

Conversion from calcineurin inhibitors to sirolimus in renal transplant patients

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ABSTRACT

Sirolimus is a potent immunosuppressive drug that prevents acute rejection episodes and is a possible alternative to calcineurin inhibitors. A retrospective study was performed to evaluate the efficacy and safety of conversion from a calcineurin inhibitor to sirolimus during maintenance immunosuppressive therapy in selected renal transplant recipients. The calcineurin inhibitor (cyclosporine – 82%, tacrolimus – 18%) was switched to sirolimus either progressively or abruptly, in 17 deceased renal transplant recipients at 0.5 to 50 (median – 8.6) months post-transplant. In 14 out of 17 patients graft dysfunction (plasma creatinine ≥ 1.8 mg/dl) was the main reason for conversion. In 10 patients graft biopsy was performed and confirmed acute CNI nephrotoxicity (n=5), chronic nephropathy (n=4) and thrombotic microangiopathy (n=1) and 4 patients had clinical chronic graft dysfunction. The other 3 patients were converted due to neoplasia: squamous cell carcinoma, renal cell cancer and polycythemia vera. All patients were also receiving steroids and mycophenolate mofetil with dose reduction after conversion. After a median follow-up of 27 ± 4 [7.6-81] months, all patients were alive and on sirolimus. Overall there was significant improvement in renal function, with creatinine clearance increasing from 39.6 ± 16 to 47 ± 16 ml/min at one month ($p=0.013$) and then remaining stable during the two year follow up period ($X=47 \pm 16$ ml/min). After conversion, darbepoetin alfa was initiated or the dose increased in 35% of the patients,

with haemoglobin stable (11-12 g/dl) and there was a significant increase of serum total cholesterol from 221.7 ± 47 to 251.8 ± 67 mg/dl, with an increase of the number of patients on statin (pre-conversion – 41%; post-conversion – 81%). Three patients had borderline acute cellular rejection with good response to methylprednisolone, two had herpes zoster and one varicella. Only two patients developed proteinuria 2 years after conversion, with one patient having chronic graft dysfunction and the other with probable sirolimus associated proteinuria.

Despite the small number of patients, in these renal transplant recipients conversion from calcineurin inhibitor to sirolimus for maintenance immunosuppression was associated with a net improvement or at least stabilisation of graft function without major side effects.

Key-Words:

Calcineurin inhibitor; chronic graft dysfunction; renal transplantation; sirolimus.

INTRODUCTION

The introduction of calcineurin inhibitors (CNI) has improved the outcomes of renal transplantation by decreasing the risk of acute rejection episodes and improving allograft function and survival¹⁻³. While CNI have great benefits they are also associated with

important adverse effects, including acute and chronic nephrotoxicity, hypertension, hyperlipidaemia and diabetes, which could compromise the outcomes of renal transplants and their recipients^{4,5}.

Sirolimus (rapamycin) is a macrolide with immunosuppressive, antiproliferative and antiangiogenic properties. Its activity is mediated through the inhibition of a key regulatory kinase in the process of cell division^{6,7}. The efficacy of sirolimus (SRL) for maintenance immunosuppressive therapy in kidney transplant recipients is well documented, with prevention of acute rejection episodes, and it is considered a possible alternative to CNI⁸⁻¹⁰.

Sirolimus does not show CNI-like nephrotoxicity and it has been used as an alternative to CNI maintenance immunosuppressive therapy for kidney transplantation, with stabilisation or improvement of renal function, better graft survival and less chronic allograft nephropathy¹¹⁻¹⁴.

A retrospective study was performed to evaluate the efficacy and safety of conversion from CNI to SRL in maintenance immunosuppressive therapy for selected renal transplant patients between October 2000 and October 2006 at the Renal Transplant Unit of Hospital Garcia de Orta.

SUBJECTS AND METHODS

The medical records of the renal transplant recipients followed at this unit from October 1999 until June 2007 were reviewed.

Calcineurin inhibitors (cyclosporine – 14 patients, tacrolimus – 3 patients) were switched to SRL in 17 deceased renal transplant recipients, between 0.5 and 50 (median – 8.6) months after transplant. All the patients were on immunosuppressive therapy with CNI, mycophenolate mofetil (MMF) and steroids. After conversion MMF dose was reduced from 1000 mg bid to 500 mg bid in all patients. The mean age was 49.2±13 [27-71] years, 71% male. The primary aetiology of end-stage renal disease included chronic interstitial nephritis (n=3), chronic glomerulonephritis (n=3), polycystic kidney disease (n=2), diabetic nephropathy (n=1), and uncertain in eight patients (n=8). The mean HLA mismatch was 3.1 [2-5].

In 14 out of 17 patients, graft dysfunction (plasma creatinine ≥1.8 mg/dl) was the main reason for conversion. In 10 patients graft biopsy was made and confirmed acute CNI nephrotoxicity (n=5), chronic nephropathy (n=4) and thrombotic microangiopathy (n=1) and 4 patients had clinical chronic graft dysfunction. The other 3 patients were converted due to neoplasia: squamous cell carcinoma, renal cell cancer and polycythemia vera (Table I).

Table I

Renal function evaluation in each patient by P_{Cr} and C_{Cr} before and after conversion from CNI to SRL (months).

Patients	Time Post Transplant (months)	P _{Cr} (mg/dl)					C _{Cr} (ml/min)				
		0	1m	6m	12m	24m	0	1m	6m	12m	24m
1	1.6	3.32	2.14	2.55	2.38	2.19	37.2	55.1	47.2	50	53.9
2	0.5	4.7	1.1	1.2	1.1		15.6	55.3	47.5	51	
3	34.6	2.2	1.8	1.9	1.7	1.6	43.2	54.8	52.1	57.8	60.8
4	1.1	1.8	1.5	1.2	1.3		28.3	30.9	43.0	39.0	
5	8.0	2.1	2.1	2.1	2.5		28.5	33.1	32.0	26.7	
6*	22.8	1.6	1.2	1	1.1		27.0	50.7	60.5	54.6	
7	2.4	4.3	3.1	4.5	3.3	3.4	18.9	23.9	17.6	23.8	22.8
8	8.6	3.6	2.3	1.9	2.5	1.8	45.1	56.2	67.9	51.4	70.7
9	4.0	2.2	1.5	1.8	1.7	1.8	52.3	43.5	35.6	62.9	58.8
10*	49.8	1.3	1.4	1.3			50.2	45.8	49.4		
11	45.0	2.2	2.3	2.3	2.4		44.4	38.6	37.5	35.5	
12	7.8	2.7	3.5	2.1	1.6	2	32.9	23.8	41.3	53.7	42.4
13*	24.9	1.8	1.8	1.5			39.7	42.0	50.0		
14	14.9	2.2	2	2.4	1.9		66.1	75.6	59.3	74.6	
15	26.3	3.9	3.1	3.4	4	4	34.0	37.7	34.8	29.1	28.8
16**	1.6	2.5	1.5	1.88	2.42	2.3	29.9	47.6	38.2	29.6	30.8
17	31.3	1.8	1.6	1.7	1.9		79.8	83.4	75.0	66.7	

*Neoplasia

** Thrombotic microangiopathy

Time post-transplantation of SRL conversion was acute CNI nephrotoxicity with a median 18.3 [0.5-34.6] months, chronic allograft nephropathy with a median 5.9 [2.4-26.3] months, chronic graft dysfunction with a median 23.1 [8.6-45] months. The other patients are presented in Table I.

Graft function was evaluated by plasma creatinine (P_{Cr}) and creatinine clearance (C_{Cr}) estimated using the Cockcroft-Gault formula.

Before 2005 CNI was gradually withdrawn over a period of 4 weeks with simultaneous introduction of SRL, after that time conversion was abrupt with CNI stopped and SRL initiated the day after. On the day of SRL introduction a loading dose (6 mg) was given followed by dosage according to the trough level (8-12 ng/ml: less than 6 months post-transplant, 3-8 ng/ml: more than 6 months post-transplant).

Statin was initiated whenever total cholesterol was above 200 mg/dl and darbepoetin was initiated or the dose increased in order to maintain haemoglobin between 11 and 12 g/dl.

The mean follow up after conversion was 27.4±20.8 [7.6-81.1] months.

The follow up data were assessed using the ANOVA test and $p < 0.05$ considered significant.

RESULTS

The baseline mean P_{Cr} was found to be 2.6±1 [1.3-4.3] mg/dl, with a baseline mean C_{Cr} of 39.6±16 [15.6-79.8] ml/min (Table I). Proteinuria (U_{prot}) before conversion was less than 500 mg/24h in all patients.

Overall, there was an improvement of renal function, with a significant decrease in P_{Cr} and an increase in C_{Cr} one month after conversion ($p=0.013$), and remaining stable thereafter for a period of two years of follow up ($p=0.016$) (Tables I and II).

The data of graft function from the patients with acute CNI nephrotoxicity, chronic allograft dysfunction, thrombotic microangiopathy and neoplasia are given in Tables I and II.

When patients with chronic allograft dysfunction are considered separately, P_{Cr} displays a trend towards increase before the conversion from CNI to SRL, followed by a stabilisation of P_{Cr} during one year of follow up (Figure 1).

The three patients with neoplasia converted to SRL had trend toward graft function improvement, however without statistical significance during the follow up and there was no cancer recurrence in the skin or renal cell cancer patients (with a follow up of 10.5 and 14.1 months, respectively) (Tables I and

Table II

Renal function evaluation by P_{Cr} (mg/dl) and C_{Cr} (ml/min) before and after conversion from CNI to SRL in all patients concerning the cause of conversion.

	Pre-conversion	1 month post-conversion	6 months post-conversion	12 months post-conversion	24 months post-conversion
Total of Patients (n)	17	17	17	15	8
P_{Cr}	2.6±1	2.0±0.6**	2.0±0.8**	2.1±0.8*	2.3±0.8**
C_{Cr}	39±16	47±16*	46±14*	46±15*	46±17*
Acute CNI nephrotoxicity (n)	5	5	5	5	2
P_{Cr}	2.8±0.9	1.7±0.4	1.8±0.5	1.8±0.6	1.9±0.4*
C_{Cr}	31±10	46±12*	44±7*	45±12*	58±4**
Chronic allograft dysfunction (n)	8	8	8	8	5
P_{Cr}	2.7±0.9	2.4±0.7	2.5±0.9	2.4±0.8	2.6±1
C_{Cr}	47±19	48±22	46±19	50±18	45±20
Thrombotic microangiopathy (n)	1	1	1	1	1
P_{Cr}	2.5	1.5	1.9	2.4	2.3
C_{Cr}	30	48	38	30	31
Neoplasia (n)	3	3	3	1	
P_{Cr}	1.8±0.4	1.5±0.3	1.3±0.2	1.1	
C_{Cr}	39±11	46±4	53±6	54.6	

* $p < 0.05$ versus pre-conversion

** $p < 0.01$ versus pre-conversion

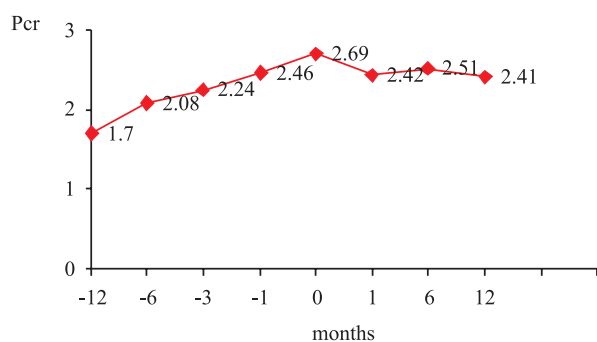


Figure 1

Plasma creatinine in patients with chronic nephropathy and chronic graft dysfunction (n=8) before and 1 year after calcineurin inhibitor conversion to sirolimus.

II). After a follow up of 7.6 months after conversion, the patient with polycythemia vera remained on the same dose of hydroxyurea.

The mean pre-conversion levels of fasting total serum cholesterol and triglycerides were 221.7 ± 47 and 205.6 ± 91 mg/dl, respectively, with 7 patients (41%) on statin therapy. During the follow up period, 81% of the patients were on statin, with a mean level of fasting total serum cholesterol and triglycerides of 251.8 ± 67 ($p=0.007$) and 240.24 ± 91 mg/dl ($p=ns$), respectively.

The mean haemoglobin before conversion was 12.1 ± 1.8 [10.8-14.9] g/dl. During follow up, either darbepoetin was initiated or the dose increased in six patients, maintaining the haemoglobin stable at 12.3 ± 1.1 [10.5-15.7] g/dl ($p=ns$). Both white cell and platelet counts remained within the normal range during the follow up period. Mouth ulcers occurred in a single patient, 12 days after conversion to SRL, with complete disappearance after dose reduction.

Three patients displayed borderline acute cellular rejection at 5, 7 and 18 months after conversion, recovering renal function after being treated with methylprednisolone pulses. Two patients presented with herpes zoster 2 and 4 years after conversion, and one was diagnosed with varicella 3 years after conversion. Only two patients developed U_{prot} two years after conversion: one patient with a maximum of U_{prot} 6.31 g/24h (SRL trough levels 6 to 8 ng/ml), which decreased to U_{prot} 1.8 g/24h after SRL dose reduction (through levels 3 to 5 ng/ml), with stable

P_{Cr} of 1.9 to 2.1 mg/dl; second patient with U_{prot} of 1 g/24h, with P_{Cr} of 5.2 mg/dl, also with SRL trough levels between 3 and 5 ng/ml.

At the end of the follow up period all patients were alive and on SRL.

DISCUSSION

Conversion from CNI to SRL for maintenance immunosuppression in these selected renal transplant recipients was globally associated with a significant improvement of the renal function.

As expected, the group of patients with acute CNI nephrotoxicity had a more relevant statistically significant improvement of renal function during the two years of follow up.

Chronic allograft nephropathy is the most prevalent cause of late kidney transplant failure, with CNI therapy an important contributing factor. The effects of SRL on the proliferation of fibroblasts and vascular smooth muscle cells, associated with its immunosuppressive properties, has been the rationale behind its use in the presence of either chronic allograft nephropathy or moderate renal dysfunction in renal transplant recipients¹⁵⁻²³. In our study, we found a clear benefit to the conversion from CNI to SRL in patients with either chronic allograft nephropathy or moderate renal dysfunction, and with an observed stabilisation of the renal function (Table II and Fig. 1).

Both conventional risk factors and the use of immunosuppression are associated with a long-term risk of malignancy in this population as compared to that of the general population. While CNI are associated with an increased incidence of cancers, both in animal models and in humans, the association of a particular immunosuppressive agent with the outcome of post-transplant malignancies is controversial, since the association of agents is common in clinical practice. Sirolimus appears, however, to suppress the growth and proliferation of tumours in both animal models and humans, and in comparison with other immunosuppressive agents may also confer a decreased risk and perhaps even modification or treatment of post-transplant malignancies^{7,24-28}. In this study, three patients with neoplasia were converted

to SRL, with the renal function improving and with no recurrence of the tumour, although the follow up post-conversion was short. It has been previously suggested that SRL might have some activity in a subset of patients with advanced myelodysplastic syndromes²⁹, but with uncertain clinical effects in myeloproliferative disorders. The CNI was converted to SRL in one patient with polycythemia vera on hydroxyurea therapy, and after a six month follow up the dose of hydroxyurea required to control the disease remained the same.

Although rare, thrombotic microangiopathy secondary to CNI is a well recognised entity that usually occurs in the first months post-transplant. Conversion to SRL in these patients has been used as a rescue therapy in the renal transplant patients³⁰⁻³². We describe a patient with thrombotic microangiopathy on cyclosporine, with a slight improvement in renal function and subsequent renal function deterioration.

SRL has been associated with U_{prot} , sometimes associated with focal segmental glomerulosclerosis probably related to reduced tubular protein reabsorption, podocyte dysregulation, and overexpression of vascular endothelial growth factor³³⁻³⁵. Conversion to SRL in chronic allograft nephropathy is usually recommended for P_{Cr} values below 2.5 mg/dl and for U_{prot} levels below 800 mg/day³⁶⁻³⁸. In our study no patient presented U_{prot} before conversion. Two patients developed U_{prot} 2 years after conversion, one associated with chronic allograft nephropathy and graft dysfunction and the other probably associated with SRL nephrotoxicity. The low rate of U_{prot} observed in this study may be explained by the fact that no patient presented U_{prot} before the conversion, and that only three of the eight patients with chronic allograft nephropathy or renal dysfunction displayed P_{Cr} values above 2.5 mg/dl before conversion.

The incidence of borderline acute cellular rejection was 17%, but all these cases were reversible with steroids. The most common adverse events associated with SRL are hyperlipidaemia, anaemia, infectious and non-infectious pulmonary problems, mouth ulcers, skin rash and diarrhoea^{15,17,19-21}. In our study anaemia and hyperlipidaemia were the most common adverse events. As in other studies, darbepoetin was initiated, or the dosage increased, in 35% of the patients in order to maintain the haemoglobin stable^{17,19}. Therapy with statins was increased

at post-conversion, allowing the levels of triglycerides to remain stable, but the total cholesterol displayed a significant increase at the end of the follow up.

Graft and patient survival was registered at 100%, with no need to withdraw SRL in any patient.

Despite the small number of patients, in these renal transplant recipients conversion from CNI to SRL for maintenance immunosuppression was associated with a net improvement or at least stabilisation of graft function without major side effects.

Conflict of interest statement. None declared.

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