

# Sirolimus and Mycophenolate Mofetil as Calcineurin Inhibitor-Free Immunosuppression in a Cardiac Transplant Patient With Chronic Renal Failure

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Chronic renal failure triggered by calcineurin inhibitor (CNI)-based immunosuppression is a common complication after cardiac transplantation. Sirolimus and mycophenolate mofetil (MMF) are 2 newer immunosuppressive agents with no documented nephrotoxic side effects. This case report describes a patient with ongoing chronic renal failure 10 months after cardiac transplantation on cyclosporine-based immunosuppressive therapy. Conversion of the immunosuppressive regimen from cyclosporine to sirolimus and MMF resulted in freedom from acute rejection, excellent cardiac graft function and consistently improved renal function. This case illustrates the beneficial potential of sirolimus and MMF as CNI-free and safe long-term immunosuppression in a patient with chronic renal failure after heart transplantation. *J Heart Lung Transplant* 2004;23:770-3.

Renal failure is a common problem in long-term follow-up after cardiac transplantation.<sup>1</sup> The main trigger of renal impairment is long-term administration of nephrotoxic calcineurin inhibitors (CNI), which are the basis of immunosuppressive therapy in thoracic organ transplantation. In these cases, further therapeutic options are rare and quality of life and life expectancy are limited.<sup>2</sup> The annual mortality rate of patients requiring long-term renal replacement therapy after cardiac transplantation ranges between 19% and 26%.<sup>1-3</sup>

## CASE REPORT

A 60-year-old man was admitted to the hospital 10 months after cardiac transplantation due to dilated cardiomyopathy. He presented with shortness of breath, pleural effusion, peripheral edema and oliguria. He had been taking his immunosuppressive medication, cyclosporine (CsA; Sandimmun, Novartis International AG, Basel, Switzerland) and mycophenolate mofetil (MMF; CellCept, Hoffmann-La Roche, Ltd., Basel, Switzerland), conscientiously and had no history of medication abuse (e.g., non-steroidal anti-inflammatory drugs) nor signs of acute infection. Laboratory parameters

(Figure 1) showed elevated levels of creatinine (3.9 mg/dl) and urea (191 mg/dl). Urine sediment showed no pathologic findings. Cyclosporine and mycophenolic acid (MPA) trough levels were stable and in the therapeutic range: CsA, 239 ng/ml (Emit Assay, Behring Diagnostics, Marburg, Germany); MPA, 2.8 µg/ml (Emit MPA Assay, Dade-Behring, Marburg).

Prior to transplantation the patient had had slightly elevated creatinine levels (1.5 mg/dl) due to chronic low cardiac output (no diabetes, no primary renal disease). Peri-operatively he suffered from primary cardiac graft failure, which required implantation of an intra-aortic balloon pump. Subsequently he developed renal failure that required 21 days of hemodialysis therapy. After cardiac and renal recovery he was discharged with normal cardiac function and moderately elevated serum creatinine levels (1.8 mg/dl).

During further clinical follow-up the patient developed progressive chronic renal failure without proteinuria while taking CNI-based immunosuppressive therapy. Causes other than chronic CNI-induced nephrotoxicity were ruled out (infection, graft failure, intoxication, diabetes, etc.). Trough levels of CsA were reduced to 150 to 250 ng/ml and CsA dosage could be reduced with co-administration of diltiazem. Further renal sparing reduction of CsA levels was limited by the occurrence of a mild, acute rejection episode (Grade ISHLT 1b) 7 months after transplantation. CsA was then continued with stable trough levels of between 180 and 250 ng/ml. Further medical treatment was minimized and consisted of diltiazem, simvastatin and furosemide.

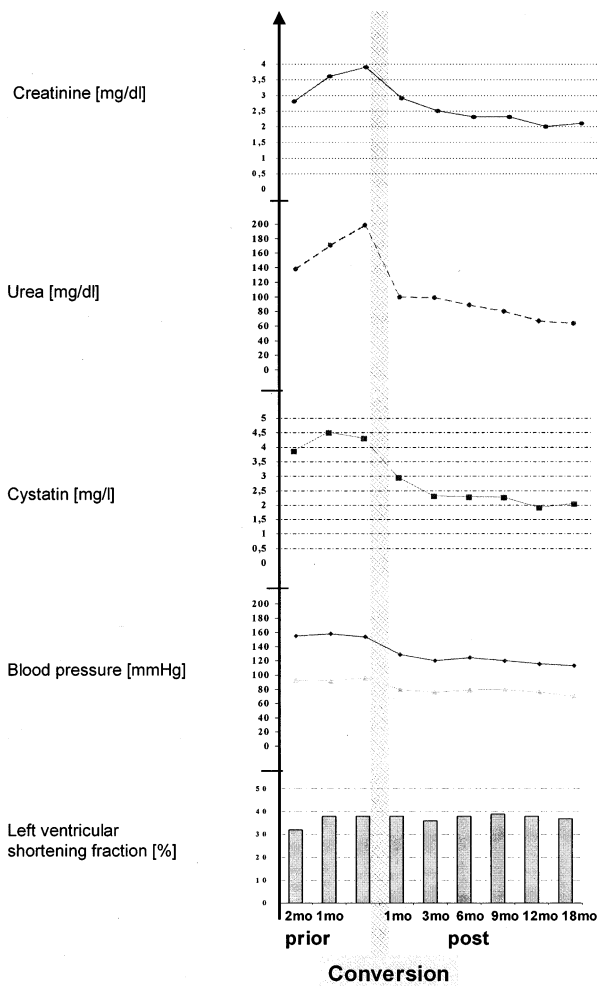
After admission, acute cardiac rejection was excluded by endomyocardial biopsy. Echocardiography showed normal left ventricular ejection fraction, regular valve motion and no regional wall motion abnormalities.

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**Figure 1.** Renal and cardiovascular parameters before and after conversion to sirolimus and MMF in long-term follow-up: creatinine (mg/dl); urea (mg/dl); cystatin (mg/liter); arterial blood pressure (mm Hg); and left ventricular shortening fraction (%).

Intravenous fluid/furosemide management was started to maintain marginal diuresis. Renal failure of origin other than long-term CNI nephrotoxicity was then excluded (e.g., glomerulonephritis, renal artery stenosis, urinary tract obstruction) by laboratory findings, ultrasound and Doppler. Renal biopsy was not performed based on the patient's clinical status and on the risk of additional renal parenchymal damage. Long-term hemodialysis therapy was considered (oliguria, uremia, pleural effusion); however, after obtaining urgent local ethics committee approval and the patient's written informed consent, the patient was converted from CsA and MMF to a CNI-free immunosuppression regimen consisting of MMF and sirolimus (Rapamune, Wyeth-Ayerst, Pharmaceuticals, Collegeville, PA).

Both drugs were administered with target trough levels of 10 to 15 ng/ml (sirolimus) and 2 to 4 ng/ml

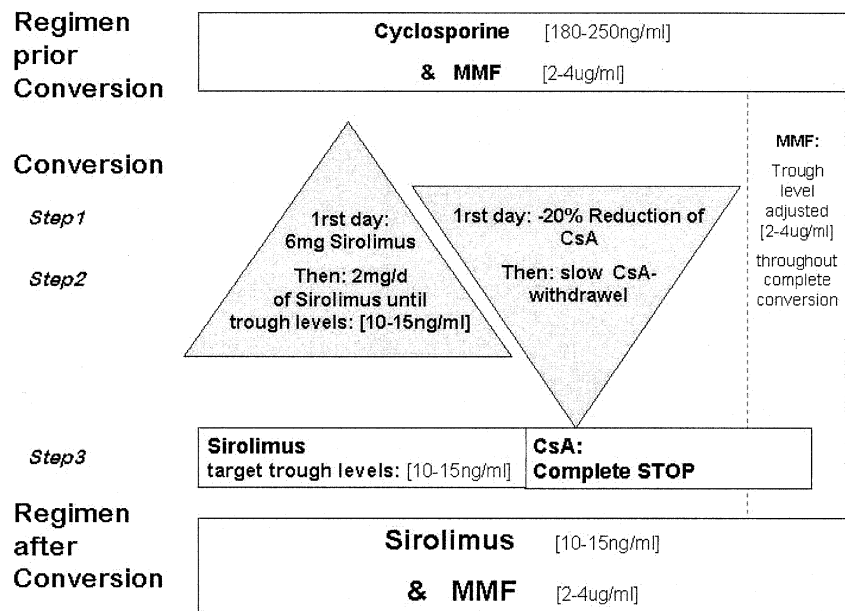
(MMF) (Figure 2). Sirolimus was started with a single 6-mg loading dose and continued at 2 mg/d until target trough levels were achieved. Concurrently, the CsA dosage was reduced by 20%, tapered over a period of 7 days, and then stopped completely. MMF was continued unaltered. When CNI withdrawal was complete, renal function recovered within 10 days: creatinine, urea and cystatin (a marker of impaired glomerular filtration when elevated) decreased significantly (Figure 1), whereas diuresis increased. Acute cardiac rejection on the altered immunosuppression regimen was excluded by endomyocardial biopsy and the patient was then discharged in excellent clinical condition. During the follow-up period of 1.5 years, cardiac graft function remained stable, as documented by monthly echocardiography (Figure 1). No acute rejection episode occurred, as demonstrated by endomyocardial biopsy every 1 to 3 months, and no graft vessel disease was detected at annual coronary angiography. Furthermore, systolic and diastolic blood pressure decreased and diltiazem therapy was reduced several weeks after conversion. The effect of the initial renal recovery was persistent and renal parameters remained stable and elevated (creatinine 2.1 mg/dl, urea 67 mg/dl, cystatin 2.04 mg/liter), but significantly lower when compared with levels prior to conversion. Since post-transplant discharge the patient has been free of hemodialysis therapy, which could be avoided as a result of complete CNI withdrawal.

Severe adverse effects did not occur during follow-up. Although his platelet count decreased and serum cholesterol increased despite moderate statin treatment, the changes were still within the normal range. Further metabolic disorders were unverifiable. Finally, a specific type of acne occurred 2 weeks after conversion (most likely related to the sirolimus administration), but disappeared within 3 weeks without further treatment.

## DISCUSSION

Avoiding renal failure after cardiac transplantation has become a major issue due to the impact of renal impairment on quality of life and life expectancy.<sup>2</sup> The increasing number of patients requiring hemodialysis or kidney transplantation following heart transplantation calls for new approaches to prevent renal failure and long-term hemodialysis. The most common causes of renal impairment are chronic low cardiac output before transplantation coupled with long-term immunosuppressive therapy, which is always based on calcineurin inhibitors.

The 2 calcineurin inhibitors used as the basic compounds of immunosuppression after cardiac transplantation (cyclosporine, tacrolimus) seem to have a similar long-term impact on renal function.<sup>4</sup> One way to reduce their nephrotoxicity is by mild reduction of CNI target



**Figure 2.** Conversion scheme. CsA dosage was reduced and sirolimus started with a single loading dose (6 mg). Sirolimus was then administered at 2 mg/d until target trough levels were achieved. Simultaneously, CsA dosage was tapered and then stopped completely, when sirolimus levels were adequate. MMF dosage was continued and trough level adjusted throughout the conversion period.

trough levels while adding MMF, admittedly with a subsequent risk of acute rejection.<sup>5</sup> In our case, CsA trough levels were already reduced (between 180 and 250 ng/ml) and MMF was added as a secondary immunosuppressant prior to conversion, but mild acute rejection occurred and renal function was impaired.

The risk of acute rejection in patients with lowered CsA trough levels can be reduced with the addition of sirolimus, a potent immunosuppressive rapamycin derivative. In patients treated with a combination of CNI and sirolimus or everolimus (another rapamycin derivative), target trough levels of both drugs can be reduced, while acute rejection can be safely prevented.<sup>6-8</sup> However, the incidence of chronic renal impairment was not decreased in these studies, indicating possible nephrotoxic interactions of CNI with sirolimus. Our case suggests that chronic renal failure in cardiac transplant recipients shows significant improvement only if cyclosporine is completely stopped.

Complete CNI withdrawal with subsequent sirolimus-steroid immunosuppression was associated with a higher number of acute rejection episodes than in sirolimus-cyclosporine-immunosuppressed renal transplant recipients in a randomized, multicenter trial.<sup>9</sup> In renal transplantation, wherein lower immunosuppression is required than in thoracic organ transplantation, a higher incidence of acute rejections indicates an insufficient immunosuppressive potency of the sirolimus-steroid combination for thoracic transplant recipients. However, Snell et al.<sup>10</sup> recently showed in a retrospective analysis that sirolimus-based immunosup-

pression was feasible in heart and lung transplant recipients and led to improved renal function in 30-day follow-up. Nevertheless, only 48% of the patients in their study could have CNI therapy stopped safely. CNI-free regimens such as MMF in combination with sirolimus, have not revealed any nephrotoxicity to date,<sup>11</sup> and prevented acute rejection safely after renal transplantation. The combination of these 2 immunosuppressants also seems to be a promising alternative for long-term follow-up of heart transplant patients with chronic renal impairment, which makes long-term CNI-free immunosuppression possible. In patients suffering from chronic CNI toxicity, conversion to a CNI-free regimen seems to be the most reasonable therapy. It must be elucidated whether CNI withdrawal is also a useful therapeutic option for renal failure of other origins after cardiac transplantation. Indicators for positive response or non-response to conversion await detection in future clinical trials.

This case report represents the first long-term follow-up of a heart-transplanted patient converted to a safe, CNI-free immunosuppressive combination of sirolimus and MMF with subsequent renal recovery and excellent cardiac graft function.

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