Conversion to a proliferation signal inhibitor in a patient with coronary artery disease—a case report

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Abstract

The calcineurin inhibitors (CNIs) ciclosporin (CsA) and tacrolimus are currently an important part of immunosuppressive regimens, but are associated with increased cardiovascular risk factors, including hyperlipidaemia, hypertension and diabetes mellitus. Conversion from CNI-based regimens to proliferation signal inhibitors or mammalian target of rapamycin inhibitors, such as everolimus and sirolimus, has been associated with an improvement in cardiovascular risk. This case study describes a 59-year-old renal transplant recipient who presented with angina pectoris while receiving immunosuppression with CsA, azathioprine and steroids. The patient developed angina pectoris 5 years after receiving a cadaveric renal transplant. At the time, the patient was obese, with hypertension controlled with diuretics and calcium channel blockers, and hyperlipidaemia controlled with statins. A scintigram revealed plurisegmental myocardial ischaemia, and a coronary angiogram showed the presence of occlusions in the left anterior descending artery and circumflex coronary artery. The patient also had 70% stenosis of the right coronary artery, which was corrected by angioplastic percutaneous intervention. The patient was converted from azathioprine to sirolimus 2 mg/day (trough blood level, 6–10 ng/ml), while the CsA dose was tapered and withdrawn. The angina pectoris subsequently resolved, no progression of coronary artery disease (CAD) has been observed during follow-up and stable renal function has been maintained throughout. Conversion to an immunosuppressive regimen of sirolimus with CsA withdrawal, along with angioplastic percutaneous correction of right coronary artery stenosis, therefore led to the complete resolution of angina pectoris and no progression of the CAD was noticed in this obese renal transplant patient with drug-controlled hypertension and hyperlipidaemia.

Keywords: cardiovascular disease; ciclosporin; everolimus; mammalian target of rapamycin inhibitors; proliferation signal inhibitors; sirolimus

Introduction

The calcineurin inhibitors (CNIs) ciclosporin (CsA) and tacrolimus have played a key role in post-transplant immunosuppression for many years, but are associated with an increase in cardiovascular risk factors, including hyperlipidaemia, hypertension and diabetes mellitus [1]. Studies have shown that immunosuppressive regimens in which CsA exposure is minimized are associated with improvements in cardiovascular risk [2–4]. Immunosuppressive regimens which include the proliferation signal inhibitors (PSIs)/mammalian target of rapamycin (mTOR) inhibitors, everolimus and sirolimus enable minimization or withdrawal of CsA [4,5]. In a review of six randomized trials, CNI withdrawal from sirolimus-based immunosuppressive regimens resulted in a significant reduction in hypertension (relative risk 0.56; \( P = 0.0006 \)) and higher creatinine clearance (mean difference 7.49 ml/min; \( P < 0.00001 \)) [4]. Here, we present a case study of a patient with several cardiovascular risk factors who developed angina pectoris after renal transplantation while receiving a CsA-based immunosuppressive regimen.

Case report

The patient was a 59-year-old woman who developed renal insufficiency of unknown aetiology in 1971. Haemodialysis was started in 1993, and in May 1994 she received a renal transplant from a cadaveric donor. The clinical course after surgery was uneventful and the patient was discharged with normal renal function (serum creatinine, 96 mmol/l). The initial immunosuppressive regimen consisted of CsA microemulsion 8 mg/kg/day, azathioprine 125 mg/day and prednisone 120 mg/day.
Between 1994 and 1999, the patient maintained stable renal function with serum creatinine levels of 88–124 μmol/l, although she experienced a number of important cardiovascular risk factors. Hypertension was successfully controlled with a combination of diuretic therapy and calcium channel blockers, while hyperlipidaemia was controlled with pravastatin 20 mg/day. The patient was also obese, and although lifestyle recommendations were made, these had no success in reducing body weight. However, there was no evidence of diabetes mellitus, and the patient did not smoke.

In December 1999, the patient developed unstable angina pectoris, and a scintigram was performed. The results showed plurisegmental (anterior apex area, and lateral and inferior left ventricular wall) myocardial ischaemia and a coronary angiogram revealed marked ectasia with occlusion of the distal portion of the left anterior descending artery, distal occlusion of the circumflex coronary artery and 70% stenosis at the third portion of the right coronary artery. As a result of the acute ischaemia, the patient was not considered for coronary artery bypass surgery, although an angioplastic percutaneous correction of the right coronary artery stenosis was performed in January 2000.

In April 2000, the patient’s immunosuppressive regimen was converted from azathioprine to sirolimus 2 mg/day (target trough blood level, 6–10 ng/ml). Over the next 4 months, CsA was gradually tapered and eventually withdrawn, and the statin dose was adjusted to a maximum of 80 mg/day to achieve serum lipid levels as close to normal as possible. There was transient proteinuria (1–2 g/day) at week 1 following conversion, this resolved to <500 mg/day soon after. Total cholesterol was 10.36 mmol/l and low-density lipoprotein cholesterol was 3.37 mmol/l with the patient receiving pravastatin 80 mg/day. In addition, standard agents for treating patients with coronary artery disease (CAD), including aspirin, furosemide 25 mg/day, enalapril 5 mg/day and atenolol 25 mg/day were prescribed. The patient’s angina subsequently resolved, with no progression of CAD. Two angiograms, performed in March 2003 and October 2003, confirmed the presence of marked ectasia with occlusion of the distal portion of the left anterior descending artery and distal occlusion of the circumflex coronary artery. There was no evident progression of vascular lesions (Figure 1). Stable renal function in the patient has since been maintained.

Discussion

Atherosclerosis is a major cause of cardiac events in patients with CAD. Formation of atherosclerotic plaques in the vessels restricts blood flow to the heart and is responsible for symptoms such as angina pectoris, and disruption of atherosclerotic plaques is often associated with major adverse cardiac events (MACE) [6]. Chronic inflammation and accumulation of cholesterol form a large component of atherosclerotic plaques, and, as such, hyperlipidaemia is a risk factor for cardiovascular morbidity and mortality. It is important to note that CAD is a disease distinct from cardiac allograft vasculopathy (CAV), which occurs in heart transplant recipients and is caused by smooth muscle proliferation, causing intimal thickening of the vessel wall [7].

The PSIs everolimus and sirolimus have both immunosuppressive and anti-proliferative activity. The effects of PSIs on inhibiting smooth muscle proliferation are associated with a reduced incidence of CAV and subsequent MACE in heart transplant recipients [8,9]. In a study of everolimus in de novo heart transplant recipients, the average increase in
intimal thickness was significantly larger with azathioprine 1.0–3.0 mg/kg/day (0.10 mm) than with everolimus 1.5 mg/day (0.04 mm; \( P = 0.01 \)) or 3.0 mg/day (0.03 mm; \( P = 0.003 \)) after 1 year of treatment [8]. The benefits of everolimus on cardiovascular disease were reflected by a significantly lower incidence of CAV in patients receiving everolimus compared with those receiving azathioprine (\( P < 0.05 \)). Whilst these data highlight that PSIs hold a significant benefit for the prevention of CAV, it is currently not well-known whether everolimus or sirolimus can cause regression of CAV, although data in maintenance heart transplant recipients suggest that conversion to sirolimus slows the progression of CAV [10]. This is being investigated further in a study in Spain, in which maintenance heart transplant recipients with established CAV will be converted to sirolimus or will remain on existing immunosuppression [11].

Neointimal tissue proliferation is also largely responsible for in-stent restenosis following coronary stent placement for CAD [12]. This observation led to the examination of the anti-proliferative role of PSIs in the management of CAD in non-transplant patients through the use of drug-eluting stents, in which a standard coronary stent is coated with a thin polymer that releases either sirolimus or everolimus. Results from clinical trials using sirolimus stents have shown that the incidence of restenosis and vessel failure are significantly reduced in patients receiving a sirolimus-coated stent compared with a control group (\( P < 0.001 \)) [13]. Preliminary data from the use of everolimus-eluting stents (EES) reported in the First Use To Underscore REduction in restenosis with everolimus I (FUTURE I) trial showed that at 6-months’ follow-up, the EES group had a lower in-stent late lumen loss (\( P < 0.0001 \)) and in-segment diameter stenoses (\( P = 0.002 \)) than did the metallic stent group, with no in-stent restenosis [14]. Following the successful use of such stents, the efficacy of oral sirolimus administration to prevent restenosis has also been evaluated. In 300 patients with in-stent restenosis, sirolimus 2 mg/day (with a 24 mg loading dose given before coronary intervention) was associated with a significantly reduced incidence of restenosis compared with placebo (\( P = 0.005 \)) [12].

In clinical trials of sirolimus, hyperlipidaemia is a common adverse event, occurring in 30–50% of the patients [15]. Although hyperlipidaemia is a risk factor for cardiovascular events in patients with CAD, there is evidence to suggest that the increased serum cholesterol levels observed with PSIs are related to cholesterol efflux from cells, leading to lower intracellular cholesterol levels [16,17]. In an apolipoprotein E mouse knock-out model, sirolimus was found to have an anti-atherosclerotic effect by reducing intracellular cholesterol accumulation, inflammatory responses and production of pro-atherogenic cytokines, even in the presence of hyperlipidaemia and inflammation [16,18]. In addition, sirolimus may also act by reducing expression of positive cell-cycle regulators [18]. Results from further studies in the same experimental model have shown that oral administration of sirolimus can significantly attenuate the progression of atherosclerotic plaques, despite substantial increases in plasma low-density lipoprotein cholesterol levels [18,19].

In conclusion, conversion from CsA to the PSI sirolimus, combined with angioplastic percutaneous correction of right coronary artery stenosis, led to the complete resolution of angina pectoris and no further progression of CAD was noticed in an obese renal transplant recipient with controlled hypertension and hyperlipidaemia. Further to the anti-proliferative effects of PSIs, reducing the incidence of CAV, PSIs may reduce the incidence of atherosclerosis and prevent the progression of CAD. The use of drug-eluting stents in the non-transplant population has provided evidence for the benefit of PSIs in CAD. The anecdotal experience provided in this case study suggests that oral PSIs given as part of an immunosuppressive regimen following renal transplantation may have beneficial effects on the progression of CAD. However, the role of oral PSIs in reducing atherosclerosis and CAD, in both transplant and non-transplant populations, requires further analysis in clinical trials.

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References


