Conversion to everolimus in maintenance patients—current clinical strategies

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Abstract
Calcineurin inhibitors (CNIs) are associated with important side effects, such as nephrotoxicity, and thus there is an interest in developing CNI-sparing protocols using agents such as the proliferation signal inhibitor/mammalian target of rapamycin inhibitor everolimus. In a 3-month pilot study using an abrupt conversion protocol, ciclosporin (CsA) treatment was stopped after the morning dose and everolimus was started at 3.0 mg/day. Mycophenolic acid (MPA)-based therapy was continued, or prednisolone increased to 10 mg/day until target everolimus trough blood levels (3–8 ng/ml) were achieved. To date, seven patients have been enrolled, with three having completed at least 3 months of follow-up. Overall, conversion was effective and well-tolerated. Patients consistently achieved everolimus trough blood levels >3 ng/ml, and no episodes of acute rejection or proteinuria were reported after 3 months. In patients who completed the study, there were no major changes in the leucocyte or platelet counts during everolimus treatment. Serum creatinine levels were maintained or decreased slightly. One patient experienced a transient increase in serum creatinine during an episode of pneumonia, but levels decreased again after resolution of infection and temporary everolimus dose reduction. Serum cholesterol and triglyceride levels increased, but remained within acceptable limits. One patient receiving enteric-coated mycophenolate sodium 1440 mg/day experienced increasing everolimus trough blood levels and anaemia after conversion, and was therefore likely to have been over-immunosuppressed. Abrupt conversion to everolimus from CsA was effective and well-tolerated in renal transplant recipients. A reduction in MPA dosage at the time of conversion may be necessary to prevent over-immunosuppression.

Keywords: calcineurin inhibitor withdrawal; ciclosporin; everolimus; mammalian target of rapamycin inhibitors; mycophenolic acid; proliferation signal inhibitors

Introduction
The calcineurin inhibitors (CNIs) ciclosporin (CsA) and tacrolimus have played a central role in post-transplant immunosuppression for many years. However, both agents are associated with considerable potential for nephrotoxicity [1]. Chronic allograft nephropathy is the main cause of graft loss in renal transplant recipients, and CNI treatment has been identified as an important risk factor [2]. As a result of this, there is now considerable interest in CNI-sparing protocols, and a number of studies involving the proliferation signal inhibitor (PSI)/mammalian target of rapamycin (mTOR) inhibitors everolimus (Certican®, Novartis Pharma AG, Basel, Switzerland) have investigated CNI dose reduction. In two 6-month CNI dose reduction studies in de novo transplant recipients, low-dose CsA was combined with concentration-controlled everolimus adjusted to maintain a trough blood level of ≥3 ng/ml [3]. This regimen was associated with a low incidence of biopsy-proven acute rejection (BPAR) (14–25%), particularly when combined with basiliximab induction, and good renal function (median serum creatinine ~130 µmol/l). Complete withdrawal of CNIs from everolimus-based regimens is currently under investigation in clinical trials, with everolimus trough blood levels being maintained at 8–12 ng/ml in these regimens [4]. More data are available for the PSI sirolimus. Meta-analysis of data from six sirolimus-based CNI withdrawal studies showed that CNI elimination was associated with a significant improvement in creatinine clearance and hypertension after 1 year (P < 0.001) [5]. However, there was a 6% increased risk of acute rejection (P = 0.002), although the incidences of graft loss and death were similar in both groups.
Tolerability to PSIs is an important consideration when converting patients to a CNI-free regimen. Conversion from CNIs to PSI-based regimens is associated with an improvement in renal function; however, sirolimus treatment is associated with an increase in proteinuria in renal transplant recipients converted from a CNI to sirolimus [6,7]. A further study showed that serum protein levels below 800 mg/day in renal transplant recipients converted from CsA to sirolimus correlated with a 90% predictive value of response [8]. In light of these observations, conversion to PSIs is not recommended in patients with proteinuria >800 mg/day [4].

A number of protocols can be employed when converting maintenance transplant recipients from a regimen involving a CNI and steroids to one involving a PSI; two types of protocols are generally used, and these are based on tapered vs abrupt withdrawal of CNI. When converting to everolimus in the tapered CNI withdrawal protocol, everolimus is usually added to the regimen at a dose of 1.5–3.0 mg/day and the CNI dose is reduced by 50%. After 1 week of overlap, CNI treatment is withdrawn and the everolimus dose adjusted to maintain trough blood levels of 8–12 ng/ml. Elimination of CsA from everolimus-based regimens is associated with a 2- to 3-fold decrease in everolimus trough blood levels [9], so a concomitant increase in everolimus dose should be expected [4]. Alternative protocols may involve a more abrupt conversion from CNI to PSI, with the addition of everolimus 1.5–3.0 mg/day and withdrawal of CNI treatment after 24–48 h. Similarly to the tapered CNI protocol, the everolimus dose after CNI withdrawal should then be adjusted to achieve trough blood levels of 8–12 ng/ml within 2–4 days of conversion. It is important to note that in both of these protocols there is usually an overlap of PSI and CNI therapy for 1–2 days. The effects of different conversion protocols are currently being investigated in clinical trials. From our experience in Austria, when converting from CsA to sirolimus in a tapered protocol with an overlap of several days, we frequently observed an increase of serum creatinine due to acute CsA toxicity and side effects because of over-immunosuppression, respectively. For conversion to everolimus from CNI-based immunosuppression, we therefore, decided to use an abrupt withdrawal protocol in which there was no overlap in PSI and CNI therapy, a ‘stop-and-go’ protocol. To assess the safety and efficacy of this protocol we carried out a small-scale pilot study in seven renal transplant recipients.

**Methods**

**Conversion to everolimus from CsA using a ‘stop-and-go’ protocol**

The ‘stop-and-go’ conversion protocol for the pilot study involved an abrupt conversion from CsA microemulsion to everolimus with no overlap in PSI and CNI therapy. On day 1, CsA treatment was stopped after the morning dose and everolimus started at 1.5 mg b.i.d. Mycophenolate mofetil (MMF) or enteric-coated mycophenolate sodium (EC-MPS) therapy was continued, and the prednisolone dose was increased to 10 mg/day, or initiated at this level, until the target everolimus trough blood level (3–8 ng/ml) was achieved (Figure 1). Laboratory tests were carried out on days 4 and 8, weekly during the first month and monthly for the remainder of the 3-month observation period.

After the target everolimus levels were achieved, the prednisolone dose was reduced to 5 mg/day and then tapered and withdrawn within 1 month of conversion. MMF or EC-MPS therapy was continued according to each patient’s previous regimen, with different patients receiving alternative regimens dependent on their tolerance to differing doses of MPA. If a reduced dose of MMF or EC-MPS, or dose interruption was required, everolimus target levels were increased and, in the case of dose interruptions, prednisolone therapy restarted (Figure 1).
Patients enrolled in the study were required to be first or second graft recipients receiving CsA-based maintenance therapy with MMF (>1000 mg/day) or EC-MPS (>720 mg/day). Patients were only converted to everolimus if they had stable or mildly deteriorating renal function measured by serum creatinine levels and glomerular filtration rate (GFR). Patients with GFR <20 ml/min were excluded from the study. The presence of subclinical acute rejection was excluded by renal biopsy. Exclusion criteria for the study included positive C4d staining or glomerulonephritis, a history of immunological graft loss, panel reactive antibodies >40%, more than one previous rejection episode, platelet count <150 G/l, leucocyte count <4 G/l, serum cholesterol >9.0 mmol/l and triglycerides >5.0 mmol/l. To date, seven patients have been enrolled into the study. These patients are aged 49–71 years and have good renal function (mean serum creatinine, 1.8 mg/dl; range 1.0–2.2 mg/dl). Prior to conversion, the mean CsA trough blood level was 102 ng/ml (range 46–139 ng/ml). Data over 1 week of observation are available for all patients, with five patients having more than 3 weeks of data and three patients having completed 3 months of follow-up.

Results

Conversion from CNI to everolimus

Overall, the conversion from CsA to everolimus was well-tolerated, and no episodes of acute rejection have been reported in the seven patients enrolled. Patients consistently achieved everolimus trough blood levels >3 ng/ml, with only one patient failing to achieve the target level by day 4. By day 8, five of the seven patients were within the target range, with two patients having a level higher than the target, while four of the five patients for whom 3-week data are available were within the target range at week 3. However, there was considerable variability between patients, and within individual patients throughout the study. Therapeutic drug monitoring of everolimus trough blood levels led to varied everolimus dosing between patients. After 3 weeks, two patients were receiving everolimus 3.0 mg/day, one patient received everolimus 2 mg/day, one patient received everolimus 1.5 mg/day and one patient received everolimus 0.75 mg/day.

As noted above, three of the seven patients enrolled into the pilot study have now completed at least 3 months of follow-up. All three of these patients were women who had received a primary renal transplant and were converted to avoid CNI nephrotoxicity. Urinary protein measurement revealed no proteinuria in these patients after 3 months of treatment and no episodes of acute rejection have been reported.

Case 1. The 49-year-old patient received a stable dose of everolimus 3.0 mg/day throughout the study, although she did not achieve the target trough blood level until after day 4 and remained at the lower end of the target range thereafter (Figure 2A). For this reason, prednisolone was not withdrawn, although the dose was gradually tapered to 5 mg/day by week 4 post-conversion. Abrupt withdrawal of CsA was associated with a mild initial decrease in serum creatinine levels and stabilization thereafter. Laboratory data for the patient show no major changes in leucocyte or platelet counts. There was an expected increase in cholesterol (6.53 and 7.54 mmol/l, pre-conversion and at month 3, respectively) and triglyceride levels (2.40 and 3.37 mmol/l, pre-conversion and at month 3, respectively); however, these remained within acceptable limits. Haemoglobin levels fell slightly during the 3-month follow-up from 11.1 g/dl to 10.6 g/dl.

Case 2. The patient was 71 years old and, unlike the patient in case 1, experienced peaks in everolimus trough blood levels that required dose reduction (Figure 2B). At day 4 post-conversion, the everolimus trough blood level was 13.5 ng/ml, as a result of which the everolimus dose was decreased to 1.5 mg/day. Although this caused an initial reduction in everolimus trough blood levels at day 8 post-conversion, by week 2 the trough blood level had increased once more, and the everolimus dose was reduced further. There was a subsequent reduction in everolimus trough blood levels, and at month 2 this dose was increased once again to maintain the recommended target level of 3–8 ng/ml. The patient also experienced an increase in serum creatinine peaking at month 2 post-conversion, as a result of pneumonia. After everolimus dose reduction and resolution of the infection, serum creatinine levels improved to below the pre-conversion baseline. The patient did not experience any significant changes in blood lipid levels or in leucocyte and platelet counts, although there was a reduction in haemoglobin levels from 11.1 g/dl to 9.8 g/dl by month 3 post-conversion.

Case 3. This patient was 59 years of age, and also experienced increases in everolimus trough blood levels (Figure 2C). Reduction of the everolimus dose to 1.5 mg/day initially brought the level within the target range, but the level subsequently increased, despite a further reduction to 0.75 mg/day. The reason for this is unclear and no drug interactions were reported. Notably, this patient was receiving full-dose EC-MPS (1440 mg/day) for the majority of the study period, and also experienced anaemia, with a reduction in serum haemoglobin from 14.7 g/dl before conversion to 9.7 g/dl after 3 months. The leucocyte count fell from 10.9 to 7.9 G/l after 3 months, and the platelet count increased, although these changes were not clinically significant. Furthermore, hyperlipidaemia was reported in this patient, with increases in both triglycerides (1.45 mmol/l pre-conversion to 3.60 mmol/l at month 2 post-conversion) and cholesterol (6.58 mmol/l pre-conversion to 8.83 mmol/l at month 2 post-conversion) (Figure 2C).

Discussion

The results of this pilot study show that patients receiving an MPA-based immunosuppressive regimen can safely and effectively be converted from CsA to...
everolimus using a ‘stop-and-go’ conversion protocol. This novel conversion protocol avoids the overlap of PSI and CNI therapy which is often employed in abrupt conversion protocols and may further reduce the risk of CNI nephrotoxicity compared with the existing protocols. Conversion was generally associated with stable or improved renal function, as shown by slight decreases in serum creatinine levels over the 3 months following conversion, with no evidence of proteinuria. In one patient, who experienced a rise in serum creatinine as a result of pneumonia, the creatinine level returned to below pre-conversion levels after resolution of the infection and a temporary reduction in everolimus dose.

‘As expected, there was a slight increase in serum cholesterol and triglyceride levels after conversion, although these levels generally remained within acceptable limits. Hyperlipidaemia has previously been observed in around 30–50% of patients receiving sirolimus or everolimus [4], although clinical
experience has shown that hyperlipidaemia in patients receiving everolimus can easily be controlled with standard doses of statins [10].

In case study 3, the patient experienced increasing everolimus trough blood levels of 8–12 ng/ml, despite successive dose reductions. In clinical trials, an everolimus dose of 3.0 mg/day was not able to achieve trough blood levels of 8–12 ng/ml in a CNI-free regimen. However, increasing experience from clinical practice suggests that this is possible in some patients. Moreover, this patient experienced decreasing serum haemoglobin levels during the course of treatment. As this patient was receiving full-dose (1440 mg/day) EC-MPS for most of the study period, with only a transient reduction to 1080 mg/day at month 2, it is highly likely that this patient was over-immunosuppressed. Anaemia is a common complication in renal transplant recipients and is also associated with use of PSI therapy, particularly sirolimus, and MMF [4,11]. There is, therefore, a clear argument for reducing the dose of mycophenolic acid (MPA)-based immunosuppression, both to reduce the risk of anaemia and to decrease the level of over-immunosuppression. Pharmacokinetic data show that MPA exposure is increased in the presence of sirolimus compared with CsA, and the dose of MMF or EC-MPS should be reduced in order to achieve comparable exposure to patients receiving MPA and CsA [12]. Indeed, some investigators now feel that an MMF dose of 1000 mg b.i.d. (or EC-MPS dose of 720 mg b.i.d.) [13], representing a 50% reduction from full dosing, provides adequate immunosuppression in patients also receiving a PSI [14].

**Conclusions**

Abrupt conversion from CsA to everolimus is well-tolerated in maintenance renal transplant recipients, and adequate immunosuppression is maintained. There is a risk of over-immunosuppression in patients also receiving MPA-based therapy, and a 50% reduction in the MMF or EC-MPS dose may be required, while increasing everolimus trough blood levels to 5–8 ng/ml. This approach enables therapeutic monitoring of one drug, everolimus, maintaining a target exposure, and use of a fixed dose of a second immunosuppressive agent, MPA. Individualization and ‘fine-tuning’ of treatment regimens should enable optimization of immunosuppression and minimize the risk of adverse events such as anaemia and hyperlipidaemia.

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**References**


