

Mohsen Nafar,¹ Behrang Alipour,² Pedram Ahmadpoor,¹
Fatemeh Pour-Reza-Gholi,¹ Fariba Samadian,¹ Shiva Samavat,¹
Soudabeh Farhangi²

¹Department of Nephrology, Shahid Labbafinejad Medical Center and Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

²Department of Nephrology, Shahid Labbafinejad Medical Center, Tehran, Iran

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Introduction. Sirolimus is the one of new immunosuppressants that may be a substitute to traditional drugs such as cyclosporine. We present our investigation on sirolimus-based immunosuppression in kidney transplant recipients as compared with cyclosporine-based immunosuppression.

Materials and Methods. We enrolled 100 patients in an open-labeled randomized clinical trial at Shahid Labbafinejad Medical Center. The patients were assigned to one of the immunosuppressive groups to receive either sirolimus or cyclosporine in combination with mycophenolate mofetil and steroids. All kidney transplant recipients were followed up by for serum creatinine and glomerular filtration rate for 4 years.

Results. There was no significant differences between the two groups regarding serum creatinine level and GFR until for years posttransplant; however, serum creatinine levels were significantly lower and the GFRs were higher in the sirolimus group after 3 and 4 years. The mean serum creatinine was 1.24 ± 0.28 mg/dL in the sirolimus group and 1.57 ± 0.33 mg/dL in the cyclosporine group at 4 years posttransplant ($P = .02$). Also, GFR was 79.8 ± 22.3 mL/min/1.73 m² in the sirolimus group and 70.3 ± 23.6 mL/min/1.73 m² in the cyclosporine group B ($P = .04$). Acute rejection was 1.7-fold higher in the cyclosporine group than in the sirolimus group.

Conclusions. Our study demonstrated that sirolimus in the immunosuppressive regimen of kidney transplant recipients had better outcomes regarding graft and patient survival. The effectiveness of sirolimus for kidney allograft recipients should be further assessed to be implemented from the first day after transplantation.

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INTRODUCTION

Since the introduction of calcineurin inhibitors in 1980s, risk of acute rejection in the first year after transplantation is reduced significantly, and the 1-year graft survival is improved; however, the 10-year graft survival is remained unchanged.¹

Different etiologies are supposed to be responsible for this discrepancy. Among them are high-risk recipients, extended-donor criteria, opportunistic infections, malignancies, and immunosuppressive drug toxicities.² The latter 3 causes are directly related to immunosuppressive agents and their side

effects. Most of the immunosuppressive regimens are calcineurin inhibitor based. Cyclosporine A, as a common calcineurin inhibitor in use, has significant nephrotoxic and nonrenal side effects, such as hypertension and hyperlipidemia. Cyclosporine can cause both acute and chronic nephrotoxicity. Acute effects of cyclosporine, which are directly related to its blood concentration, are due to acute reversible vasoconstriction of the renal arterioles, leading to hypertension, hyperkalemia, sodium retention, and reduced glomerular filtration rate (GFR).^{3,4}

The point prevalence of chronic calcineurin inhibitor toxicity was 67.3% in 5 years and 100% in 10 years posttransplantation. The histological changes include arteriolar hyalinosis, luminal narrowing, ischemic glomerulosclerosis, tubular microcalcifications, and interstitial fibrosis or tubular atrophy, which result in chronic allograft nephropathy (CAN).⁵ Previous studies have shown CAN happens during 2 phases after transplantation. Early injury correlates with immunologic factors, including severe acute rejection and subclinical rejection. On the other hand, late damages happen by arteriolar hyalinosis, glomerulosclerosis, and interstitial fibrosis associated with long-term calcineurin-inhibitor nephrotoxicity. Acute vascular rejection results in immediate histologic damage and initiation of CAN. In contrast, acute cellular rejection caused minimal damage unless it was severe or persistent subclinical rejection. Despite excellent 1-year rates of graft survival achieved by the introduction of cyclosporine and then tacrolimus, reservations have frequently been expressed about the long-term nephrotoxicity of these calcineurin inhibitors. Long-term exposure to these agents over a period of many years makes nephrotoxic effects a largely unavoidable complication of kidney transplantation. Chronic allograft nephropathy represents cumulative and incremental damage to nephrons from time-dependent immunologic and nonimmunologic causes.⁶

In order to improve long-term graft survival and reduce calcineurin-inhibitor toxicity, attempts are made to change immunosuppressive regimen by reducing calcineurin inhibitors dosage and adding other agents such as sirolimus, conversion from calcineurin inhibitors to other agents, and even avoidance of calcineurin inhibitors from the beginning. These facts brought mammalian target

of rapamycin (mTOR) inhibitors, sirolimus and everolimus, into the spot light. A randomized placebo-controlled multicenter phase II clinical trial by Kahan and colleagues, using cyclosporine and steroid in combination with sirolimus or placebo showed that the incidence of biopsy-proven acute rejection in the first 6 months posttransplantation was reduced in the sirolimus group compared with the placebo group. Regimen of reduced-dose cyclosporine with sirolimus resulted in better kidney function without any increase in rejection rate.⁷

In a United States study, the rate of biopsy-proven acute rejection and graft loss was lower in the sirolimus group than in the azathioprine group, but serum creatinine concentration was higher in the sirolimus-cyclosporine combination group. One-year graft and patient survival were alike.⁸ The same results were obtained from a European trial (the Global study), as it compared sirolimus with placebo in combination with cyclosporine and steroids. However, the sirolimus (5 mg/d) group had higher serum creatinine level at 3 and 6 month posttransplantation.⁹

The previously-mentioned studies led to the Food and Drug Administration approval of the combination of sirolimus-cyclosporine-steroid for kidney transplantation in 1999, and the European Agency for the Evaluation of Medical Products recommendation for cyclosporine withdrawal at 3 month.¹⁰ The Sirolimus European Renal Transplant Study Group, in an attempt to establish a cyclosporine-free protocol, used sirolimus instead of cyclosporine and demonstrated similar graft and patient survival, and lower serum creatinine level in sirolimus group, but higher incidence of side effects.¹¹ In the ORION trial, the rate of biopsy proven acute rejection and death was higher in sirolimus-mycophenolate mofetil (MMF) group.¹⁰ In the SYMPHONY study, daclizumab, MMF, steroid and low-dose tacrolimus regimen had been beneficial for kidney function and allograft survival in comparison with regimens containing sirolimus or cyclosporine.¹²

To evaluate effects of cyclosporine withdrawal after 3 months of combination therapy with cyclosporine-sirolimus-steroid, Johnson and colleagues performed a study, the results of which showed the same graft and patient survival and lower serum creatinine level and blood pressure after cyclosporine withdrawal.¹³ Apart from sirolimus-

enhanced cyclosporine nephrotoxicity, sirolimus-cyclosporine combination has various side effects, some of them might be reduced by cyclosporine withdrawal, such as hypertension, fatigue, uric acid and magnesium levels. There are also sirolimus-related side effects like hyperlipidemia, thrombocytopenia, abnormal liver function tests, lymphocele formation, prolonged recovery from delayed graft function and impaired wound healing, which are more common after cyclosporine withdrawal and might be related to higher trough sirolimus levels.^{14,15} Weir and the colleagues, studied efficacy of MMF-based immunosuppression with sirolimus in a randomized clinical trial. Compared with MMF-calcineurin inhibitor treatment, a 2-year regimen of MMF-sirolimus resulted in similar measures of kidney function, but with fewer deaths and a trend to less graft loss.¹⁶

In this study, we evaluated outcomes and side effects of sirolimus-cyclosporine-steroid regimen with 3-month replacement of cyclosporine by MMF in comparison with the standard cyclosporine-MMF-steroid protocol.

MATERIALS AND METHODS

This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences and is registered by the Iran RCT registry (IRCT138804333049N7). One hundred patients were enrolled in a randomized clinical trial at Shahid Labbafinejad Medical Center and were randomly divided into 2 groups of 50 patients each. We enrolled kidney transplant recipients between years 2004 and 2007 in Shahid Labbafinejad Medical Center. All patients signed the consent form before enrollment. The subjects were selected using the following inclusion criteria: end-stage renal disease; receiving a primary or secondary kidney allograft from a living-unrelated donor or from a living-related donor, a serum triglyceride less than 400 mg/dL (with or without medication), a serum cholesterol less than 300 mg/dL, age between 18 and 70 years, a leukocyte count greater than $4 \times 10^9/L$, and a platelet count greater than $100 \times 10^9/L$. The exclusion criteria were evidence of active systemic or localized major infection at the time of initiation of sirolimus administration; history of malignancy within 5 years before enrollment into the study; use of any investigational drug other than the specified in the protocol during

the 4 weeks before enrolling in the study; use of planned antibody induction therapy at the time of transplantation; active gastrointestinal disorder that may interfere with drug absorption; high risk of rejection (eg, a panel reactive antibodies greater than 50% and losing a previous graft within the first 6 months); evidence of infiltration, cavitations, or consolidation on chest radiography obtained during the prestudy screening; multiple organ transplant; and known hypersensitivity to sirolimus, MMF, or cyclosporine or its derivatives. If the patients experienced delayed graft function (DGF) as surgical complication, the patients were excluded from the study in each group. The antithymocyte globulin use for DGF was the other exclusion criterion.

After transplantation, the patients randomly received one of the immunosuppressive protocol as follows: a combination of cyclosporine, sirolimus, and steroids was administered in the sirolimus group during the first 3 months, and cyclosporine was changed to MMF from the 4th month on. The control group received cyclosporine, MMF, and steroids. Immunosuppressive drugs were administered with the following dosages: sirolimus, 6 mg/d as a loading dose and continuing with dosages to reach the trough levels of 8 ng/mL to 15 ng/mL as maintenance; cyclosporine, trough levels of 150 ng/mL to 250 ng/mL; MMF, 1 g/d to 2 g/d; and corticosteroid, 5 mg/d.

The rates of biopsy-proved acute rejection, graft loss, and death within 12 months posttransplantation were compared between two groups. In addition, all of the kidney transplant recipients were followed up by assessment of serum creatinine and GFR (Cockcroft-Gault formula) for 4 years. Infections, histologically-confirmed lymphoproliferative disease, and anemia were recorded at 12 months after transplantation.

For data analysis we used the SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, Ill, USA). The Student *t* test was used for comparison of the quantitative data and the chi-square test for qualitative ones. The graft and patient survival rates were presented using the Kaplan-Meier method. A *P* value less than .05 was considered significant.

RESULTS

The baseline characteristics were similar between the two groups (Table 1). The mean of

Table 1. Baseline Demographic and Clinical Data in Kidney Transplant Recipients Receiving Sirolimus-based and Cyclosporine-based Immunosuppressive Regimen*

Characteristic	Sirolimus Group	Control Group
Age, y	38.5	42.5
Gender, %		
Male	58	52
Female	42	26
Cause of kidney failure, %		
Hypertension	54	48
Diabetes mellitus	20	22
Unknown	16	26
Serum cholesterol, mg/dL	167	159
Serum triglyceride, mg/dL	162	158
Fasting blood glucose, mg/dL	92	116
Serum alanine aminotransferase, U/mL	38.8	38.4
Serum aspartate aminotransferase, U/mL	25	27
Systolic blood pressure, mm Hg	133	130
Diastolic blood pressure, mm Hg	77	78

*Values are means unless otherwise explained.

age was 38.5 ± 12.5 years in the sirolimus group and 42.5 ± 14.3 years in the control group. After 4 years of follow-up, 47 patients remained in the sirolimus group and 45 patients in the control group. Two patients in the sirolimus group were excluded because of severe leukopenia and anemia, and 4 patients died in the control group because of cardiovascular accident and sepsis. One patient was missed to follow-up in each group.

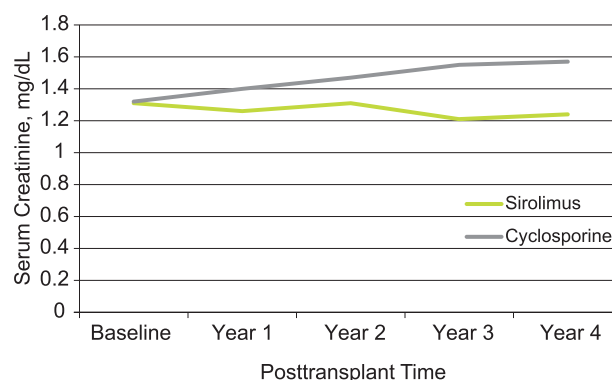
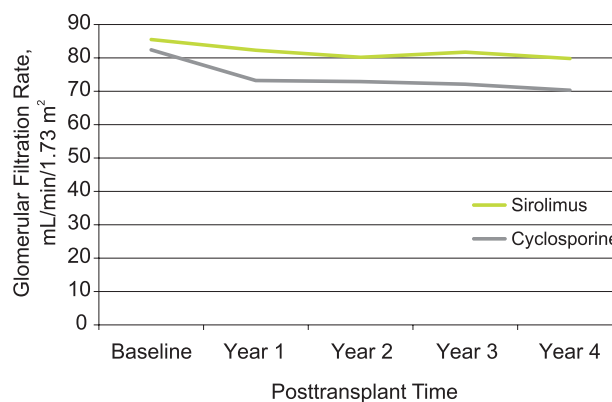
There was no significant differences between the two groups regarding serum creatinine level and GFR until for years posttransplant; however, serum creatinine levels were significantly lower and the GFRs were higher in the sirolimus group after 3 and 4 years (Table 2 and Figures 1 and 2).

Table 2. Mean Serum Creatinine Level and Glomerular Filtration Rate During a 4-year Follow-up

Parameter	Sirolimus Group	Control Group	P
Serum creatinine, mg/dL			
1 year	1.26 ± 0.32	1.40 ± 0.35	> .05
2 years	1.31 ± 0.42	1.47 ± 0.57	> .05
3 years	1.21 ± 0.25	1.55 ± 0.91	.03
4 years	1.24 ± 0.28	1.57 ± 0.33	.02
Glomerular filtration rate, mL/min/1.73 m ²			
1 year	82.3 ± 24.3	73.2 ± 19.2	> .05
2 years	79.2 ± 26.3	72.9 ± 19.6	> .05
3 years	81.7 ± 21.9	72.1 ± 22.4	.04
4 years	79.8 ± 22.3	70.3 ± 23.6	.04

Acute rejection was 1.7-fold higher in the control group than the sirolimus group, during the 1st year after transplantation ($P < .001$). Acute rejection occurred in 9 patients in the control group (34 episodes) and in 4 patients (20 episodes) in the sirolimus group. Most of the rejections happened during the first 6 month after transplantation (87% in the sirolimus group and 91% in the control group; $P > .05$). Histopathological grades of biopsy-confirmed cellular acute rejection episodes were grade 1 (55% and 51%), grade 2 (32% and 36%), grade 3 (3% and 5%), and grade 2-3 (10% and 8%) in the sirolimus and control groups, respectively ($P > .05$). There was not any significant difference between the two groups regarding patient survival (Figure 3). Graft survival rates were better in the sirolimus group as shown in Figure 4.

Rehospitalization occurred 52 times in the sirolimus group and 44 times in the control group ($P > .05$). Cyclosporine toxicity rates were not

**Figure 1.** Serum creatinine level during the 4-year posttransplant follow-up in patients receiving sirolimus-based and cyclosporine-based immunosuppressive medication.**Figure 2.** Glomerular filtration rate during the 4-year posttransplant follow-up in patients receiving sirolimus-based and cyclosporine-based immunosuppressive medication.

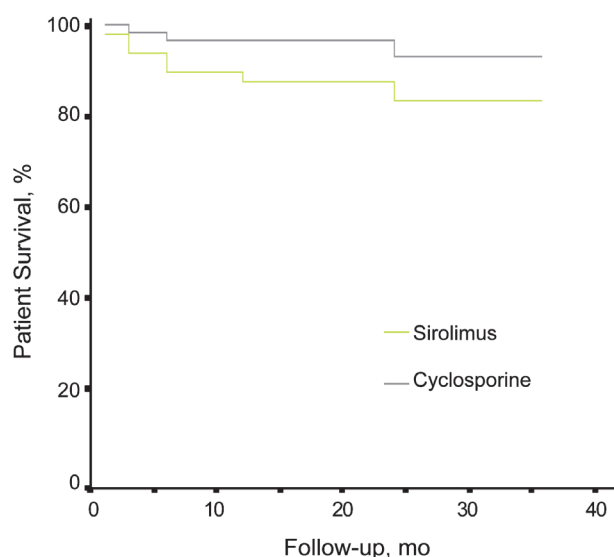


Figure 3. Patient survival in patients receiving sirolimus-based and cyclosporine-based immunosuppressive medication.

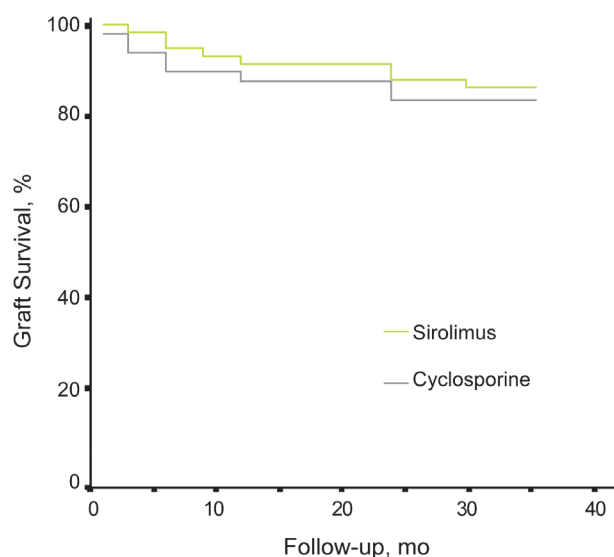


Figure 4. Graft survival in patients receiving sirolimus-based and cyclosporine-based immunosuppressive medication.

different between the two groups ($P > .05$). The comparison between other clinical and laboratory variables did not show any significant differences after 1-year follow-up (Table 3).

The side effects of immunosuppressants were reported in 61%, 20%, and 19% of the patients in the sirolimus group and in 52%, 30%, and 18% of the patients in the control group within 3 months, 3 to 6 months and more than 6 months posttransplantation, respectively. Of all the patients in the sirolimus group that had diabetes, 90% finished the study as compared to 55% in the cyclosporine group

Table 3. Mean Clinical and Laboratory Values in Kidney Transplant Recipients Receiving Sirolimus-based and Cyclosporine-based Immunosuppressive Regimen After 1 Year of Follow-up

Parameter	Sirolimus Group	Control Group	<i>P</i>
Serum cholesterol, mg/dL	194	190	> .05
Serum triglyceride, mg/dL	205	189	> .05
Fasting blood glucose, mg/dL	96	105	> .05
Serum alanine aminotransferase, U/mL	38.8	38.4	> .05
Serum aspartate aminotransferase, U/mL	25	27	> .05
Systolic blood pressure, mm Hg	127	121	> .05
Diastolic blood pressure, mm Hg	78	76	> .05

($P = .02$). About the hypertension, these data were 78% in the sirolimus group and 67% in the control group ($P > .05$).

DISCUSSION

In the current study, it was showed the graft survival after 4 years in the sirolimus group was better than the cyclosporine group. Also, the side effects and complications in the two groups were similar, expect for acute rejections that were significant in the cyclosporine group. Four patients died in the cyclosporine-based group in contrast to sirolimus-based group. Weir and the coworkers studied the efficacy of MMF-based immunosuppression with sirolimus in contrast to MMF plus cyclosporine in the United States. Their findings showed compared with MMF and cyclosporine treatment, a 2-year regimen of MMF and sirolimus resulted in similar measures of kidney function, but with fewer deaths and a trend to less graft loss.¹⁶

In our study, the rate of acute rejection was higher in the cyclosporine group than the sirolimus group in contrast to some previous studies. Kreis and coworkers reported higher rates of acute rejection in the sirolimus-based immunosuppression than the cyclosporine-based one, but graft survival in the sirolimus group was better than the other group.¹⁷ In MacDonald's study, the rate of acute rejection was lower in the sirolimus group in contrast to the placebo group in combination with cyclosporine and prednisolone.¹⁷ Kreis and colleagues' findings showed the same acute rejection rate in the two immunosuppression regimen based on cyclosporine and sirolimus.¹⁷ In our study, the higher rate of rejection in the cyclosporine group maybe due to

the cyclosporine toxicity in Iranian patients with optimal dose of cyclosporine that sirolimus ones. Maharaj and Assounqa in South Africa surveyed the conversion of cyclosporine to sirolimus before 12 months. Evaluating 30 patients, they showed that sirolimus therapy was associated with improved GFR and also an increase in urine protein excretion rates. They recommended the maximum benefit was achieved when patients were switched to sirolimus within the first transplant year.¹⁸ In a same study in the United States, Pankewycz and colleagues studied on conversion of cyclosporine to tacrolimus or sirolimus 3 months after transplantation.¹⁹ Fifty-eight patients were enrolled in this randomized trial and were followed up for 1 year. One-year graft function rates were equally well maintained with either low-dose tacrolimus or sirolimus immunosuppression.

Uslu and coworkers studied the conversion from cyclosporine to sirolimus in Turkey, in 2009. Thirty-one kidney transplant recipients were enrolled in the dual-center study. Their data were selected and completed at least 12 months of follow-up. They concluded that sirolimus might be a good therapeutic strategy against chronic cyclosporine toxicity, particularly for patients whose conversion biopsy specimens demonstrated mild interstitial fibrosis or tubular atrophy, glomerulosclerosis, and chronic vasculopathy scores.²⁰

Anil Kumar and colleagues reported a comparison between 4 immunosuppressive protocols without long-term steroid therapy in kidney allograft recipients, within a 4-year follow-up in 2008. Their data showed that the rates of clinical acute rejection and subclinical acute rejection in the first year posttransplant were significantly lower in the cyclosporine conversion to sirolimus and tacrolimus conversion to sirolimus groups. Despite significant differences in the incidences of acute rejection and prevalence of different types of chronic allograft injury at 5 years, kidney function and patient and graft survival rates at 5 years were comparable among kidney recipients maintained on 4 different immunosuppression protocols without long-term steroid therapy. In this study, 50 patients evaluated in each group.²¹

Saurina and coworkers evaluated the conversion from cyclosporine to sirolimus in chronic allograft dysfunction. They studied on 14 patients with proteinuria during the 8 months' follow-up. Their

data showed that kidney function reserve decreased and proteinuria increased after conversion. They recommended the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in these patient.²² In France, Bumbea and colleagues studied on conversion from cyclosporine or tacrolimus to sirolimus. They enrolled 43 transplant recipients and followed up for 2 years. They showed the conversion was associated to improving in kidney function; however, in 33% of patients proteinuria improved, too.²³

CONCLUSIONS

Our study demonstrated that sirolimus in the immunosuppressive regimen of kidney transplant recipients had better outcomes regarding graft and patient survival. The effectiveness of sirolimus for kidney allograft recipients should be further assessed to be implemented from the first day after transplantation.

CONFLICT OF INTEREST

None declared.

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Correspondence to:
Mohsen Nafar, MD
Department of Internal Medicine, Shahid Labbafinejad Medical
Centre, Pasdaran Ave, Tehran, Iran
E-mail: nafarm@sbmu.ac.ir

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