Conversion to everolimus in a patient with arterial hypertension and recurrent cutaneous neoplasia—a case report

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Abstract
Calcineurin inhibitors (CNIs) are frequently associated with side effects such as nephrotoxicity and hypertension, so CNI withdrawal from immunosuppressive regimens is desirable in certain cases. The proliferation signal inhibitors/mammalian target of rapamycin inhibitors everolimus and sirolimus may play an important role in achieving CNI withdrawal. Studies on sirolimus have shown that conversion from CNIs is associated with improvements in renal function and hypertension. A case report is presented of a renal transplant recipient who experienced hypertension and recurrent cutaneous neoplasia while receiving a ciclosporin (CsA)-based immunosuppressive regimen. After transplantation, the patient received full-dose CsA and prednisolone. After 7 years, the patient’s serum creatinine increased from 1.9 mg/dl to 2.5 mg/dl, and mycophenolate mofetil (MMF, 1000 mg/day) was introduced, enabling the CsA dose to be reduced to 100 mg b.i.d. The patient also required resection of five cutaneous neoplastic lesions; this led to the decision to stop CsA and start treatment with everolimus 1.5 mg/day, which was increased to 3.0 mg/day to achieve target trough blood levels of 3 ng/ml. To avoid immunosuppression, the MMF dose was reduced to 500 mg/day. After conversion, the patient experienced a substantial improvement in blood pressure, from 175/85 mmHg to 155/70 mmHg. Serum creatinine levels decreased to 1.6 mg/dl, and there has been no recurrence of cutaneous neoplasia in 9 months of follow-up. Therefore, conversion to everolimus from CsA in a renal transplant recipient led to improvements in blood pressure and resolution of recurrent cutaneous neoplasia, with no evidence of rejection or changes in renal function.

Keywords: calcineurin inhibitors; cutaneous neoplasia; ciclosporin; everolimus; hypertension; mammalian target of rapamycin inhibitors; proliferation signal inhibitors

Introduction
The calcineurin inhibitor (CNI) ciclosporin (CsA) has played a central role in post-transplant immunosuppressive regimens since its efficacy in reducing rates of acute rejection and improving graft survival was first demonstrated in the early 1980s [1,2]. Unfortunately, the CNIs, which also include tacrolimus, are associated with a number of side effects, including nephrotoxicity and hypertension [3]. It is, therefore, desirable to minimize or withdraw CNIs from treatment regimens without compromising the level of immunosuppression. In recent years, the proliferation signal inhibitors (PSIs)/mammalian target of rapamycin (mTOR) inhibitors everolimus (Certican®, Novartis Pharma AG, Basel, Switzerland) and sirolimus (Rapamune®, Wyeth Pharmaceuticals, USA) have become available. PSIs have the potential to enable minimization of CNIs from immunosuppressive regimens with no loss of efficacy. Furthermore, there is now a considerable body of evidence from sirolimus studies to support the use of PSIs after CNI withdrawal. For example, a systematic review of controlled trials of CNI withdrawal in patients receiving combined CNI and sirolimus therapy showed that CsA or tacrolimus withdrawal is associated with significant improvements in creatinine clearance (mean difference 7.49 ml/min; \( P < 0.00001 \)) and hypertension (relative risk 0.56; \( P = 0.006 \)) after 1 year [4]. Although there was no overall difference with regard to patient and graft survival, CNI withdrawal was associated with an increased rate of acute rejection, suggesting that withdrawal should not take place before 3 months post-transplant. In a systematic review of conversion to sirolimus in CNI-treated patients focussing on renal function, CNI withdrawal was again associated with significant improvements in creatinine clearance (mean difference 7.9 ml/min; \( P < 0.001 \)) at 6 months in randomized, controlled trials; mean change from
baseline 5.82 ml/min; *P* = 0.02 at 12 months in non-randomized trials) and a trend towards lower serum creatinine levels [5]. However, there was a significant increase in cholesterol (mean change 0.55 mmol/l; *P* < 0.0001) and triglyceride (mean change 0.60 mmol/l; *P* < 0.0001) levels in patients converted to sirolimus. The authors of these studies note that additional trials are now needed to evaluate the role of the PSIs more fully in permitting the protocol and timing for CNI minimization and withdrawal. Withdrawal of CNI from everolimus-based regimens is currently being investigated, and this may provide further guidance on the optimal timing of CNI withdrawal in renal patients.

Further to the immunosuppressive efficacy of PSIs, everolimus and sirolimus have been associated with a reduced incidence of post-transplant malignancies [6]. In a multivariate analysis of over 30,000 renal transplant recipients, the incidence of any *de novo* malignancy in patients receiving a PSI was 0.6% compared with 1.8% in patients receiving CNI monotherapy [6]. Moreover, conversion from CNI-based regimens to a PSI has been shown to cause regression of Kaposi’s sarcoma in renal transplant recipients [7]. Here, we present our experience with a renal transplant recipient who was converted to everolimus from CsA as a result of hypertension and recurrent cutaneous neoplasia.

**Case report**

The patient was a 64-year-old man who had received a renal transplant 9 years earlier. The patient had a history of hypertension, beginning in 1985, which had resulted in haemorrhagic stroke in the right hemisphere, with residual hemiparesis and bilateral cataracts.

In 1996, the patient received a renal transplant after 18 months of haemodialysis as the result of renal failure secondary to nephroangiosclerosis. Graft function was immediate, and initial immunosuppression was achieved with full-dose CsA (initially 10 mg/kg/day to achieve trough blood levels of 250–350 ng/ml) and prednisolone (0.5 mg/kg/day tapered to 10 mg/day). Seven years after the transplant, CsA nephrotoxicity was observed, with an increase in serum creatinine from 1.9 mg/dl to 2.5 mg/dl. Mycophenolate mofetil (MMF) was introduced at a dose of 1000 mg/day, and the CsA dose was reduced to 100 mg b.i.d. This resulted in the stabilization of serum creatinine levels at 1.9–2.0 mg/dl.

The patient’s hypertension continued after transplantation, and important left ventricular hypertrophy was observed during echocardiography. The patient also experienced prostatic syndrome, which was treated in 1997 by transurethral resection, and dizziness, which was revealed by an electroencephalogram to be related to an epileptogenic focus in the right temporal region of the brain. In May 2005, the patient’s concomitant medications included doxazosin (4 mg/day), atenolol (50 mg b.i.d.), losartan (50 mg/day), atorvastatin (10 mg/day), clopidogrel (75 mg/day) and carbamazepine (200 mg t.i.d.).

In the post-transplant period, the patient also experienced recurrent cutaneous neoplasia, requiring resection of five lesions. As a result of this, the patient’s CsA was stopped and treatment with everolimus started at 1.5 mg/day. The dose was increased to 3.0 mg/day as a result of low trough blood levels caused by concomitant administration of carbamazepine, and a target trough blood level of 3 ng/ml was achieved (Figure 1). Prednisone dose was maintained at 10 mg/day. Finally, after 8 months the MMF dose was reduced to 500 mg/day to avoid over-immunosuppression. Nine months after conversion,
withdrawal of CNIs may reduce the incidence of these events, which are highly prevalent in older transplant recipients.

Our patient did not experience any reappearance of recurrent cutaneous neoplasia after conversion to everolimus. Again, this is consistent with published data on PSIs, with sirolimus-treated patients withdrawn from CNI therapy having a lower incidence of malignancies compared with those remaining on CNIs [15,16]. Everolimus is also associated with a low incidence of malignancies in clinical studies. For example, in a 36-month study of everolimus 1.5 mg/day or 3.0 mg/day vs MMF, the incidences of malignancy were 5.2%, 4.5% and 4.6%, respectively [17], and in a second 36-month study, the rates were 4.7%, 5.2% and 6.1% [18]. These promising results have led some authors to investigate the use of conversion to a PSI from a CNI as a means of treating malignancies. Campistol et al. report results from two renal recipients who, after conversion to sirolimus from CsA, experienced complete resolution of Kaposi’s sarcoma [19], and in a prospective study, complete resolution of Kaposi’s sarcoma was observed in 15 renal transplant recipients 3 months after conversion to sirolimus from CsA [7]. Moreover, conversion to sirolimus was not associated with any reports of acute rejection or changes in graft function.

In conclusion, conversion from CsA to everolimus in a renal transplant recipient with hypertension and recurrent cutaneous neoplasia led to substantial improvements in systolic and diastolic blood pressure, stabilization and even improvement in graft function, and resolution of the neoplastic condition. There was no evidence of graft rejection or proteinuria after conversion. Conversion from CNI-based regimens to PSIs is associated with improvements in both cardiovascular disease and post-transplant malignancies, and may improve long-term patient survival in renal transplant recipients.

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