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ORIGINAL ARTICLE

Early experience with conversion to sirolimus in a pediatric renal transplant population

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Abstract Sirolimus is an immunosuppressive agent that offers potentially significant benefits for young transplant patients facing life-long treatment. Its action of reducing cell proliferation may reduce the risk of chronic allograft nephropathy and posttransplant neoplasia. Twenty-nine children were converted from calcineurin inhibitors to sirolimus after renal transplantation and followed for a minimum of 12 months. Glomerular filtration increased transiently in those converted before 12 months after transplantation but not in those converted later, when chronic histological changes had developed. Mild acute rejection occurred after conversion in 10%, and side effects led to cessation of sirolimus in 31%. Anemia occurred in 55% of patients and responded well to darbepoetin. Most side effects (anemia, hypercholesterolemia, mouth ulcers, and myalgias) became less severe with time. The number of antihypertensive drugs required decreased significantly on sirolimus. Although side effects are frequent on sirolimus, in the majority of children, they are mild enough to allow the patient to continue taking the drug, and for these children the long-term benefits are potentially valuable.

Keywords Sirolimus · Calcineurin inhibitors · Mycophenolate · Pediatric renal transplantation · Glomerular filtration rate · Nephrotoxicity

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Introduction

The search for an effective antirejection drug regimen, free of chronic nephrotoxicity, is especially important in pediatric transplantation because very-long-term graft survival is needed for young patients hoping to avoid multiple grafts in a lifetime. The use of calcineurin inhibitors tacrolimus and cyclosporin has reduced the incidence of acute transplant rejection and improved early graft survival, but these drugs cause nephrotoxicity, which may contribute to development of chronic allograft nephropathy. It has been suggested [1] that avoidance of calcineurin-induced nephrotoxicity may result in longer graft survival.

Sirolimus is an immunosuppressive agent that is thought to have no known direct renal toxicity and to result in lower blood pressure than calcineurin inhibitors [2]. Its antiproliferative properties may help prevent the intimal changes associated with chronic allograft nephropathy [3, 4], and it has potential to reduce the incidence of posttransplant neoplasia [5–7]. Adult studies have shown that when cyclosporine is discontinued from a sirolimus/cyclosporine/steroid regimen, there is no difference in graft survival, but there is better renal function, lower blood pressure, and less neoplasia up to 4 years posttransplant [8, 9].

There have been only a few reports of the use of sirolimus in pediatric renal transplant recipients. Use immediately posttransplant has been described in conjunction with a calcineurin inhibitor in a series of 66 pediatric renal transplant recipients, with effective immunosuppression but adverse effects necessitating drug withdrawal in 20% of patients [10]. The combination of interleukin (IL)-2 receptor antibody, sirolimus and mycophenolate, has been used occasionally [11–13] and, as it avoids the need for nephrotoxic drugs, there is potential for this combination to increase long-term graft survival.

The objective of this study was to examine our early experience in the use of sirolimus in terms of graft survival, change in renal function, and blood pressure and the adverse events observed in our pediatric population after conversion to sirolimus from calcineurin-based immunosuppression. The potential improvement in serum creatinine, as reported in the Rapamune Maintenance Regimen Trial [8], was particularly noted in relation to the time of conversion after transplantation.

Patients and methods

This was a retrospective review. Hospital records were reviewed for all current renal transplant recipients under the care of the Royal Children's Hospital in Melbourne. Children on sirolimus were identified and the data collected. All patients were given basiliximab at the time of transplantation and received a calcineurin inhibitor, mycophenolate mofetil, and prednisolone initially.

Since the end of 2004, a policy has been adopted of reducing calcineurin exposure, and all new transplant recipients at our hospital have been electively converted, between 6 and 12 weeks posttransplant, from calcineurin inhibitors to sirolimus-based immunosuppression while continuing with mycophenolate and reducing or ceasing prednisolone. In addition, a number of patients transplanted before 2004 have been converted to sirolimus because biopsy findings suggested drug toxicity or chronic allograft nephropathy.

Eight children were electively changed to sirolimus on or before 3 months posttransplant. Twenty-one children were converted to sirolimus later than 3 months posttransplant because of biopsy changes or symptomatic drug side effects. Of these 21 children, nine were changed to sirolimus between 3 and 12 months posttransplant and 12 after 12 months posttransplant. Twenty of those converted after 3 months had transplant biopsy findings suggesting calcineurin toxicity (nine patients), chronic allograft nephropathy (eight patients), or borderline rejection (three patients).

Conversion to sirolimus involved giving an initial loading dose of 4–5 mg/m^2 once and then 2–3 mg/m^2 daily according to blood levels. The calcineurin inhibitor was reduced and ceased after about 1 week, when sirolimus levels reached 6–12 ug/l. As mycophenolic acid plasma levels are known to be higher on cyclosporine than on sirolimus or tacrolimus [14], mycophenolate mofetil dose (600 mg/m^2 twice daily) in those on cyclosporin was reduced to 300 mg/m^2 twice daily on conversion to sirolimus, but the mycophenolate dose (300 mg/m^2) on tacrolimus was kept at 300 mg/m^2 on conversion from tacrolimus to sirolimus. Steroid dose was not changed during conversion.

The 29 children, who were changed to sirolimus over the past 3 years and followed for a minimum of 12 months, represent 44% of our current posttransplant population. Their mean age was 9.6 (range 3–18) years. Eighteen were from parent or grandparent donors and 11 were from deceased donors.

Primary renal diseases in these 29 children included eight with congenital dysplasia, five with nephronophthisis, three with posterior urethral valves, two each with antineutrophil cytoplasmic antibody (ANCA) +ve glomerulonephritis, focal glomerulosclerosis, and reflux nephropathy, and one each with Denys-Drash syndrome, IgA nephropathy, prune belly syndrome, congenital nephrotic syndrome, branchiootorenal syndrome, cystinosis, and recessive polycystic kidney disease. Statistical comparisons of groups was achieved by the use of unpaired Student's *t* tests.

Results

There was 100% graft and patient survival during the study period of 12 months after conversion to sirolimus. Twenty-two children, 76%, remained on sirolimus at the end of the study. The estimated mean glomerular filtration rate (GFR) in all patients was calculated as creatinine clearance using the Schwartz formula after calcineurin inhibitor withdrawal and conversion to sirolimus. GFR increased from a mean of 54 ml/min per 1.73 m^2 preconversion to 61.3 ml/min per 1.73 m^2 at 6 months (Fig. 1), but the change was not

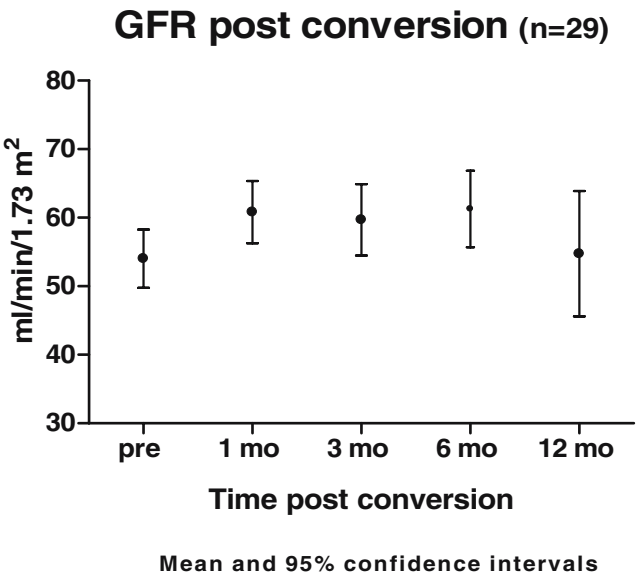

Fig. 1 Mean glomerular filtration rate (ml/min per 1.73 m^2) in all patients in the 12 months after conversion from calcineurin inhibitor to sirolimus

significant (p=0.3). There was a statistically insignificant decrease in GFR to 54.7 ml/min per 1.73 m^2 at 12 months.

A difference in the response to conversion to sirolimus was found between those patients converted to sirolimus earlier than 12 months posttransplant and those converted later. In those converted before 12 months, mean GFR before conversion was higher, at 57.8 ml/min per 1.73 m^2 compared with 48.7 ml/min per 1.73 m^2 in the later conversion group. Mean GFR increased from 57.8 ml/min per 1.73 m^2 preconversion to 72.8 ml/min per 1/73 m^2 at 6 months in those converted to sirolimus before 12 months after transplantation and did not change in those converted after 12 months (48.7 ml/min per 1.73 m^2 preconversion, 48.7 at 6 months after conversion). The mean change in GFR up to 6 months was significantly (p=0.03) greater in those converted before 12 months posttransplant compared with those converted after 12 months (Fig. 2). However, the importance of the increase in GFR up to 6 months in those converted early is unclear, as the increase did not seem to be sustained, and the change in GFR at 12 months after conversion was not significantly different between those converted early and late (p=0.19). There was no difference between those converted before 3 months and those converted between 3 and 12 months (Fig. 2) after transplantation.

The number of antihypertensive drugs used in the 29 patients decreased significantly (p=0.05) from 1.1 drugs per patient preconversion to 0.7 drugs per patient at 12 months. Mean blood pressure on treatment did not change (preconversion 109/60, 12 months postconversion 106/60 mmHg). Biopsy-proven mild acute cellular rejection occurred in three children (10%) in the 2 months after conversion when plasma sirolimus levels were 4.7, 7.1, and 9.7 ug/l, respectively. All responded to high-dose oral or intravenous corticosteroids, with improvement in serum creatinine. Sirolimus and mycophenolate were continued in higher dosage in two patients after the rejection episode and tacrolimus replaced sirolimus in the third patient.

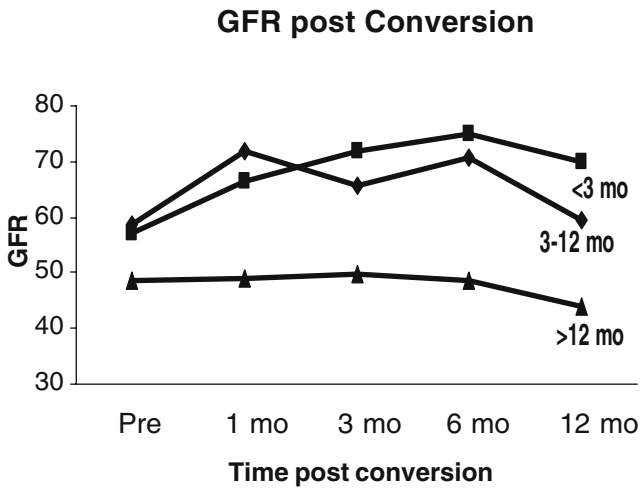

Fig. 2 Mean glomerular filtration rate (GFR) (ml/min per 1.73 m^2) in patients converted to sirolimus before 3 months, 3–12 months, and more than 12 months after transplant

Mean serum cholesterol was 173 mg/100 ml (4.56 mmol/l, range 2.9–7.9) prior to starting sirolimus, and 60% had a serum cholesterol greater than 186 mg/100 ml (4.9 mmol/l). Serum cholesterol increased significantly (p=0.004), to a mean of 211 mg/100 ml (5.55 mmol/l, range 4.6–6.2) at 3 months, and then decreased to 188 mg/100 ml (4.96 mmol/l, range 2.9–6.2) at 12 months. Five children (17%) commenced treatment with statins for serum cholesterol levels above 240 mg/100 ml (6.3 mmol/l). The mean serum cholesterol also decreased at 12 months in those not starting statins, from 207 mg/100 ml (5.45 mmol/l) at 3 months to 189 mg/100 ml (4.97 mmol/l) at 12 months, but these changes were not significant (p=0.14). The majority of patients were managed with dietary adjustment. No child had statin side effects.

The mean serum triglyceride prior to the change in medication was 198 mg/100 ml (2.2 mmol/l, range 0.5–5.4). This increased significantly (p=0.04) to a mean of 279 mg/100 ml (3.1 mmol/l, range 1.2–9.2) after 3 months of follow-up but decreased to 216 mg/100 ml (2.4 mmol/l, range 0.5–3.3) at 6 months, with only dietary intervention.

Two children had proteinuria prior to starting sirolimus. Both had chronic changes on biopsy. One has shown no increase in proteinuria over 6 months; the other developed nephrotic-range proteinuria and returned to tacrolimus after 1 year. Three other children, who had been on calcineurin inhibitors for 4–8 years since their transplants, developed new-onset mild proteinuria at 1 month, and all had chronic allograft nephropathy on biopsy. One later developed nephrotic-range proteinuria and was changed back to tacrolimus. He was not rebiopsied because the temporal relationship of the proteinuria to introduction of sirolimus suggested that sirolimus was the cause. The proteinuria remitted when sirolimus was ceased.

Twelve (41%) children developed mouth ulceration. In two, the ulcers did not heal until withdrawal of the sirolimus after several weeks. Three patients experienced delayed wound healing after gastrostomy button removal. No lymphoceles were identified. Ten of the 29 children (34%) described lower-limb pain. In most, this resolved spontaneously without change in treatment. One child had pain severe enough to limit weight bearing, and sirolimus was ceased with good recovery.

Mean hemoglobin prior to starting sirolimus was 113.4 g/l (range 93–135), with 12 of the 29 patients (41%) anemic as defined by a hemoglobin of less than 110 g/l. After 1 month on sirolimus, the mean hemoglobin was 108.3 (range 83–142), and 106.0 g/l at 3 months (range 88–137) with 16 patients (55%) having a hemoglobin less than 110 g/l. In one patient, mycophenolate was ceased

because of anemia. The other fifteen children required a period of support of their hemoglobin with darbepoetin, with satisfactory increase in hemoglobin. Mean hemoglobin rose to 114.3 g/l at 6 months (range 83–132) and was 117.3 g/l at 1 year (range 96–131). Mean darbepoetin dose in those on treatment with this drug was 1.16 micrograms/kg per week at 6 months after starting sirolimus, and the dose had decreased to 0.53 micrograms/kg per week in the seven patients still on darbepoetin at 12 months.

Diarrhea occurred in 11 children. Five experienced episodes with dehydration requiring hospital admission. All recovered with fluid management. One child developed ischemic sigmoid colon ulceration, possibly due to hypotension during the episode of dehydration, and sirolimus was withdrawn to allow mucosal healing.

Six of the 29 (21%) developed new Epstein Barr virus infection detected in serum by polymerase chain reaction. None had significant illness, and four were asymptomatic. The serum was clear of detectable virus within 2 months in five patients but persisted positive in one for 6 months without illness. No child developed overt lymphoproliferative disease. There were two episodes of cytomegalovirus reactivation (7%) and two of herpes simplex reactivation. None of these infections needed any change in immunosuppression.

Isolated thrombocytopenia was not observed. Two children developed pancytopenia, which recovered after withdrawal of the drug.

Sirolimus was discontinued in nine of the 29 children (31%). Reasons for this are shown in Table 1.

Diarrhea and pancytopenia leading to withdrawal occurred within a month of starting sirolimus. Withdrawal because of increasing proteinuria occurred later, with one child on sirolimus for more than a year before changing back to tacrolimus. Sirolimus was restarted successfully in three children with pancytopenia, diarrhea, and delayed wound healing after resolution of the acute episode. One adolescent experienced mouth ulceration shortly after starting sirolimus on two occasions and declined a further attempt at restarting.

Table 1 Reasons for withdrawal of sirolimus

Adverse effect	Number of patients
Mouth ulcers	2
Limb pains	1
Proteinuria	2
Rejection	1
Diarrhea	1
Pancytopenia	2
Total	9 out of 29 (31%)

Discussion

Sirolimus is an immunosuppressive agent that offers potentially significant benefits for young patients facing life-long treatment. Its action of reducing cell proliferation may reduce the incidence of late graft failure due to chronic allograft nephropathy, and there may be some reduction in posttransplant neoplasia on sirolimus. The average duration of renal graft survival is only 10 years, as reflected by the 50% graft survival at 10 years in the 273,467 renal transplants between 1985 and 2005 recorded worldwide by the Collaborative Transplant Study [15]. Ten years is a short period when compared with the potential life expectancy of a normal child. Most childhood transplants will need to be replaced several times in a lifetime. Therefore, the need to prolong graft survival and improve long-term morbidity is especially important for children. Sirolimus has the potential to address these needs.

Increased GFR is well known in adult patients converting early from calcineurin inhibitors to sirolimus [8, 16] but was seen in our pediatric population only in those converted before 12 months posttransplant. There was no benefit in GFR in patients converted after 12 months, most of whom had significant biopsy changes. This is consistent with adult experience, where it has been recommended to convert early before chronic histological changes occur [16].

Side effects limit the use of sirolimus, particularly hyperlipidemia, poor wound healing, anemia, proteinuria, pneumonitis, mouth ulcers, limb pains, viral infection, and diarrhea. The effect of sirolimus in delaying wound healing and causing lymphoceles suggests that this drug may be better introduced a few weeks or months after transplantation, with calcineurin inhibitors being used initially, as in this study.

Sirolimus provided effective immunosuppression in our population, with 100% graft survival over the 12 months of the study period, and all our patients benefited from the change by the reduced number of antihypertensive drugs needed after conversion. Mild rejection occurred after conversion in 10% of patients, and side effects were common, leading to drug withdrawal in 31% of patients. Anemia was a significant complication when sirolimus was used with mycophenolate mofetil. Unlike in adult studies, proteinuria was not a common finding. The more frequent occurrence of anemia, mouth ulcers, and myalgia, and the less frequent occurrence of proteinuria, seemed to distinguish our pediatric patients from adult series. Otherwise, the rejection and side-effect profile of our patients was similar to adult experience.

Our experience in this study shows that anemia caused by the combination of the antiproliferative immunosuppressive drugs mycophenolate and sirolimus can be successful-

ly treated with darbepoetin, and the requirement for darbepoetin seemed to decrease with time. This improvement with time also occurred with other side effects, particularly mouth ulcers, myalgias, hypercholesterolemia, and hypertriglyceridemia.

Rejection and side effects were frequent (31%) causes of withdrawal of sirolimus in our patients, and these effects of the drug need to be balanced against the potential long-term benefits of reduced chronic allograft nephropathy and neoplasia. Our early experience of sirolimus indicates that, whereas side effects are common, the majority of patients tolerate the drug well and potentially will benefit from long-term avoidance of calcineurin inhibitors.

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Ethics Statement This study is a retrospective review of our practice and therefore ethics committee approval was not sought.

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