Sirolimus Dose Requirement in Kidney Transplant Recipients in Iran

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Introduction. Sirolimus (Rapamune) is an important immunosuppressive drug in kidney transplant patients. The usual maintenance dose of Sirolimus in these patients is 2 to 5 mg/d and its optimal maintenance trough level is 5 to 10 ng/mL. The required Sirolimus doses may differ markedly from patient to patient. It is because of high inter and intrapatient variability in its pharmacokinetics. There have been no studies in Iran on the correlation of Sirolimus blood level and its target dose. This study has been done to show the target dose of Sirolimus in kidney transplanted patients in Isfahan.

Methods. This is a longitudinal cross-sectional study conducted from June 2018 to September 2019. The study population included all kidney transplanted patients treated with Sirolimus in a nephrology private clinic. Inclusion criteria were age (equal or more than 18 years old) and the existence of complete data in the patient's file. The participants were excluded if there were not at least two Sirolimus levels in the patient's file. Demographics and other variables were extracted from the patient's files.

Results. Sirolimus was prescribed for seventy-three patients. Sixteen patients did not have the inclusion criteria. Fifty-seven renal transplanted patients were included in the study. The mean starting dose of Sirolimus in these patients was 2 ± 0.19 mg/d. The mean of the Sirolimus dose was 1.2 ± 0.44 mg/d. There was more than 20% GFR improvement in 68% of the patients after changing the Calcineurin Inhibitor to Sirolimus ($P < .05$).

Conclusion. In a significant number of patients changing CNI to Sirolimus accompanied by GFR improvement. Contrary to the recommended dose of Sirolimus in the references (2 to 5 mg/d) Iranian kidney transplant recipients needed lower daily doses of Sirolimus (1.2 mg/d) to achieve the desired whole blood level. Further studies are recommended to confirm it.

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INTRODUCTION

Renal transplantation is considered a definite treatment for End Stage Renal Disease (ESRD). Tens of thousands of kidneys have been transplanted around the world; today in the U.S., more than 180000 patients have functional transplanted kidney.[1] By the end of 2016 in Iran, more than 58000 ESRD patients have undergone Renal Replacement Therapy (RRT). Of which about 29200 received hemodialysis, 1624 peritoneal dialysis, and 27000 kidney transplants.[2] Recent research has extensively been focused on factors

impacting the life expectancy of patients with transplanted kidney.[3] Therefore, during recent years we have witnessed extensive prescription of immunosuppressive drugs for kidney transplant patients. Although these drugs have caused a decline in acute transplant rejection and indicated favourable consequences for renal transplant,[3] patients face another implication; which is the side effects of long term immunosuppressive therapy.[4]

Immunosuppressive drugs, used in transplant patients, have a narrow therapeutic index, i.e. there is a small difference between their effective and toxic dosage.[5] Thus, the measurement of blood level for some of these drugs is of particular importance. These drugs fall into two categories: induction and maintenance. Maintenance drugs are also categorized into several sub-categories, among which the two major ones are Calcineurin inhibitors and mTOR inhibitors. Calcineurin inhibitors include Cyclosporine and Tacrolimus, which are extensively used for renal transplant patients.[1] An important drug among mammalian Target of Rapamycin (mTOR) inhibitors is Sirolimus (previously known as Rapamycin). Similar to Tacrolimus, this is a type of fungal macrolide but with a different mechanism. mTOR is a protein kinase. It is in T lymphocytes and many other cells and is involved in cell cycle progression from the G1 to S phase, cell survival and autophagy.[6] "Rapamycin inhibits late signals in T cell activation that are transduced by either the IL-2R or CD28 costimulatory signal transduction pathways. In contrast, cyclosporine and Tacrolimus inhibit an early signal in T cell activation that is transduced by the T Cell Receptor (TCR) signal transduction pathway. The mTOR inhibitors are potent inhibitors of vascular endothelial growth factor, which may explain their role in preventing the progression of many forms of cancer."[7]

In most renal transplant centres in Iran, Sirolimus is normally not considered as the first line treatment, and initially, a Calcineurin inhibitor is prescribed and later, regarding the drug indication, it will shift to Sirolimus. There is no specific guideline for shifting to Sirolimus; however, according to some experts, the side effects of Calcineurin inhibitors, including nephrotoxicity, diabetes, hypertension, tumor development or progression, can be considered as the indications of shifting to Sirolimus.[8] Based on the scientific resources, the blood level of Sirolimus is determined to be 5 to 10 ng/mL;[9] the dose is different depending on the patient's condition and concurrent use of Calcineurin inhibitors; the daily maintenance dose is 2 to 5 mg.[10] In general, due to their different pharmacodynamics and pharmacokinetics, immunosuppressive dosage varies considerably in various patients. For instance, the required dose of Tacrolimus to reach the determined blood level may vary from 2 mg/d to 10 times of this dosage. Regarding this distinction, in a study conducted on Tacrolimus in Iran, the average required dose of the drug for renal transplant patients to reach the determined blood level was lower than the specified dose by manufacturers and scientific resources. According to scientific resources, the recommended initial dosage of Tacrolimus after renal transplant was 0.1 to 0.2 mg/kg/d, while according to the results of the aforementioned study, the required dosage was determined to be 0.08 mg/kg for ideal body weight.[11] In a study conducted in Korea, the mean dose of Sirolimus was 1.79 mg/d and more than half of the participants were treated with a dose of less than 2 mg/d.[12]

Therefore, regarding the fact that no study has ever been performed on the mean serum levels of Sirolimus in Iranian kidney transplant patients, the study was designed to achieve this goal.

MATERIALS AND METHODS

This is a descriptive Longitudinal Cross-Sectional study, which was conducted from June 2018 to July 2019. The research population consisted of all renal transplant patients, being treated with Sirolimus as the main immunosuppressive drug (with other immunosuppressive). The participants were selected from a private nephrology clinic. A convenient non-random method was used for the selection of the patients. The inclusion criteria were as follows: age equal to or more than 18 years old, the existence of complete data in the patient's file. The participants were excluded if there were not at least two Sirolimus levels in the patient's file. The sample size equals all available samples and data collection was based on document investigation (medical records of patients) through checklist completion. The checklist consisted of two parts: A) demographic variables of patients (including age, gender, weight, height, education level, marital

status, and occupation); and B) principle variables (including transplant date, type of transplant, etiology of ESRD, serum creatinine, BUN, starting date of Sirolimus, creatinine level at the starting point of Sirolimus, cause of change to Sirolimus, complications after initiating Sirolimus, Sirolimus level, comorbidities, medications that affect Sirolimus level (including Amlodipine, Diltiazem, Gemfibrozil, etc.), and immunosuppressive drugs combination with Sirolimus. After obtaining informed consent from the patients, the required information was extracted and recorded. The immunosuppression protocol of the patients was as follows: induction therapy with Thymoglobulin in high risk patients (Complement-Dependant Cytotoxicity Panel- Reactive Antibodies (CDC-PRA) ≥ 10% or second transplant). In other patients pulse of Methylprednisolone (15 mg/kg/d for 3 days) was prescribed. In all participants (except 2 patients) immunosuppression protocol started with CNI, antimetabolites and prednisolone. Then during the follow-up CNI changed to Sirolimus due to the incidence of malignancy or chronic allograft injury (mostly based on kidney biopsy). The dose of Mycophenolate Mofetil and Azathioprine was 1 to 2 g/d, 1 to 2 mg/kg/d; respectively, based on the tolerance of the patients. Sirolimus (Rapamune®, Pfizer Inc.) was introduced in Iran in 2006. The drug was provided as 1 mg oral tablets and the initial dose for all patients was 2 mg (every morning). The dosage was later adjusted based on the trough level (one week after each dose change[13]) and renal function. Patients' response to the treatment was determined through the following factors:

a) Stable or decreased creatinine or increase in eGFR (Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI)) creatinine equation
b) Therapeutic range of Sirolimus level (5 to 10 ng/mL).

Patients categorized based on changing in eGFR into 3 groups:

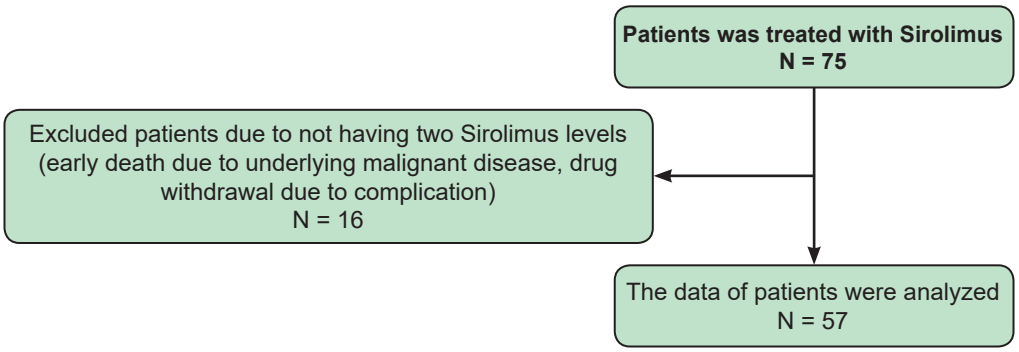
1. Improvement group (≥ 10% increase in eGFR)
2. Deterioration group (≥ 10% decrease in eGFR)
3. No-Change group (< 10% change in eGFR)

Visit intervals after renal transplantation was as follows: once a week during the first 3 months, once a month from the 4th to the 12th month after transplant, every two months from the 13th to the 24th month after transplant, every three months from the 25th to the 36th month after transplant, and after that every 4 months. To avoid an excessive increase or decrease in the drug level, toxicity, and rejection in patients with fluctuating Sirolimus dosage, creatinine was checked several times in short intervals (one, two, four weeks after changing the dose) and also as mentioned before, trough level was measured one week after each dose change. Sirolimus level could only be checked in a center in our city (Semi-automated electrochemiluminescence immunoassays (ECLIA) Roche Cobas e411 analyzer).

The following laboratory tests were investigated based on transplant vintage every 1 to 4 months: CBC, BUN, Cr, FBS, ALT, AST, Na, K, Ca, Ph., TG, Chol, Alb, uric acid, urinalysis, and urine culture.

Safety

The complications of Sirolimus were evaluated. These complications include: 1) bone marrow suppression; 2) severe edema; 3) nephrotic syndrome; 4) pneumonitis; 5) unhealed wounds; 6) increase in liver enzymes; and 7) severe hyperlipidemia. The obtained data were analysed by SPSS22, using descriptive statistics, One-way ANOVA, General Linear Model, and Independent T-test.



Flowchart of the study

RESULTS

Of 73 patients being treated by Sirolimus, 16 of them (21.9%) were excluded for various reasons (Figure 1). The patients' average age was 52.4 ± 13.2 years. The number of male participants was 43 (75.4%) who were mostly educated at diploma level or higher (79%). The average BMI of the samples was 24.3 ± 4.9 kg/m^2. It was 26.9 ± 7.1 kg/m^2 and 23.5 ± 3.7 kg/m^2 for females and males respectively (P < .05). The most common underlying diseases for ESRD were Glomerulonephritis (21.1%) and hereditary disease (17.4%). The most common transplant was of Living donor type (73.7%). Malignancy (49.1%) and chronic allograft injury (38.6%) were the main reasons for shifting to Sirolimus. Table 1 presents the demographic characteristics of the patients. The results of the study indicated that the average Sirolimus dosage to maintain the therapeutic level of 5 to 10 ng/mL was 1.2 ± 0.44 mg/d (Table 2). Besides, according to the obtained results, 39 (68.4%) patients were in the improvement group, 9 (15.8%) patients were in the deterioration group and 9 (15.8%) patients remained in no-change group. The results of principal variables (Sirolimus dose, Sirolimus level, GFR stabilization time, first GFR, and stable GFR) in three groups were showed in Table 2. The significantly different factors were the first GFR (P < .05) and stable GFR (P < .05). The value for the first GFR was the lowest in the improvement group; however, after changing CNI to Sirolimus, GFR increased to a higher value and was significantly higher than other groups. According to the results, after Sirolimus started, 29.8% of patients had no complication and among the observed side effects in the other patients the most common one was Hyperlipidemia (50.9%). The frequency of complications caused by Sirolimus was presented in Table 3. Sirolimus dosage based on age, gender, and weight variables has been shown in Table 4. These variables are calculated based on 25, 50, and 75 percentiles. The mean of Sirolimus dose was compared in percentiles of each variable, using ANOVA. The average dose of Sirolimus was significantly different only in age sub-groups (P < .05). It must be noted that, to remove the effect of the low number of samples in the sub-groups, age and weight were categorized as follows:

A) Into 4 groups based on percentiles of 25, 50, and 75.
B) Into two groups (below or equal the average and higher than average) based on the average age and weight of the research samples.

Their correlation with Sirolimus dosage was calculated by both ANOVA and Independent-t-tests and no significant difference was observed

Table 1. Demographic Variables

Variable	Frequency/ Mean
Age, y	52.4 ± 13.2
Gender, n (%)	
Female	14 (24.6)
Male	43 (75.4)
Weight, kg	67.2 ± 12.6
Height, m	1.66 ± 0.1
BMI, kg/m^2	24.3 ± 4.9
Occupation, n (%)	
Nongovernmental	17 (29.8)
Job Housewife	8 (14.0)
Employee	21 (36.8)
Student	1 (1.8)
Others	10 (17.5)
Marriage, n (%)	
Single	6 (10.5)
Married	50 (87.7)
Divorced	1 (1.8)
Education, n (%)	
Illiterate	2 (3.5)
Elementary	2 (3.5)
Intermediate	8 (14.0)
Diploma	25 (43.9)
Academic	20 (35.1)
Etiology of End Stage Renal Disease, n (%)	
Diabetes Mellitus	9 (15.8)
Hypertension	8 (14.0)
Glomerulonephritis	12 (21.1)
Urologic Disease	5 (8.8)
Hereditary Disease	10 (17.4)
Lupus Nephropathy	3 (5.3)
ACN (Acute Cortical Necrosis)	1 (1.8)
Unknown	9 (15.8)
Donor source, n (%)	
CD	15 (26.3)
NRLD	40 (70.2)
RLD	2 (3.5)
Cause of Change to Sirolimus, n (%)	
CAI	22 (38.6)
With Biopsy	15 (68.1)
Without Biopsy	7 (31.9)
Malignancy	28 (49.1)
CNI Intolerance	4 (7.0)
Denovo	2 (3.5)
Diffuse Cutaneous Wart	1 (1.8)
Transplant Survival, mo	129.5 ± 66.6

CAI, chronic allograft injury; CNI, calcineurin inhibitor

Table 2. Biochemical Results of the Study

Variable	GFR				
	Improvement (≥ 10%) (n = 39)	No Change (n = 9)	Deterioration (≤ 10%) (n = 9)	Total (57)	*P*
Sirolimus Dose, mg/d	1.2 ± 0.44	1.0 ± 0.43	1.4 ± 0.33	1.2 ± 0.43	> .05
Sirolimus Level, ng/mL	8.5 ± 3.2	9.8 ± 3.8	9.5 ± 3.9	8.8 ± 3.3	> .05
GFR Stabilization Time, mo	53.0 ± 33.3	84.4 ± 52.2	53.7 ± 37.8	58.1 ± 38.5	> .05
First GFR, mL/min/ 1.73m^3	48.8 ± 16.7	65.3 ± 19.0	50.3 ± 17.9	51.6 ± 17.9	< .05
Stable GFR, mL/min/ 1.73m^3	65.9 ± 17.1	63.43 ± 18.7	40.8 ± 17. 1	61.6 ± 19.3	< .05

Table 3. Disribution of Sirolimus Complications

Complication	Frequency (%)
Edema	15 (26.3)
Rash	3 (5.3)
Proteinuria	6 (10.5)
Elevated Liver Enzymes	1 (1.8)
Hyperlipidemia	29 (50.9)
Cytopenia	5 (8.8)
No	17 (29.8)

between the two sub-groups. (The second category for both variables is highlighted on the Table 4).

The transplantation vintage to reach the steady-state of GFR after initiation of Sirolimus was divided into four time-groups, among which there was no significant difference in mean of Sirolimus dosage. Medications used with Sirolimus were divided into two groups: immunosuppressive and non-immunosuppressive. Immunosuppressive drugs included three combinations: 1) Mycophenolate Mofetil + Prednisolone, 2) Azathioprine + Prednisolone, and 3) Prednisolone. Non-immunosuppressive drugs that affect Sirolimus level

Table 4. Mean of Sirolimus Dose

Variable	Classification	Frequency	Sirolimus Dose	*P*	F.
Sex	Female	14 (24.6)	1.4 ± 0.5	< .05	4.1
	Male	43 (75.4)	1.1 ± 0.4		
Age, y	≤ 42.0	15 (26.3)	1.3 ± 0.5	> .05	0.4
	43.0 to 53.0	16 (28)	1.1 ± 0.5		
	54.0 to 62.0	12 (21.1)	1.2 ± 0.3		
	≥ 63.0	14 (24.6)	1.1 ± 0.4		
Age, y	≤ 53	31 (54.4)	1.2 ± 0.5	> .05	T = 0.3
	> 53	26 (45.6)	1.2 ± 0.4		
Weight, kg	≤ 58.5	15 (26.3)	1.1 ± 0.5	> .05	1.2
	58.6 to 67.0	14 (24.6)	1.3 ± 0.4		
	67.1 to 74.0	16 (28)	1.0 ± 0.3		
	≥ 74.1	12 (21.1)	1.3 ± 0.5		
Weight, kg	≤ 67	29 (50.9)	1.2 ± 0.5	> .05	T = 0.5
	> 67	28 (49.1)	1.1 ± 0.4		
Transplant Survival at the Steady-state of GFR with Sirolimus, mo	≤ 68.5	15 (26.2)	1.2 ± 0.4	> .05	1.7
	68.6 to 105.0	14 (24.6)	1.0 ± 0.3		
	105.1 to 147.0	14 (24.6)	1.1 ± 0.5		
	≥ 147.1	14 (24.6)	1.4 ± 0.5		
Time to the Steady-state of GFR After Change to Sirolimus, mo	≤ 26.00	16 (28)	1.3 ± 0.4	> .05	1.1
	27.00 to 52.00	13 (22.8)	1.2 ± 0.4		
	53.00 to 90.00	14 (24.6)	1.1 ± 0.4		
	≥ 91.00	14 (24.6)	1.1 ± 0.5		
Immunosuppressive Drugs Combination with Sirolimus	MMF* + Prednisolone	39 (68.4)	1.1 ± 0.4	> .05	2.2
	Azathioprine + Prednisolone	5 (8.8)	1.2 ± 0.4		
	Prednisolone	13 (22.8)	1.4 ± 0.5		
Non-Immunosuppressive Drugs* Combination with Sirolimus	No Drug Used	32 (56.1)	1.1 ± 0.4	> .05	T = -1.6
	Drug Used	25 (43.9)	1.3 ± 0.5		

MMF, mycophenolate mofetil;
*Amlodipine or Diltiazem or Gemfibrozil

including Amlodipine, Diltiazem, and Gemfibrozil, which increase Sirolimus concentration. Patients were divided into two groups according to whether or not they took these medications. The results indicated that the effective Sirolimus dosage was not significantly different for any individual co-medication (immunosuppressive and non-immunosuppressive) (Table 4).

DISCUSSION

The study has been conducted to determine Sirolimus dosage for renal transplant patients in Isfahan. The results of the study indicated that the average effective Sirolimus dosage to maintain an appropriate blood level is 1.2 ± 0.44 mg/d. This is lower than the determined dosage in scientific resources (2 to 5 mg/d).[8] The result is consistent with the results of the study by Dashti *et al.* (2016) which was conducted on renal transplant patients to investigate Tacrolimus maintenance dosage, in Tehran. They concluded that during the early weeks after renal transplant, required Tacrolimus dosage to maintain appropriate blood level was lower than the determined value by pharmaceutical companies and scientific resources.[11] These two studies suggest that the dose of immunosuppressive drugs in Iranian renal transplant patients may be lower than in western countries. Also in another study in Korea (2018) the mean dose of Sirolimus in renal transplant patients was lower than in western countries (1.79 mg/d).[12]

The results of the present study indicated that over half of the patients (68.4%) had witnessed GFR improvement after Sirolimus initiating, i.e. GFR level had increased by 10% or higher, after initiating Sirolimus. Through a randomized trial study in France, Gatault *et al.* (2015) also compared two groups of renal transplant patients being treated by Sirolimus and Cyclosporine; the results of his study suggested that the average GFR is better for the patients treated by Sirolimus.[14] In a similar study in Iran by Nafar *et al.* (2012) renal transplant patients in the Sirolimus group, four years after transplantation, had higher GFR than the Cyclosporine group.[15] Based on the results of the study in univariate analysis, the Sirolimus dosage was only significantly different in the gender sub-group. It must be noted that, due to the higher BMI of the female than the male participants (26.9 ± 7.1 kg/m^2 vs. 23.5 ± 3.7 kg/m^2), the possibility of the impact of BMI on Sirolimus dosage was suggested. Therefore, it was evaluated by the Covariance test. The effect of gender on Sirolimus dosage was due to a significant BMI difference between males and females ($P > .05$). The two variables of age and weight were categorized by two different methods to correct the effect of the small size of the samples. There was no significant difference between the two categories (Table 4). Tang (2016) conducted a study on two groups of old and young patients with transplanted kidneys in the Netherlands to investigate the impact of age on pharmacodynamics and pharmacokinetics of Mycophenolic acid, and concluded that age has no significant impact on pharmacodynamics and pharmacokinetics of the studied medication.[16] However, in a cohort study by Scott *et al.* (2014) which was conducted to evaluate the impact of Sirolimus clearance and dependent variables of patients including age, race, gender, weight, and body surface area (BSA) on young children suffering from Neurofibromatosis type I, it was determined that age and body size (identified by weight and BSA) are significantly correlated to Sirolimus clearance; however, no significant relationship was found between gender, and race and Sirolimus clearance.[17] Besides, Passey *et al.* (2011), conducted a study on 681 renal transplant patients to specify effective clinical and genetic factors on Tacrolimus clearance and concluded that age, as a clinical factor, is effective on Tacrolimus clearance.[18] The difference between the results of the two above-mentioned studies with the present study is probably due to different sample types and sizes. In the study by Scott, children were the target group; while the research sample of the present study consisted of middle-aged adults. According to a review article on investigating mTOR inhibitors in the U.S. (2016), researchers concluded that despite some significant complications, these drugs cause lower nephrotoxicity and prevalence of viral infections.[19] The present study also did not show any complications in about one-third of the patients after taking Sirolimus; among the side effects, the most common one was Hyperlipidemia which was observed in about half of the patients. A major side effect of mTOR inhibitors is non-infectious Pneumonitis (NIP).[19] In the present study, there have been cases of NIP among renal transplant patients treated by Sirolimus; however, due to the severity of the complication, Sirolimus had been discontinued

early. Therefore, two levels of Sirolimus did not exist in their files and the patients were excluded.

The low number of samples was one of the restrictions of the study. The effect of this restriction was lowered by using various categorizations and various statistical analyses. Another limitation was excluding some patients with severe complications due to early drug discontinuation or death before performing two Sirolimus levels (according to the methods). Studies with a higher number of sample size with proper inclusion criteria are recommended to be conducted.

CONCLUSION

In a significant number of patients changing CNI to Sirolimus accompanied by GFR improvement. Contrary to the recommended dose of Sirolimus in the references (2 to 5 mg/d) Iranian kidney transplant recipients need lower daily doses of Sirolimus (1.2 mg/d) to achieve the desired whole blood level. Further studies are recommended to confirm it.

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