Original Article

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Sirolimus-based, calcineurin inhibitor- free regimen in kidney transplant patients: An open-label, randomized, controlled trial

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ABSTRACT

Background/Aim: We report a prospective, open-label, randomized study to evaluate the safety and efficacy of converting patients with stable renal function from Tacrolimus (Tac)-based regimen to a Sirolimus (SRL)-based regimen after kidney transplantation.

Methods: Fifty eight low risk renal allograft recipients who were eligible to the study, 6 months posttransplant and receiving Tac, were randomly assigned to continue Tac (n=29) or convert to SRL (n=29). We evaluated the 3-year outcomes including patient and graft survival, graft function and safety profile.

Results: 3-year patient and graft survival in SRL and Tac groups was 93.1% vs. 100% (P=0.04), and 89.7% vs. 100% (P=0.04), respectively. However, the SRL group had significantly better renal function, from the second year post-transplant until the last follow-up. Four (13.8%) patients in the SRL group and 3 (10.3%) in the Tac group (P=0.5) developed biopsy proven acute rejection. Mean urinary protein excretion increased significantly after SRL conversion. Diastolic blood pressure was significantly lower in patients who eliminated tacrolimus (80.4 vs. 75.6 mmHg) (P = 0.03). Mean hemoglobin concentrations decreased after SRL conversion and remained significantly lower from 12 months to 36 months (P=0.01). The mean serum cholesterol and triglyceride levels increased significantly in the SRL group, (P < 0.05).

Conclusions: our experience demonstrates that conversion to sirolimus from calcineurin inhibitors (CNI)-based therapy may result in better renal function and blood pressure control in renal transplant recipients without an increased risk of acute rejection. However, these benefits have not resulted in a growing advantage in graft or patient survival.

Key words: Kidney transplant- Sirolimus- outcome

INTRODUCTION

Although the use of cyclosporine and tacrolimus has markedly improved 1-year kidney transplant survival and decreased the acute rejection rate in most centers, both of these CNIs are nephrotoxic, and it is well recognized that their long-term use does not solve the problem of chronic rejection. The use of calcineurin inhibitors (CNI), cyclosporine (CsA), and tacrolimus (Tac), has been associated with both acute and chronic nephrotoxicity and contribute to the development of chronic allograft nephropathy (CAN).

Biopsy-proven CAN was found in 62% of the Tac- and 72% of the CsA-treated patients within 2 yr post-transplantation. Notably, 68% of the biopsy specimens with CAN were obtained from patients who developed CNI nephrotoxicity during the first year post-transplantation. In the short-term, CNI produce renal arteriolar vasoconstriction and a decrease in glomerular filtration rate (GFR) that is dose related and reversible (1–5). Long-term exposure to CNI causes chronic non-reversible changes that are characterized by interstitial fibrosis and obliterative arteriolar changes due to fibrous intimal thickening (6). Nankivell et al. (7) showed histological evidence of CNI toxicity in all renal allografts within 10 years by adopting annual protocol biopsies. Such a long-term attrition effect of CNI is thought to contribute to the pathogenesis of chronic allograft damage despite the serum level being maintained within the therapeutic range. In order to avoid or even to ameliorate this effect, a variety of strategies have been explored. These include complete withdrawal of CNI at some point in the post-transplant period, substitution of CNI with mycophenolate mofetil (MMF), or simply minimizing the cyclosporine maintenance dose (8–12). Although some success has been achieved with these strategies, withdrawal of CNI as late as 1 year post-transplant is often associated with acute rejection and the risk of late graft damage (13).

Sirolimus (SRL) has been shown to be effective as a de novo therapy after renal transplantation (14) and as long-term maintenance therapy with steroids (15–17). It may also have a role as an effective substitute for CNI therapy late after transplantation to avoid further CNI nephrotoxicity (18–23). However, the potential risk and benefit of this conversion strategy is not yet fully known, especially in the long term.

The aim of this study was to evaluate the safety and efficacy of conversion to SRL-based immunosuppression in stable kidney transplant recipients 6 months posttransplant.

PATIENTS AND METHODS

Patients

Patients included in this analysis were low risk group of patients transplanted between January 2005 and October 2009

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and receiving Tac-based maintenance treatment and followed-up at our center, were invited to participate. The characteristics of the patients are outlined in Table 1. Inclusion criteria were: first transplant patients aged >21 years old; serum creatinine levels <140 µmol/L; no past history of acute antibody mediated rejection or recent acute cellular rejection 3 months before randomization; unsensitized patients; and had baseline total serum cholesterol <5.2 mmol/L, triglycerides <1.8 mmol/L, total white blood cell count (WBCs) of more than 3000; platelet counts of more than 100, 000; and/or willingness to participate in the study.

Table 1: *Baseline demographics and clinical characteristics*

	Sirolimus Group (n = 29)	Tacrolimus group (n = 29)	P value
Patient characteristics			
Age, yr	44.8 ± 13.1	50.5 ± 12.3	0.09
Gender (M/F)	17/12	20/9	0.6
Nationality (Bahraini/Non-Bahraini)	29/-	27/2	0.5
Mismatches on HLA (<3) (%)	25%	25%	0.1
Causes of End Stage Renal Disease (%)			0.7
Diabetes mellitus	11 (37.9%)	9 (31.1%)	
Interstitial nephritis	7 (24.1%)	7 (24.1 %)	
Glomerulonephritis	2 (6.9%)	1 (3.4%)	
Others	5 (17.3%)	8 (27.6%)	
Inapplicable	4 (13.8%)	4 (13.8%)	
Pre-emptive transplantation (%)	2 (6.9%)	4 (13.8%)	0.4
Dialysis duration	14.1 ± 9.7	11.5 ± 8.7	0.6
Donor characteristics			
Age, yr	28.9±7.5	30.9±8.5	0.5
Gender (M/F)	19/10	16/13	0.1
Related donors/ Deceased donors	5/1	7/3	0.3
Pre-transplant HCV infection	-	1 (3.4%)	0.5
Treated rejections before randomization	1 (3.4%)	1 (3.4%)	0.5
Delayed graft function (%)	-	1(1.8%)	0.3

Study design

This was a randomized, parallel-group, prospective study comparing continued triple therapy with Tac (Prograf, Fujisawa Healthcare, Al Hekma Inc. Amman, Jordan), corticosteroids and MMF (Tac group; control), with withdrawal of Tac and addition of SRL (Rapamune, Wyeth-Ayerst Philadelphia, USA) (SRL group). The 6-month time point was chosen to minimize the risk of early acute rejection. Patients were randomly to one of the two treatment groups (1:1) using a computer-generated sequence after obtaining informed, written consent for participation in the study (Fig. 1). The study was undertaken in accordance with the Declaration of Helsinki, and all subsequent amendments, and was approved by the local ethics committees.

Immunosuppression protocol

All patients in both groups received 20 mg basiliximab (Simulect, Novartis Basel, Switzerland) intravenously at surgery and on day 4 post-operatively. Patients in both groups received 500 mg of intravenous methyl prednisolone on the day of surgery. Oral prednisolone was then given at a dose of 1 mg/kg per day, and then gradually tapered down to 5 mg/day by the 3rd month post-transplantation. Tacrolimus was started at a dose of 0.075 mg/kg/day in two divided doses targeting a 12-h whole blood trough level of 10–15 ng/mL in the first 3 months and then from 3 to 7 ng/ml thereafter. Concomitant immunosuppression and other treatments (i.e. MMF) (Cellcept, Hoffmann-La Roche, Basel, Switzerland) were mandatory at a minimum of 500 mg bid and the maximum dose of MMF not to exceed 1500 mg daily. Steroid therapy remained unchanged.

Conversion protocol

After randomization, patients were either to discontinue Tac and start SRL at once (SRL Group) or to continue treatment with Tac (Tac Group). In SRL group, sirolimus was initiated by giving SRL loading dose of 5 mg/day for 7 days then, 24-hour blood trough level was measured and the dose of SRL was adjusted to maintain target trough serum levels of 4–7 ng/mL.

Evaluation

Scheduled visits were at weekly for 1 month, monthly for 3 months and then every 3 months till the end of the study. At each visit, there was a complete clinical examination, a recording of vital signs, an assessment of parameters including hematological (hemoglobin, WBCs, platelet count), biochemistry (serum creatinine, serum cholesterol, liver function tests), calculated glomerular filtration rate (GFR) according to the Cockroft–Gault formula, and SRL and Tac trough levels according to the standard techniques.

Clinical assessment: The patients were assessed clinically with particular emphasis on blood pressure measurement. A patient is considered hypertensive if blood pressure exceeds 140/90 mmHg. The number of anti-hypertensive drugs was reported for every patient to express severity of hypertension. Diabetes was defined as two random blood sugar values ≥11.1 mmol/L and/or fasting blood sugar values ≥7.0 mmol/L, taken on separate occasions, as per the WHO guidelines. Clinical tolerance to the given medications was assessed, which included the safety profile and the occurrence of any adverse events.

Study outcomes

The efficacy end-points were patient and graft survival, renal function and the incidence and severity of biopsy-proven acute rejection (BPAR) according to the Banff criteria. The safety evaluation was based on the incidence of adverse events, and change in laboratory parameters (hematological and biochemical). Graft loss was defined as death or a return to long-term dialysis. Withdrawal from the study was defined as stoppage of Tac or SRL drugs.

End point

After at least 36 months of follow-up or patient loss or withdrawal from the study.

Statistical analysis

All data were evaluated using SPSS for Windows Version 20 (SPSS Inc. Chicago, IL, USA). Actuarial patient and graft survival were calculated according to the Kaplan–Meier method, comparisons were performed by log-rank analysis. t-Test was used to compare between the two groups in continuous data. Chi-square was used to compare categorical variables. Principal analysis will be undertaken using an intention to treat approach. For all the above tests, p-value <0.05 was considered as significant.

RESULTS

Patient demographics

Entry and participant flow through the study are shown in Figure 1. A total of 124 patients were recruited, of whom 38

proceeded beyond randomization. Forty-one patients refused to participate, and 16 were excluded for reasons other than those specified in the inclusion criteria, including relocation (4), undergoing investigation for co-morbidity (8), delayed decision until after study closure (4). Baseline demographic, transplant-related and clinical data of the randomized patients are presented in Table 1 and 2. No differences in either demographic or transplant data were observed between the 2 groups. No between-group differences were found as regards clinical and laboratory parameters as shown in Table 2. All patients in both groups completed the 3-year follow-up and were included in the final intention-to-treat analysis.

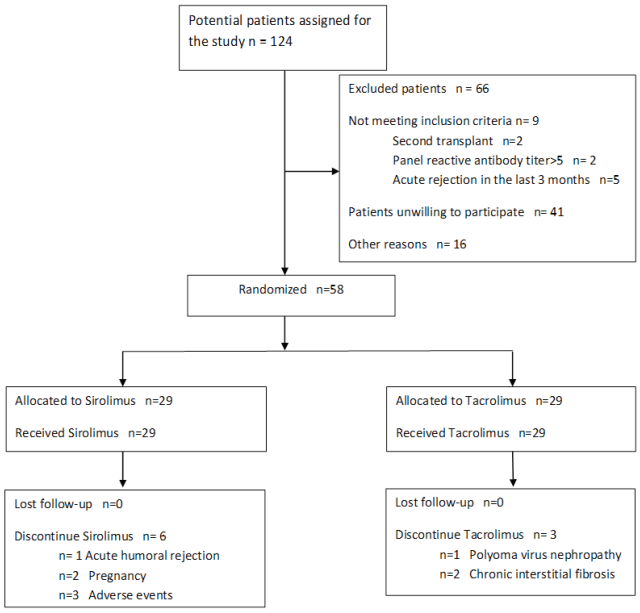

Figure 1: *Study flow diagram. The diagram illustrates the study enrolment and disposition of the trial participants*

Table 2: *Baseline biochemical and clinical values in both groups*

	Sirolimus Group (n = 29)	Tacrolimus group (n = 29)	P value
Serum creatinine, µmol/L	94.1±19.2	96.6±19.1	0.2
Fasting Blood Sugar, µmol/L	8.2±4.9	9.2±5.6	0.6
Total cholesterol, µmol/L	5.8±1.0	5.7±0.6	0.1
Triglycerides, µmol/L	1.6±0.8	1.7±0.8	0.5
Hemoglobin, g/dl	12.5±1.5	12.1±1.3	0.4
WBCs, mm3	6.8±1.4	9.9±1.3	0.4
Platelets, mm3	274±73	285±71	0.7
Proteinuria, g/day	0.1±0.1	0.1±0.1	0.1

Immunosuppressive regimen

At 1-year post randomization, 26 (89.7%) patients in the SRL group and 28 (96.6%) patients in the Tac group were still receiving the initially allocated study drug. Afterward, SRL was discontinued in further 3 (10.3%) patients and Tac in further 2 (6.9%) patients. In the two groups, the primary reason for discontinuing Tac or SRL was the occurrence of adverse events. The majority of adverse events occurred in the SRL group during the first year.

All patients in the two groups were treated with MMF and corticosteroids at 3 years post-transplant with no between-group differences as regards their doses (Table 3). In the two groups, mean study drug trough levels were in the accepted therapeutic levels.

Table 3: *Immunosuppressive regimen at 3 years*

	Sirolimus (n = 29)	Tacrolimus (n = 29)	p-value
Patients still receiving the study drug as randomized initially	23 (79.3%)	26 89.7%)	0.7
Dose of allocated study drug (mg/day)a			
Mean ± SD	2.2 ± 1.1	2.7 ± 1.2	-
Median/Range	1.5/1.5-4.0	2.0/1.5-4.5	-
Trough levels (C0) of allocated study drug (ng/mL)			
Mean ± SD	7.0 ± 2.3	7.2 ± 2.1	-
Mean/Range	6.9/3.6-11.9	5.6/3.8-9.1	-
Patients receiving mycophenolate mofetil	29 (100%)	29 (100%)	0.1
Mycophenolate mofetil dose (gm/day)	1.6± 0.4	1.6 ± 0.3	0.5
Patients receiving corticosteroids	29 (100%)	29 (100%)	0.1
Corticosteroid dose (mg/day)	5.0 ± 0.5	5.0 ± 0.3	0.2

Immunosuppressive regimen

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Acute rejection and immunological complication

During the follow-up, 4 (13.8%) patients in the SRL group and 3 (10.3%) in the Tac group (P=0.5) developed BPAR. The median time to the first acute rejection was 20.3 months in the SRL group and 23.1 months in the Tac group (p= 0.19), and one patient in the Tac group developed 2 acute rejection episodes. In SRL group, one developed chronic antibody mediated rejection with no response to therapeutic treatment including methyl prednisolone pulses in addition to IV Immunoglobulin plus plasmapheresis session followed by four doses of rituximab therapy over 4 weeks and patient returned back to dialysis.

Patient and graft survival

Patient survival at 3-years was 93.1% in the SRL group and 100% in the Tac group (P= 0.04). Two patients died between 1 and 3 years in the SRL group, death was due to brain tumor (n = 1) and cerebral stroke (n = 1). Censored death graft survival at 3-years was 89.7% in the SRL group and 100% in the Tac group (P=0.04). Three graft losses in the SRL were reported between 1 and 3 years due to death with functioning graft (n=2) and chronic antibody mediated graft rejection (n=1).

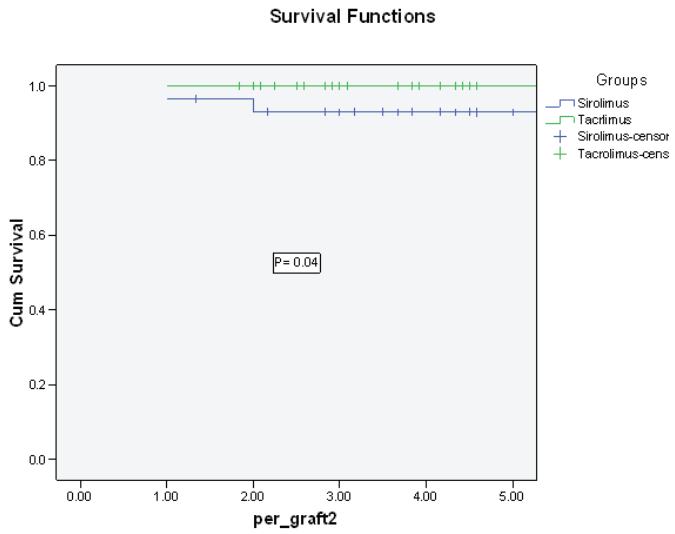

Figure 2: *Kaplan-Meier graft survival curve in both groups*

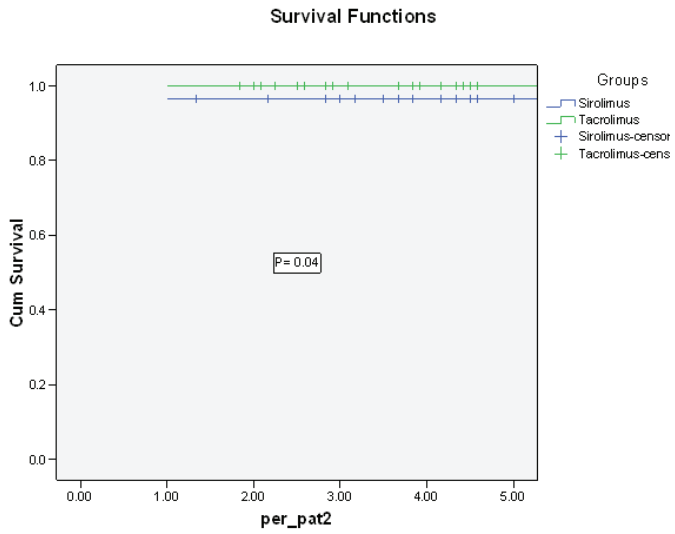

Figure 3: *Kaplan-Meier patient survival curve in both groups*

Renal outcome

Renal outcome

During the 3-year observation period, GFR decreased in the Tac group (from 73.2±8.3 to 71.3±13.6 ml/min 1.73 m2, P=0.07), and increased in the SRL group (from 72.8±7.1 to 74.2±7.5 ml/min 1.73 m2, P=0.06); comparison analysis showed significantly different 3-year changes in GFR in the 2 groups (Table 4). Urinary protein excretion rate increased in the SRL group (from 0.1 ±0.1 to 0.7±0.5 g/24 hours, P=0.001), whereas non-significant changes were observed in the Tac group (from 0.1±0.1 to 0.2±0.3 g/24 hours, P=0.1). In the SRL group, 6 (23%) patients developed de novo proteinuria after conversion with a median value 1.2 gm/day, 2 (7.6%) of whom were at a nephrotic level, therefore, SRL was stopped and Tac was reintroduced in these 2 patients. In the Tac group, 2 (7.4%) patients developed de novo proteinuria after conversion with a median value 0.4 g/day, none of them were at a nephrotic level.

Table 4: *One year and 3-year changes in laboratory parameters after randomization in both groups*

	Months post-randomization	Change from baseline		Mean difference between groups (95% CI)	p-value
		Sirolimus	Tacrolimus		
Creatinine (µmol/L)	12	− 5.3	+ 0.8	− 5.6 (− 56 to +85)	0.003
	36	− 18.3	− 11.0	− 7.3 (− 35 to +7)	0.04
GFR, ml/min	12	+1.3±1.0	+1.2±0.7	− 0.1 (− 1.0 to +7.3)	0.05
	36	+1.1±0.7	−1.9±0.9	− 3.0 (− 4.9to + 8.3)	0.001
Proteinuria, g/day	12	− 0.4±0.2	− 0.3±0.1	− 0.2 (− 0.1 to +1.3)	0.5
	36	+ 0.7±0.5	+ 0.2±0.3	− 0.4 (− 0.2 to +1.3)	0.03
Fasting blood sugar (mmol/L)	12	+0.9	+1.3	− 0.4 (+ 0.3 to + 2.3)	0.1
	36	− 0.2	− 0.5	− 0.3 (−1.0 to +0.3)	0.09
Total cholesterol (mmol/L)	12	+ 0.15	− 0.22	− 0.37 (−0.01 to +1.0)	0.04
	36	+1.9	− 1.1	− 3 (+2.9 to −1.2)	0.02
Triglycerides (mmol/L)	12	+1.1	− 0.1	− 1.0 (−0.08 to +1.8)	0.04
	36	+1.4	− 0.8	− 2.2 (− 1.1 to +1.6)	0.01
Hemoglobin (g/dl)	12	− 1.0	− 0.2	− 0.8 (−0.1 to −1.6)	0.02
	36	− 1.2	− 0.3	− 0.9 (−0.5 to −1.1)	0.01
White blood cell count (×109/L)	12	− 1.2	− 0.3	− 1.4 (+1.3 to −0. 7)	0.04
	36	− 1.4	+ 0.1	−1.5 (−2.3 to −0.1)	0.01
Platelet count (×109/L)	12	− 45	− 30	−15 (− 58 to +60)	0.3
	36	− 46	− 48	− 2 (− 46 to +75)	0.5
SBP, mm Hg	12	− 12	− 2	− 5 (−17 to +8.5)	0.03
	36	− 10	+ 2	− 8 (−26 to +16)	0.001
DBP, mm Hg	12	− 3.3	− 0.8	− 2.5 (− 6.9 to +4.5)	0.04
	36	− 8.1	+ 2.3	− 10.4 (− 8.9 to +9.9)	0.001

Blood pressure

Before randomization, the blood pressure was non signifi cantly diff erent in both groups (the mean systolic blood pressure (128±16 mmHg and 129±17 mmHg; P= 0.2) and diastolic blood pressure (77±13 mmHg and 81±13 mmHg; P=0.3) in the SRL and Tac groups, respectively. At 12 month, the mean systolic blood pressure (130±15 mmHg and 138±19 mmHg; P= 0.03) and diastolic blood pressure (73±11 mmHg and 80±12 mmHg; P=0.04) in the SRL and Tac groups, respectively. At 36 month, the mean systolic blood pressure (132±19 and 141±21 mmHg; P=0.001) and diastolic blood pressure (74±14 mmHg and 82±10 mmHg; P=0.001) in the SRL and Tac groups, respectively. At 36 month, 44% and 30% of the patients were not taking anti-hypertensive medications in the SRL group and the Tac group, respectively, (P=0.02 (Tables 4, 5).

Hyperlipidemia

Before randomization, the blood cholesterol (5.8±1.0 µmol/L and 5.7±0.6 µmol/L; P= 0.1) and triglycerides (1.6±0.8 µmol/L and 1.7±0.8 µmol/L; P=0.5) were non significantly different in the SRL and Tac groups, respectively. At 12 months, the mean serum cholesterol level was 5.8±1.0 mmol/l vs. 4.7 ±0.5 mmol/l (P= 0.02), and at 36 months, 5.85 mmol/l vs. 4.96 mmol/l (P=0.01) in the SRL and the Tac group, respectively. At 12 months, the mean serum triglyceride level was 2.3±0.6 mmol/l vs. to 1.8±0.6 mmol/l (P=0.01) and at 36 months, 2.5±0.6 mmol/l vs. 1.6±0.5 mmol/l (P=0.01), in the SRL and the Tac group, respectively. At 36 months, 24% of the patients in the Tac group, and 58% of the patients in the SRL group were taking lipid-lowering medications (P < 0.0001) (Tables 4, 5).

Hematology

Mean hemoglobin concentrations were similar between groups at baseline (Table 2) significantly different from 12 months (11.9 and 12.7 gm/dl, P=0.02) to 36 months (11.4 and 12.3 g% (P=0.01)), in the SRL and Tac groups, respectively (Table 4). Erythropoietic drug use was similar at baseline 4.7% and 4.8%, increased to 12.7% vs. 5.6% in the SRL and Tac groups, respectively, at 36 months. The total leucocyte count fell significantly at 12 months in patients on SRL (P=0.04) and at 36 months (P=0.01). There was no significant difference in the change of platelet count between groups at either time point (Table 5).

Table 5: *Principal side effects following randomization*

Side effects	Sirolimus (n = 29)	Tacrolimus (n = 29)	P value
NODAT1	10	11	0.3
Polyoma virus nephropathy	0	1	0.2
Hypercholesterolemia			
Requiring new statin therapy	8	3	0.04
Requiring increased statin therapy	9	4	0.03
Hypertension			
Treatment increased	1	7	0.03
Treatment reduced	8	1	0.02
Leg edema	2	2	0.5
Mouth ulcers	1	0	0.1
Infection			
Hospitalized	2	2	0.6
Out-patient clinic	3	7	0.4
Malignancy	1	0	0.2
Hematological			
Anemia	9	2	0.03
Leucopenia	1	0	0.1
Thrombocytopenia	0	0	-

1=NODAT, New onset diabetes after transplant

Other significant events

There were eleven cases of post-transplant diabetes mellitus in the tacrolimus group (37.9%) and ten in the SRL group (34.5%) (P=0.3). There was one case of polyoma virus infection in the Tac group. One case of post-transplant malignancy (brain tumor) was diagnosed in the SRL group. One case of systemic CMV infection in the SRL group and one case of H1N1 virus infection in the Tac group were diagnosed during the study period. Other cases which required admissions were one case of pneumonia in each group. Other adverse events were shown in table 5.

Discontinuation from the study

Sirolimus was discontinued in six patients in SRL group (20.7%; pregnancy, acute humoral rejection and heavy proteinuria) vs. in three patients in Tac group (10.3%; chronic interstitial fibrosis in two and polyoma virus nephropathy in one; p= 0.2).

DISCUSSION

Prolonging renal allograft survival remains one of the most important challenges in kidney transplantation. Indeed, long-term kidney transplant survival rates have not kept pace with the striking improvements achieved in short-term outcomes (24). A major cause of long-term allograft injury, fibrosis and functional decline, is CNI toxicity (19). This study examines the safety and efficacy of converting patients with stable renal function from Tacrolimus-based regimen to a Sirolimus-based regimen after kidney transplantation.

SRL-based immunosuppressive therapy is thought to be less nephrotoxic and continues to be evaluated as a CNI sparing therapy. In the de novo setting, SRL therapy combined with mycophenolic acid (MPA) has not provided superior outcomes or adequate protection from acute rejection (17). However, conversion from CNI to SRL therapy after transplantation improved short-term renal function but did not decrease allograft fibrosis (25, 26). Moreover, in conversion trials, SRL treated patients typically experienced higher rejection rates and adverse events, further confounding the results (27, 28).

In our study, we found the incidence of BPAR was 13.8% in SRL group and 10.3% in Tac group patients (p = 0.5). Most of patients in both groups experienced one rejection episode. However, in SRL group, one developed chronic antibody mediated rejection with no response to therapeutic modalities and patient returned back to dialysis. A previous meta-analysis of mTOR inhibitor use in kidney transplant recipients had been shown no difference in acute rejection and superior graft function when SRL are used as CNI replacement (29). They found that when mTOR inhibitor replaced CNI, there was no difference in acute rejection. In a study done by Budd et al (28) on conversion of CsA to everolimus at 4.5 months posttransplant, found that the incidence of BPAR from randomization to month 36 was significantly higher in the everolimus group (13.0%) vs. (4.8%) in the CsA arm, P=0.015). On the other hand, Lebranchu and co-workers (30), although, they noticed a similar pattern of BPAR after SRL conversion, however, two graft losses due to acute rejection were observed in the SRL group during the follow-up period and they concluded that SRL may therefore expose to the risk of graft loss due to resistant acute rejection.

Our results show that the rates of graft loss (including death with a functioning graft) were significantly higher in the SRL group, despite improved graft function in those surviving with functioning grafts. Two patients died between 1 and 3 years in the SRL group, death was due to brain tumor and cerebral stroke. Results from large registry database analyses (17) suggest that Tac/SRL- or SRL/MMF-based immunosuppression may be inferior to Tac/MMF-based immunosuppression in long-term graft survival. In Symphony study (13), it was found that allograft survival differed significantly among the four groups (P=0.02) and was highest in the low-dose tacrolimus group (94.2%), followed by the low-dose cyclosporine group (93.1%), the standard-dose cyclosporine group (89.3%), and the low-dose sirolimus group (89.3%). In a recent large UNOS-based observational study of 139370 kidney transplant patients, de novo use of mTORi was associated with increased allograft loss and mortality throughout 8 years of longitudinal follow-up (31). The higher incidence of allograft loss may be due to

the increased rate of acute rejection seen with mTORi and the known association of acute rejection with allograft loss. Interestingly, in this study, that mortality did not correlate with acute rejection, suggesting a mechanism independent of effect on allograft function. This phenomenon was also observed in a prior observational investigation of Hungarian allograft recipients, in which mTORi were associated with increased mortality, but not worse allograft outcomes (32). Further studies are needed to firmly establish this association and the responsible mechanism for high mortality among these patients. However, in spare the nephron study (11), they found better graft and patient survival after two years of follow-up of their patients and explained this for lower incidence of acute rejection (9.5% and 11.3% in MMF/SRL group and MMF/CNI group, respectively), and less deaths in the sirolimus group. Compared to our results, it may be explained by the shorter period of follow-up, the higher number of patients allocated and the multi center nature of the study design.

Estimation of renal allograft function by calculated GFR revealed better renal function in group SRL patients as compared to Tac patients at most time points. This finding came in accordance with what had been previously reported by Lebranchu et al. (30) and Weir et al (11) that CNI-free regimens based on SRL have better renal function than CNI-based regimens. In the Spare the Nephron study (11), they found at 1 year, the mean percentage change in directly measured GFR was greater in the sirolimus arm (24.4 versus 5.2%; P=0.054), but this benefit was no longer evident at 2 years. The evidence suggests that in patients without markedly compromised kidney function or proteinuria, conversion from a CNI to mTOR inhibitors may preserve GFR, but offers no definitive benefit on the hard outcomes of mortality or allograft loss.

In our study, as observed at the end of the follow-up observational period, urinary protein was higher in the SRL group. Severe proteinuria was not frequent (7.6%), but may have resulted in the reconversion to CNI in these cases. Thus, the small increase in protein excretion was considered clinically acceptable, especially in the presence of the improved GFR values in the SRL group. However, in view of indications that early low-grade proteinuria may predict subsequent graft loss (33), urinary protein excretion should be carefully monitoring during the long-term follow-up of the these patients.

The decrease in blood pressure in the SRL group versus Tac controls has potentially more advantages on patient and graft survival. The avoidance of CNI with the use of SRL may allow more effective long-term blood pressure control (34). The profile of adverse events reported here in the SRL group was as expected, including the effect on lipid profile, diabetes mellitus and hematological values. Cholesterol levels requiring statin therapy was significantly higher in SRL group, as shown in the present trial. Sirolimus has been observed to elevate blood lipids in almost all clinical trials (14) and the dyslipidemic effect appears to be dose-related. Hyperglycemia has been reported in more than a third of patients on sirolimus and tacrolimus. CNI therapy is well-known to increase the rate of new-onset diabetes after kidney transplantation, and in few small, single-centre studies have suggested that sirolimus may have a diabetogenic effect. In one retrospective analysis, the authors showed that SRL is associated with a similar risk of diabetes compared to Tac (35). There was a significant increased incidence of anemia and the percentage of patients receiving erythropoietin in the SRL groups. Augustine et al (36), reported a prevalence of anemia of 31% in patients on Tac-based compared with 57% on SRL-based therapy in renal transplant patients at 1 year post-transplantation.

Of course, some limitations must be acknowledged in our study. First of all, it was a single-center study with a small sample size (n = 58) and also, the relatively short observation period which may lighten the sound of conclusions. The fundamental rationale for SRL conversion is the potential for improved long-term outcome, measured over decades, with respect to proteinuria, renal function, and graft survival. Secondly, some methodological factors should be taken into account in the interpretation of this study including statistical power which is needed to estimate the total sample size needed based on the expected outcome in each group. Moreover, we did not include protocol biopsy in our study which may have some benefits in diagnosing histopathological changes in grafts over time and also, we did not assess graft biopsies for CADI.

In conclusions, our experience demonstrates that conversion to sirolimus from CNI-based therapy may result in better renal function and blood pressure control in renal transplant recipients without an increased risk of acute rejection, but was associated with higher discontinuation rate attributable to adverse events. However, these benefits have not resulted in a growing advantage in graft or patient survival.

Conflict of interests: The authors have nothing to declare.

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