The side effect profile of sirolimus and its relationship with some variables: A retrospective study of Iranian renal transplant patients

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Background: Sirolimus is a potent immunosuppressive in renal transplantation. However, its use is limited by some reported side effects. The objective of this study was to determine the side effect profile of sirolimus in renal transplant patients. **Materials and Methods:** In the present study, we retrospectively reviewed the medical records of 116 renal transplant patients treated with sirolimus alone or in combination with other immunosuppressive agents at private therapeutic centers in Isfahan, Iran, between March 2009 and February 2020. A checklist was used to collect data on demographic and clinical variables. Data were analyzed with independent samples *t*-test and Chi-squared test. **Results:** Our findings indicated that the most prevalent sirolimus-related side effects were edema (42.3%), proteinuria (37.5%), cytopenia (26.9%), abnormal level of liver enzymes (11.7%), and pneumonitis (9.7%). Stratification of side effects by sirolimus dose (<2 mg and ≥2 mg) demonstrated their dose-independent occurrence ($P > 0.05$). Pneumonitis was the most frequent reason for sirolimus cessation (58.7%). No significant differences were observed between males and females regarding the frequency of reasons for sirolimus cessation ($P > 0.05$). **Conclusion:** Edema, proteinuria, cytopenia, abnormal level of liver enzymes, and pneumonitis were the most prevalent sirolimus-related side effects in renal transplant patients. Further prospective cohort studies are warranted to detect underlying mechanisms and determinants of these side effects in renal transplant patients treated with sirolimus.

Key words: Renal transplantation, side effects, sirolimus

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INTRODUCTION

Sirolimus, also known as rapamycin, is a macrocyclic lactone derived from *Streptomyces hygroscupicusan*. It was initially approved as an antifungal agent; however, later researchers discovered its potential immunosuppressive and antiproliferative properties. It was approved by the Food and Drug Administration as an immunosuppressive drug for renal transplant patients in 1999.[1,2] Lower nephrotoxicity and malignancy rates have made sirolimus a beneficial alternative for calcineurin inhibitors in renal transplant patients.[3-5] It has also been demonstrated that early conversion from a calcineurin inhibitor-based immunosuppression to sirolimus following renal transplantation improves renal function and survival.[6,7]

Despite its promising effects in renal transplant patients, the use of sirolimus-based immunosuppression has been limited by numerous side effects. Although the frequency of sirolimus-related side effects is different among various populations, the most prevalent reported side effects are known as hyperlipidemia, posttransplant diabetes, hematologic complications (anemia, leukopenia, and thrombocytopenia), proteinuria,

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mouth ulcers, impaired wound healing, pneumonitis, and edema.[8-10] According to previous studies, some of the sirolimus-associated side effects are dose dependent and readily manageable through dose reduction, while sirolimus discontinuation is necessary for other side effects such as proteinuria, pulmonary toxicity, and oral ulcers.[11-13] As a result, early detection of sirolimus side effects is necessary for their management and possible immunosuppressive regimen alteration or cessation.

The prevalence of sirolimus discontinuation because of various side effects has been reported between 8% and 46% according to previous studies. The prevalence and reasons for sirolimus discontinuation vary in different studies possibly because of the diversity in treatment procedures and clinical characteristics of studied patients.[14-16] Sirolimus discontinuation because of serious side effects such as edema, proteinuria, mucositis, and pneumonitis happened in 9 out of 112 (8%) patients in a study by Gois *et al*.[14] However, sirolimus discontinuation occurred in 46% of patients because of correlated side effects, mainly proteinuria, ulcers, and edema, in a retrospective study on 219 renal transplant patients converted from calcineurin inhibitors to sirolimus regimen.[16] To our knowledge, no previous study has assessed the side effect profile of sirolimus in the Iranian population. The findings from the present study will provide evidence for the clinical relevance of sirolimus in the management of kidney transplant patients. The objective of this study was to investigate the frequency of sirolimus-related side effects in a sample of renal transplant patients in the center of our country.

METHODS

Data collection

In the present study, we retrospectively reviewed the medical records of renal transplant patients treated with sirolimus alone or in combination with other immunosuppressive agents at private therapeutic centers in our city between March 2009 and February 2020. An standarad checklist was used to collect data regarding age (year), gender, weight(kg), dialysis type (hemodialysis and peritoneal dialysis), dialysis vintage (months), reasons for switching to sirolimus (cancer,chronic allograft nephropathy, resistant infections, and others), sirolimus dose (0.5 (1 mg every other day), 1,1.5 (1 and 2 mg on consecutive days), and 2 mg/day), sirolimus treatment duration(months), and sirolimus cessation variables were provided to collect data. Patients were excluded from the study if investigated side effects were related to other conditions than sirolimus treatment. The protocol of this study was approved by Isfahan University of Medical Sciences, Isfahan, Iran (research number: 49891).

Statistical analysis

Continuous variables were reported as mean ± standard deviation and median (minimum and maximum), while categorical data were reported as frequency (percentage). The normality of continuous variables has been evaluated by Kolmogorov–Smirnov and Q-Q plot and nonnormally distributed data were subjected to logarithmic transformation. Continuous variables were compared between groups (male/female and patients affected and nonaffected by sirolimus-related side effects) by independent samples *t*-test. Categorical variables were compared between groups by Chi-squared test. All statistical analyses were conducted by SPSS 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, version 23.0., Armonk, NY, USA: IBM Corp).

RESULTS

In total, 166 patients with a mean age of 47.31 ± 13.75 years and a mean weight of 70.60 ± 13.88 kg were included in the analysis. The demographic and clinical characteristics of renal transplant patients in the total sample and across the sex subgroups are summarized in Table 1. Patients were most likely to be nonpreemptive (81.8%), and the mean dialysis duration was 20.14 ± 20.90 months. The mean duration of sirolimus treatment and graft survival was 65.73 ± 41.23 and 117.98 ± 63.80 months, respectively, and more than half of patients received sirolimus 2 mg/day. Cancer (42.7%) was the most frequent reason for switching to sirolimus treatment followed by chronic allograft nephropathy (24.5%). There was no significant difference between males and females concerning age, dialysis type, dialysis duration, graft life span, reasons for switching to sirolimus, sirolimus dosage, and treatment duration ($P > 0.05$). In addition, the most prevalent reason for sirolimus cessation was interstitial pneumonitis in the total sample (58.7%), as well as sex subgroups (males: 60%, females: 57.1%); however, there was not any significant difference between males and females regarding sirolimus cessation variables ($P > 0.05$).

The comparison of demographic and clinical variables between patients with side effects and patients without side effects showed no significant differnce was observed between patients with and without sirolimus-related side effect in terms of age,weight, sex, renal replacement therapy before kidney transplantation, dialysis type, and duration,sirolimus dose, and death [$P > 0.05$, Table 2]. Our findings indicated that the most prevalent sirolimus-related side effects were edema (42.3%), proteinuria (37.5%), cytopenia (26.9%), abnormal levels of liver enzymes (11.7%), and pneumonitis (9.7%) [Table 3]. No significant difference was observed in the prevalence of sirolimus-related side effects including proteinuria, cytopenia, abnormal

Table 1: Basic and clinical characteristics of kidney transplanted patients in the total sample and in sex subgroups

Variables	Total (*n*=116)	Male (*n*=81)	Female (*n*=35)	*P*
Age	47.31±13.75	49.00±14.08	43.60±12.56	0.05
Weight (kg)	70.60±13.88	73.44±12.66	63.20±14.42	0.001
Preemptive transplant, *n* (%)	20 (18.2)	14 (18.7)	6 (18.2)	
Nonpreemptive transplant, *n* (%)	88 (81.8)	61 (81.3)	27 (81.7)	0.95
Dialysis duration (months)	20.14±20.90	19.48±28.73	21.60±26.87	0.75
Graft survival (months)	117.98±63.80	116.25±57.52	117.29±73.65	0.94
Reason for switching to sirolimus, *n* (%)				
Cancer	46 (42.7)	31 (41.9)	15 (47.1)	0.95
Chronic allograft nephropathy	24 (24.5)	17 (24.3)	7 (23.5)	
Resistant infections	8 (7.3)	6 (8.1)	2 (5.9)	
Others	27 (25.5)	19 (25.7)	8 (23.5)	
Sirolimus dose (mg/day)*				
0.5	2 (1.9)	1 (1.4)	1 (3.4)	0.54
1	20 (20.2)	13 (18.8)	7 (24.1)	
1.5	23 (22.1)	19 (25.7)	4 (13.8)	
2	57 (55.8)	40 (54.1)	17 (58.7)	
Sirolimus treatment duration (months)	65.73±41.23	69.33±40.28	59.55±42.46	0.27
Reasons for sirolimus cessation, *n* (%)				
Interstitial pneumonia	10 (58.7)	6 (60.0)	4 (57.1)	0.54
Graft rejection	2 (11.8)	1 (10.0)	1 (14.3)	
Proteinuria	1 (5.9)	0	1 (14.3)	
Ulcer	1 (5.9)	1 (10.0)	0	
Hemoglobin reduction	1 (5.9)	1 (10.0)	0	
Tremor	1 (5.9)	1 (10.0)	0	
Death	1 (5.9)	0	1 (14.3)	

*The number of patients for categorical variables is different from total number of cases in each group due to missing data. Values in table are mean±SD for continuous variables and percentage for categorical variables, *P* values were obtained from independent samples *t*-test for continuous variables and Chi-square test for categorical ones. *P*<0.05 is considered significant. SD=Standard deviation

liver enzyme, and pneumonitis when stratification was done based on the dose of sirolimus (<2 mg and 2 mg) [$P > 0.05$, Table 3]. However, the prevalence of edema was marginally significantly higher in patients who received sirolimus 2 mg (65.9%) than those who received sirolimus <2 mg (34.1%) ($P = 0.08$).

DISCUSSION

Our results suggested that edema, proteinuria, cytopenia, abnormal liver enzyme, and pneumonitis were the most prevalent side effects in renal transplant patients treated with sirolimus in a dose-independent manner. Edema was the most prevalent side effect; however, pneumonitis was the least prevalent side effect of sirolimus treatment. Our study also demonstrated that the most prevalent cause of sirolimus treatment cessation was interstitial pneumonitis.

Interstitial pneumonitis is one of the severe pro-inflammatory side effects of sirolimus in solid organ transplant patients. It is hard to estimate the incidence of sirolimus-related pneumonitis because most patients are asymptomatic initially; however, in solid organ transplant patients, the estimated incidence ranged from 5% to 15%.[17-19] The known risk factors for sirolimus-related pneumonitis are age, male sex, late switching from calcineurin to sirolimus, and sirolimus level.[10] In the present study, interstitial pneumonitis was the least prevalent side effect that was observed in 9.7% of patients. However, it was the most prevalent reason for sirolimus cessation possibly because of its severity and persistence despite sirolimus dose reduction. We did not find any significant differences between pneumonitis and nonpatients with pneumonitis regarding demographic and clinical variables.

Peripheral edema has been reported among the most common side effects of sirolimus treatment in solid organ patients.[20-22] The results of a study by Peddi *et al*. reported edema as one of the most common side effects with a frequency of 35% in renal transplant patients switching from calcineurin inhibitors to sirolimus.[23] Peripheral edema was also observed in 37% of renal transplant patients treated with sirolimus as an alternative to calcineurin inhibitors in a retrospective cohort study by Verhave *et al*.[16] Edema is usually mild to moderate and resolves with dose reduction. Edema was observed in 42.3% of renal transplant patients in the present study with no cases of drug discontinuation due to it. It has been postulated that sirolimus leads to edema by increased prostacyclin release from endothelial cells and consequent vasodilation and edema.[24]

Table 2: The comparison of basic and clinical characteristics of kidney transplanted patients treated with sirolimus between patients with and without side effects

Variables	Pneumonitis		*P*	Cytopenia		*P*	Abnormal liver enzyme level		*P*	Edema		*P*	Proteinuria		*P*
	Yes	No		Yes	No		Yes	No		Yes	No		Yes	No	
Age	48.50±12.89	47.23±13.95	0.76	43.97±14.11	48.49±13.50	0.12	52.42±11.02	46.93±13.85	0.19	49.32±13.23	45.60±14.05	0.15	48.15±12.28	46.75±14.70	0.59
Weight (kg)	75.50±15.23	70.64±13.89	0.97	69.68±12.98	70.99±14.33	0.68	69.22±8.91	70.86±14.41	0.74	71.42±15.64	69.85±12.17	0.59	71.93±12.82	69.75±14.56	0.47
Sex															
Male	58.3	70.9	0.51	66.7	70.9	0.65	69.2	70.6	0.92	71.2	68.8	0.78	80.0	63.4	0.05
Female	41.7	29.1		33.3	29.1		30.8	29.4		28.8	31.2		20.0	36.6	
Renal replacement therapy before transplantation															
Dialysis	81.8	81.6	>0.99	83.3	81.3	>0.99	83.3	81.4	>0.99	85.1	79.4	0.47	85.0	80.0	0.61
Preemptive	18.2	18.4		16.7	18.7		16.7	18.6		14.9	20.6		15.0	20.0	
Dialysis type															
Hemodialysis	88.9	100.0	0.10	100.0	98.5	>0.99	100.0	98.7	>0.99	100.00	98.0	1.0	100.0	98.2	>0.99
Peritoneal dialysis	11.1	0.0		0.0	1.5		0.0	1.3		0.0	2.0		0.0	1.8	
Dialysis duration (months)	17.44±16.50	20.53±29.16	0.76	16.73±16.06	21.29±30.92	0.51	18.80±19.70	20.50±29.03	0.86	21.69±27.40	18.87±28.52	0.64	17.59±24.52	21.77±29.98	0.50
Sirolimus dose (mg/day)															
0.5	0.0	2.2	0.77	3.6	1.3	0.56	0.0	2.2	0.95	2.3	1.7	0.21	2.6	1.5	0.73
1	10.00	21.5		25.0	18.4		16.7	19.8		11.4	26.7		15.4	23.1	
1.5	30.00	21.5		14.3	25.0		25.0	22.0		20.5	23.3		20.5	23.1	
2	60.00	54.8		57.1	55.3		58.3	56.0		65.8	48.3		61.5	52.3	
Death	9.1	0.0		0.0	10.0		0.0	6.7		0.0	10.0		0.0	10.0	

Values in table are mean±SD for continuous variables and percentage for categorical variables, *P* values were obtained from independent samples *t*-test for continuous variables and Chi-square test for categorical ones. $P<0.05$ is considered significant. SD=Standard deviation

Table 3: Comparing the prevalence of sirolimus-related side effects in the total sample and across patients receiving <2 and 2 mg sirolimus

Sirolimus-related side effects	Prevalence in total sample, *n* (%)	Prevalence based on sirolimus dose		*P*
		<2 mg, *n* (%)	2 mg, *n* (%)	
Edema	44 (42.3)	15 (34.1)	29 (65.9)	0.08
Proteinuria	39 (37.5)	15 (38.5)	24 (61.5)	0.36
Cytopenia	28 (26.9)	12 (55.3)	16 (44.7)	0.39
Abnormal liver enzyme	12 (11.7)	5 (41.7)	7 (58.3)	0.88
Pneumonitis	10 (9.7)	4 (40.0)	6 (60.0)	1.00

*Some patients have more than one sirolimus–related side effect and the number of patients for some side effects is different from total number of cases in each group due to missing data. *P*<0.05 is considered significant

Proteinuria, as a determinant of progressive renal damage, is another prevalent side effect of sirolimus treatment in renal transplant patients and has caused great concern, especially in patients switching from calcineurin inhibitors to sirolimus.[25-27] Letavernier *et al*. in a retrospective study of 68 renal transplant patients suggested that switching from calcineurin inhibitors to sirolimus is associated with proteinuria development even in the nephrotic range.[25] An increase in proteinuria was also observed in renal transplant patients switched from azathioprine to sirolimus.[28] However, it seems that the development of proteinuria is not related to *de novo* sirolimus treatment.[11] In our study, proteinuria was among the most prevalent side effects of sirolimus with a prevalence of 37.5%. Sirolimus was discontinued in 5.9% of patients with this side effect.

Cytopenia occurs in the first 4–8 weeks of sirolimus treatment in 20% of renal transplant patients. Bone marrow toxicity is associated with cytopenia in renal transplant patients receiving sirolimus.[29,30] It has been demonstrated that cytopenia is more pronounced when it is administered as an adjuvant to mycophenolate mofetil.[31,32] According to previous studies, cytopenia is dose dependent in renal transplant patients treated with sirolimus. Dansirikul *et al*. reported that there is a significant association between the dose of sirolimus (10 mg/day) and white blood cell and hematocrit levels.[33] Cytopenia occurred in 26.9% of patients in our study. However, we could not find any association between cytopenia and sirolimus dose possibly because of differences in treatment procedures in our study compared to the study by Dansirikul *et al*.

Abnormal level of liver enzymes is a rare side effect of sirolimus treatment. In addition, there is no precise information regarding the incidence of this side effect. Groth *et al*. in a randomized, open-label study demonstrated that sirolimus treatment was associated with several abnormal laboratory findings like increased levels of liver enzymes.[34] In addition, the incidence of abnormal levels of liver enzymes was significantly higher in renal transplant patients who had been treated with a sirolimus-based regimen with early elimination of cyclosporine compared to patients who received a conventional dose of cyclosporine and a fixed amount of sirolimus.[35] The prevalence of abnormal levels of liver enzymes was 11.7% in our study. In direction with previous studies, no cessation related to abnormal levels of liver enzymes was reported in the present study.

The current study had some limitations. First, the sample size was nearly small. In addition, the retrospective design of the study limited our access to data regarding factors that possibly were associated with the occurrence of sirolimus-related side effects, such as sirolimus serum levels, the type and dose of concomitant or previous immunosuppressive treatments.

CONCLUSION

The most prevalent sirolimus-related side effects in Iranian renal transplant patients were edema, proteinuria, cytopenia, abnormal level of liver enzymes, and interstitial pneumonitis. Most of the side effects of sirolimus in the population were easily controllable and did not cause treatment discontinuation or patient death. Further prospective cohort studies are warranted to detect underlying mechanisms and determinants of these side effects in renal transplant patients treated with sirolimus.

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Conflicts of interest
There are no conflicts of interest.

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