Transplant International ISSN 0934-0874

CASE REPORT

Sirolimus in *de novo* heart transplant recipients with severe renal impairment

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Keywords
heart transplantation, immunosuppression, renal failure and sirolimus.

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Received: 16 August 2005
Revision requested: 5 September 2005
Accepted: 15 November 2005

doi:10.1111/j.1432-2277.2005.00258.x

Summary

Two patients with end-stage heart failure and advanced renal dysfunction (under chronic dialysis therapy) underwent heart transplantation. In order to avoid further renal impairment, a calcineurine inhibitor-free immunosuppression regimen based on the sirolimus was used. Although temporary perioperative support with hemofiltration and dyalisis was needed, both patients eventually regained a reasonable renal function with no episodes of clinical rejection and normal cardiac function at 13 and 11 months, respectively, after transplantation. Sirolimus-based immunosuppression might be an interesting alternative to calcineurine inhibitors in the management of patients with significant renal impairment.

Sirolimus in *de novo* heart transplant recipients with severe renal impairment

Sirolimus is a new immunosuppressive agent, which reduces acute rejection in solid transplants and may permit the avoidance of calcineurin inhibitors (CNI) nephrotoxicity. Most of the current experience with this drug comes from the field of renal transplantation. In cardiac transplantation, the experience with sirolimus is limited. In heart recipients with significant nephrotoxicity related to CNI, late conversion to sirolimus has been reported. Sirolimus has also been studied *de novo* after cardiac transplantation, although in addition to reduced dosages of cyclosporine. However, there is not much experience with the use of sirolimus *de novo* without associated CNI in cardiac transplantation. We report two heart transplant recipients with severe pre-existent nephrotoxicity – requiring chronic dialysis therapy – in whom an immunosuppressive regimen based on the sirolimus (without association of CNI) was used *de novo* and was successful in avoiding the development of permanent renal impairment, with eventual recovery of a reasonable spontaneous renal function.

Case 1

A 70-year-old patient received a heart transplant 10 years ago. He developed significant chronic nephrotoxicity on cyclosporine therapy (creatinine 2.5 mg/dl). In February 2004, he was listed for retransplantation because of the presence of diffuse and severe coronary vasculopathy with advanced graft dysfunction. Shortly afterwards, the patient developed refractory heart failure. In spite of inotropic support with dobutamine and high doses of diuretics, the clinical condition progressively worsened. Oligoanuria and rising levels of creatinine (4–5 mg/dl

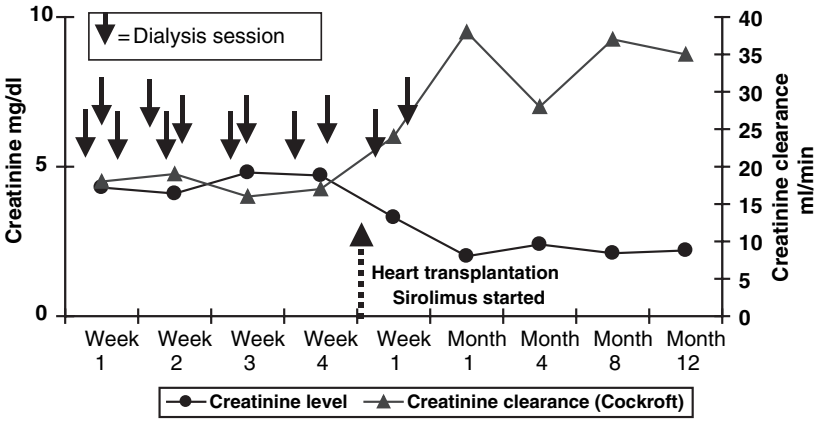

Figure 1 Creatinine levels (mg/dl) and creatinine clearance (calculated according to the Cockroft–Gault formula) before and after transplantation in patient # 1 (Arrows represent dialysis sessions. Sirolimus was started on postoperative day 1).

range) required nine dialysis sessions over a 4-week period. On April 2nd, 2004, the patient was retransplanted. In the immediate postoperative period, he developed acute tamponade, needing emergency reoperation. In order to avoid further renal impairment, the immunosuppression regimen was based on the sirolimus, started on the first postoperative day (2–3 mg/day, trough levels 8–12 ng/ml), mycophenolate and prednisone in standard dosages. No induction therapy was used. The postoperative period was complicated with a pneumonia (Staphylococcus epidermidis), which resolved with antibiotic therapy (imipenem and linezolid). Also, he developed generalized muscular debility, consistent with the syndrome of 'polineuropathy of the critically ill patient'. In the first 10 postoperative days, the patient required two additional dialysis sessions. The creatinine level progressively decreased and stabilized around 2 mg/dl with restoration of diuresis (Fig. 1). After intensive rehabilitation, the patient regained adequate muscular function and mobility, and was discharged in good clinical condition 65 days after retransplantation. Echocardiographic monitorization of graft function showed excellent biventricular ejection fraction. On the 4th month after transplantation, the patient developed intermittent fever. A cytomegalovirus infection was diagnosed, which responded adequately to valganciclovir. Thirteen months after retransplantation, the patient is asymptomatic and leading an active life. Sirolimus dosage is 3 mg/day and trough levels range from 7 to 9 ng/ml. Prednisone dosage is 5 mg/day. Because of persistent leukopenia in spite of progressive Mycophenolate dosage reductions, the drug was finally stopped at the end of the first year after transplantation. There have been no clinical rejection episodes, and the graft function is completely normal, with an ejection fraction of 63% and normal wall thickness at the last follow-up visit. The creatinine level is 2.2 mg/dl, the estimated creatinine clearance (Cockroft-Gaul) is 35 ml/min and diuresis is adequate without diuretics.

Case 2

A 60-year-old patient with a terminal dilated cardiomyopathy and severe malignant arrhythmias was listed for elective transplantation. He also had severe renal impairment (creatinine 3.5 mg/dl), oligoanuria and fluid retention, which needed seven dialysis and ultrafiltration sessions over a 7-week period before transplantation. While on the last preoperative dialysis procedure, the patient became hemodynamically unstable and developed a severe arrhythmic storm, with repetitive ventricular fibrillation episodes. The patient required mechanical ventilation, intra-aortic counterpulsation and inotropic support with catecholamines. An emergency transplant was performed 24 h later. The immediate postoperative period was characterized by vasoplegic shock, which responded to noradrenaline and vasopresine infusion. In spite of adequate graft function and normal cardiac output, anuric renal failure persisted and was managed with the use of continuous hemofiltration for 5 days. The immunnosuppresive regimen was based on the sirolimus (1 to 3 mg/day, trough levels 8–12 ng/ml), mycophenolate, and steroids at standard dosages. Three doses of daclizumab (1 mg/kg) were also given along the first 4 weeks. Over the ensuing 5 week period, 10 additional dialysis sessions were performed. The creatinine level finally stabilized around 2 mg/dl, and the patient regained normal diuresis with furosemide. He was discharged in excellent clinical condition. At subsequent follow-up visits, the creatinine levels progressively decreased and the diuretic dose could be reduced. One year after transplantation, the creatinine level is 1.1 mg/dl and the estimated creatinine clearance is 80 ml/min (Fig. 2). The patient leads a normal physical activity without symptoms. No fluid retention is present on 20 mg of furosemide. Immunosuppression consists in sirolimus (dosage 2 mg/day, trough levels of 7.5–12 ng/ml), mycophenolate (500 mg b.i.d.), and prednisone (5 mg every other day). There have been no clinical

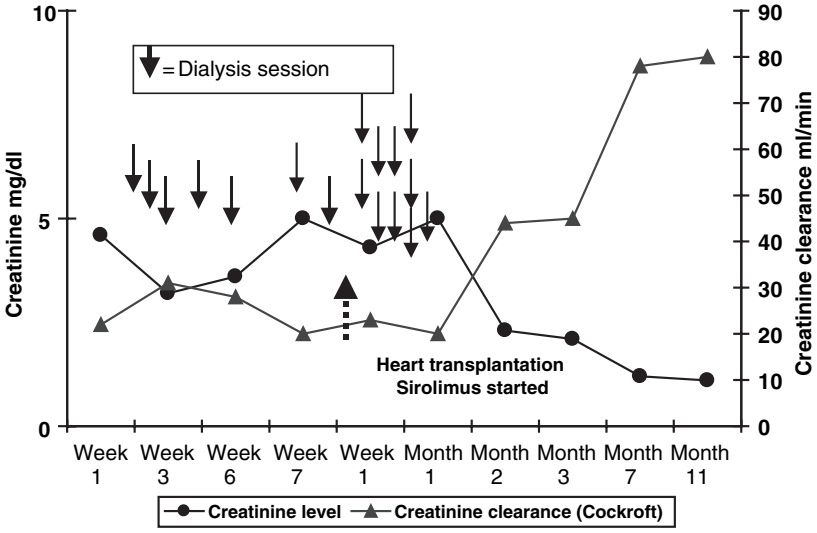

Figure 2 Creatinine levels (mg/dl) and creatinine clearance (calculated according to the Cockroft–Gault formula) before and after transplantation in patient # 2 (Arrows represent dialysis sessions. Sirolimus was started on postoperative day 1).

rejection episodes, and the graft function is completely normal by echocardiography. The left ventricular ejection fraction is 69%, with normal wall thickness.

Discussion

Standard *de novo* immunosuppression in solid organ transplantation is currently based on CNI (cyclosporine or tacrolimus) with the addition of antimitotic agents and corticosteroids. Although CNI have a proven record of efficacy in rejection prophylaxis, they are frequently associated with significant nephrotoxicity. Moreover, advanced renal dysfunction is frequently seen in the setting of heart failure [1]. Therefore, renal dysfunction often complicates the already difficult perioperative period after heart transplantation. Severe acute nephrotoxicity because of CNI can be anticipated in heart recipients with pre-existent renal impairment. Thus, new immunosuppressive agents without inherent nephrotoxicity – like sirolimus and everolimus – are being actively investigated.

Sirolimus has been extensively studied in renal transplantation [2]. Several immunosuppressive regimens have been tried, either in combination with reduced dosages of cyclosporine [3] (which may be withdrawn after some time [4]) or in CNI-free protocols [5,6]. There is also an evolving experience in hepatic [7] and lung transplantation [8].

In heart recipients, sirolimus has been introduced at different intervals after transplantation in patients in whom CNI resulted in significant nephrotoxicity. Late conversion to sirolimus (eliminating the CNI) usually – but not always – results in at least partial recovery of the renal function, and has been reported both in adults [9–11] and children [12].

In the acute setting, i.e. right after transplantation, sirolimus has been used in most cases in association with the reduced doses of CNI, usually cyclosporine. In a recent randomized study, sirolimus combined with a relatively low cyclosporine dosage has been compared with full dose cyclosporine and azathioprine [13]. Although both the rate of rejection and transplant vasculopathy were reduced in sirolimus randomized patients in comparison to those randomized to azathioprine, the incidence of nephrotoxicity was very high, probably because of the pharmacological interaction between sirolimus and cyclosporine. The results of another similar trial with everolimus (a derivative of sirolimus) combined with cyclosporine also showed reduced rejection and graft vasculopathy rates, but nephrotoxicity was also higher with the everolimus–cyclosporine combination [14].

On the other hand, the experience with sirolimus *de novo*, i.e. in CNI free immunosuppressive regimens, is somewhat limited in cardiac recipients [15]. Our two reported patients underwent the transplantation procedure in complicated clinical scenarios, and the renal function was severely impaired, requiring temporary dialysis therapy. In those situations, we considered that the nephrotoxic effects of CNI, especially in the perioperative period, would possibly perpetuate the loss of renal function. Thus, we decided to use sirolimus based, CNI-free immunosuppressive regimens. Although the perioperative course was certainly complicated in both patients, needing ultrafiltration and dyalisis therapy for some time, a reasonable spontaneous renal function was eventually reached and remains stable at a follow-up of 13 and 11 months respectively. In patient 1, a significant degree of renal dysfunction persists (creatinine clearance of 35 ml/min), probably reflecting the previous long-time

exposure to CNI (he was on cyclosporine for almost 10 years). In any case, sirolimus use prevented the total loss of renal function, which could have most likely ensued if CNI were used after the retransplantation, and the patient has adequate diuresis and no fluid retention without the need of diuretics. In patient 2, in whom there was no previous contact with CNI, renal function returned to practically normal levels (creatinine clearance of 80 ml/min). Also, there were no clinical or echocardiographic signs of graft dysfunction. As is the current practice at our institution, no routine cardiac biopsies are performed in asymptomatic patients with no signs of heart failure, a good ejection fraction and normal ventricular thickness by echocardiography. This has been the case of the two reported patients, which had completely normal graft function as assessed by echocardiography at regular intervals during the follow-up.

Our experience suggests that a sirolimus based, CNI-free immunosuppression might be a very interesting alternative for patients receiving a heart transplant in the context of significant renal impairment, by avoiding the likely development of permanent renal failure because of CNI. However, further experience is needed to confirm the apparently appropriate anti-rejection efficacy of sirolimus when this drug is used without concomitant CNI. Also, the correct therapeutic range and the side effects profile of this promising immunosuppressant should be elucidated before its widespread use could be recommended [16].

Acknowledgement

Dr Fernandez Valls was funded with a grant from the 'Red Temática de Trasplantes, C03/03', Organización Nacional de Trasplantes, Spanish Ministry of Health.

References

1. Shlipak M, Massie B. The clinical challenge of cardiorenal syndrome. *Circulation* 2004; **110**: 1514.
2. Nashan B. Maximizing the clinical outcome with mTOR inhibitors in the renal transplant recipient: defining the role of calcineurin inhibitors. *Transpl Int* 2004; **17**: 279.
3. Kahan BD for the Rapamune US Study Group. Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomised multicentre study. *Lancet* 2000; **356**: 194.
4. Oberbauer R, Segoloni G, Campistol JM, *et al.* Early cyclosporine withdrawal from a sirolimus-based regimen results in better renal allograft survival and renal function at 48 months after transplantation. *Transpl Int* 2005; **18**: 22.
5. Flechner SM, Goldfarb D, Modlin C, *et al.* Kidney transplantation without calcineurin inhibitor drugs: a prospective, randomized trial of sirolimus versus cyclosporine. *Transplantation* 2002; **74**: 1070.
6. Flechner SM, Kurian SM, Solez K, *et al.* De novo kidney transplantation without use of calcineurin inhibitors preserves renal structure and function at two years. *Am J Transplant* 2004; **11**: 1776.
7. Montalbano M, Neff GW, Yamashiki N, *et al.* A retrospective review of liver transplant patients treated with sirolimus from a single center: an analysis of sirolimus-related complications. *Transplantation* 2004; **78**: 264.
8. Snell GI, Levvey BJ, Chin W, Kotsimbos TC, *et al.* Sirolimus allows renal recovery in lung and heart transplant recipients with chronic renal impairment. *J Heart Lung Transplant* 2002; **21**: 540.
9. Groetzner J, Meiser B, Landwehr P, *et al.* Mycophenolate mofetil and sirolimus as calcineurin inhibitor-free for late cardiac-transplant recipients with chronic renal failure. *Transplantation* 2004; **77**: 568.
10. Cabezon S, Lage E, Hinojosa R, Ordoñez A, Campos A. Sirolimus improves renal function in cardiac transplantation. *Transplant Proc* 2005; **37**: 1546.
11. Lyster H, Panicker G, Leaver N, Banner NR. Initial experience with sirolimus and mycophenolate mofetil for renal rescue from cyclosporine nephrotoxicity after heart transplantation. *Transplant Proc* 2004; **36**: 3167.
12. Lobach NE, Pollock-Barziv SM, West LJ, Dipchand AI. Sirolimus immunosuppression in pediatric heart transplant recipients: a single-center experience. *J Heart Lung Transplant* 2005; **24**: 184.
13. Keogh A, Richardson M, Ruygrok P, *et al.* Sirolimus in de novo heart transplant recipients reduces acute rejection and prevents coronary artery disease at 2 years. A randomized clinical trial. *Circulation* 2004; **110**: 2694.
14. Eisen HJ, Tuzcu EM, Dorent R, *et al.* Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. *N Engl J Med* 2003; **349**: 847.
15. Meiser B, Reichart B, Adamidis I, Uberfuhr P, Kaczmarek I. First experience with de novo calcineurin-inhibitor-free immunosuppression following cardiac transplantation. *Am J Transplant* 2005; **5**: 827.
16. Kahan BD. Sirolimus-based immunosuppression: present state of the art. *J Nephrol* 2004; **17**(Suppl. 8): S32.