

Everolimus in clinical practice—renal transplantation

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Abstract

Everolimus is a proliferation signal inhibitor (PSI)/mammalian target of rapamycin inhibitor that is structurally similar to sirolimus, but with a number of important pharmacokinetic differences, including a shorter half-life and time to steady state. In clinical trials, the efficacy of everolimus 1.5 mg/day and 3.0 mg/day combined with ciclosporin (CsA) and steroids in *de novo* renal transplant recipients is similar to that of mycophenolate mofetil, with one study showing a significantly lower risk of antibody-treated acute rejection with everolimus. When combined with reduced-dose CsA, everolimus is associated with improved renal function compared with full-dose CsA, with no decrease in efficacy. Thus, everolimus may play an important role in calcineurin inhibitor (CNI)-sparing regimens for renal transplant recipients. Studies with sirolimus have shown that CNI withdrawal is associated with a significant improvement in renal function, although there may be an increase in the risk of acute rejection. However, patient and graft survival are not adversely affected by CNI withdrawal. Notably, proteinuria <800 mg/day before conversion is a strong predictor of successful response to sirolimus treatment, and hypertensive therapy and serum lactate dehydrogenase levels may also predict response. Adverse events commonly associated with the PSIs include dyslipidaemia, proteinuria and anaemia, although these can usually be managed without difficulty. Data are also available to suggest that the PSIs are associated with a lower risk of malignancy than other immunosuppressive agents. In conclusion, everolimus may permit reduced exposure to CNIs in renal transplant recipients, with the potential to improve tolerability and renal function.

Keywords: acute rejection; everolimus; mammalian target of rapamycin inhibitors; proliferation signal inhibitors; renal transplantation; sirolimus

Introduction

Everolimus (Certican[®], Novartis Pharma AG, Basel, Switzerland) and sirolimus (Rapamune[®], Wyeth Pharmaceuticals, USA) belong to the novel class of immunosuppressant agents known as proliferation signal inhibitors (PSIs)/mammalian target of rapamycin (mTOR) inhibitors. Both everolimus and sirolimus are macrolide derivatives with similar chemical structures. However, despite the similarities, there are important pharmacokinetic differences between the two molecules. Notably, the half-life of everolimus (28 h) is considerably shorter than that of sirolimus (62 h) and, owing to differences in treatment regimens, everolimus reaches steady state in 4 days, compared with 6 days for sirolimus [1].

This review will summarize the clinical data for everolimus and assess its clinical role in renal transplant recipients, including *de novo* and maintenance patients.

Everolimus in clinical trials

To date, results from the everolimus clinical development programme have been published from one long-term Phase II study [2] and four pivotal Phase III studies [3–6]. These studies have evaluated two doses of everolimus (1.5 mg/day and 3.0 mg/day) in comparison with mycophenolate mofetil (MMF), and either with full- or reduced-dose ciclosporin (CsA).

The efficacy of everolimus compared with MMF was assessed in two similarly designed, double-blind Phase III studies in which *de novo* renal transplant recipients were randomized to receive everolimus 1.5 mg/day, everolimus 3.0 mg/day or MMF 2.0 g/day for 1 year, followed by 2 years of open-label treatment [3,4,6]. Patients also received full-dose CsA and corticosteroids. Efficacy failure in both studies was defined as the incidence of biopsy-proven acute rejection (BPAR), graft loss, death or loss to follow-up. Secondary endpoints included the incidence of acute rejection, allograft and patient survival and safety parameters. In both studies, the incidence of efficacy failure was similar in the MMF and everolimus

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treatment groups at 12 months (25–31%) and 36 months (31–39%) [3,4,6]. However, in one study, a significant difference in the incidence of antibody-treated acute rejection was observed between the everolimus 1.5 mg/day (7.8%) and MMF (16.3%) groups at 12 months ($P=0.01$) [4]. This difference was maintained at 36 months (9.8% vs 18.4%; $P=0.014$). Further analysis of the data from the two studies showed that patients with an everolimus trough blood level ≥ 3 ng/ml had a significantly reduced risk of BPAR after 6 months of treatment compared with those with trough blood levels < 3 ng/ml ($P < 0.0001$) [7]. In addition, patients receiving everolimus had higher mean serum creatinine levels than those receiving MMF [3,4,6]. After 12 months, protocol amendments were introduced, permitting lower CsA trough blood levels (50–75 ng/ml) in the everolimus groups, provided that everolimus trough blood levels were maintained above 3 ng/ml. After the amendment, mean serum creatinine levels decreased slightly or remained stable, with no increase in BPAR [3,4].

The finding that everolimus combined with reduced CsA exposure could result in improved renal function without an increased risk of rejection is supported by results from a 3 year Phase II study in which *de novo* renal transplant recipients received everolimus 3.0 mg/day in combination with basiliximab, corticosteroids and either full- (trough blood level, 125–250 ng/ml) or reduced-dose (50–100 ng/ml) CsA [2]. After 12 months, CsA dosing was adjusted to achieve trough blood levels of 50–75 ng/ml, with the everolimus dose adjusted to ensure trough levels ≥ 3 ng/ml. The incidence of efficacy failure was significantly lower in the reduced-dose group compared with the full-dose CsA group at 6, 12 and 36 months ($P < 0.05$), with BPAR also less frequent in the reduced-dose group than in the full-dose group at each time-point [2]. Serum creatinine levels were also numerically lower in the reduced-dose group compared with the full-dose group at 6 and 12 months, while mean creatinine clearance was significantly higher in the reduced-dose group at 6 and 12 months ($P < 0.01$).

Following on from these initial findings, two similarly designed Phase III studies were conducted to optimize everolimus dosing with reduced-dose CsA [5]. In both the studies, everolimus 1.5 mg/day or 3.0 mg/day (adjusted to maintain trough blood levels ≥ 3 ng/ml) was combined with reduced-dose CsA and corticosteroids, while patients in one study also received basiliximab on the day of transplantation and after 4 days, with correspondingly lower CsA C2 target levels. The primary endpoint of both trials was renal function, and after 6 months, serum creatinine levels were substantially lower than those previously observed in patients receiving everolimus with full-dose CsA [5,7]. Efficacy failure, and particularly BPAR within 6 months of transplantation, generally occurred less frequently in the patients who received basiliximab [5].

Everolimus dosing and administration

Treatment algorithms for the management of *de novo* and maintenance renal transplant recipients have recently been published [1]. In *de novo* patients, it is recommended that everolimus treatment is initiated at a dose of 0.75 mg b.i.d. and adjusted to achieve trough blood levels of 3–8 ng/ml (Figure 1). CsA C2 concentrations should be monitored, with a target level of 1000–1400 ng/ml in the first month after transplant, reduced to 250–350 ng/ml by month 12. In patients receiving an interleukin-2 receptor antibody, lower CsA C2 targets may be more appropriate.

In maintenance renal transplant recipients, the use of everolimus may enable minimization or elimination of CsA from treatment regimens (Figure 2) [1]. In clinical trials of sirolimus, CsA has been reduced or withdrawn in progressive steps of $\sim 25\%$ over a 4 week period, although abrupt cessation of CsA has been used in clinical practice outside of the trial setting [1]. However, few data are available from maintenance renal transplant recipients with CsA C2 levels below 350 ng/ml. Experience suggests that CsA can be discontinued in some everolimus-treated patients, although the dose of everolimus must simultaneously be increased because CsA withdrawal is associated with a 2–3-fold decrease in everolimus blood levels [8]. After CsA withdrawal, everolimus trough blood levels of 8–12 ng/ml may be required when using everolimus and corticosteroids alone, while addition of a mycophenolic acid (MPA)-based agent may require a reduction in everolimus trough blood levels (Figure 2) [1].

In recent years, there has been an increased interest in immunosuppressive regimens that go beyond CsA dose reduction to allow complete elimination of calcineurin inhibitors (CNIs). CNI withdrawal from everolimus-based regimens is currently being evaluated in clinical trials, and a number of studies have been carried out with sirolimus regimens. In a meta-analysis of such studies, CNI withdrawal was associated with improvement in renal function, as shown by a significantly higher creatinine clearance after 1 year compared with continued CNI therapy (mean difference, 7.49 ml/min; $P < 0.00001$) [9]. This was accompanied by a significant increase in the risk of acute rejection (8% difference; $P = 0.002$), although there was no difference in graft loss or death between the CNI withdrawal and CNI continuation groups. In a study in 59 renal transplant recipients with chronic allograft dysfunction, 54% were classed as responders on the basis of stable or improved renal function [10]. Factors that appeared to predict response included proteinuria, histological grade of allograft nephropathy, grade of vascular intimal thickening and number of acute rejections before conversion (all $P < 0.05$). However, in a multivariate analysis, proteinuria < 800 mg/day before conversion was the only significant predictor of response, with a positive predictive value of 90% [10]. A more recent study confirmed the role of proteinuria in predicting

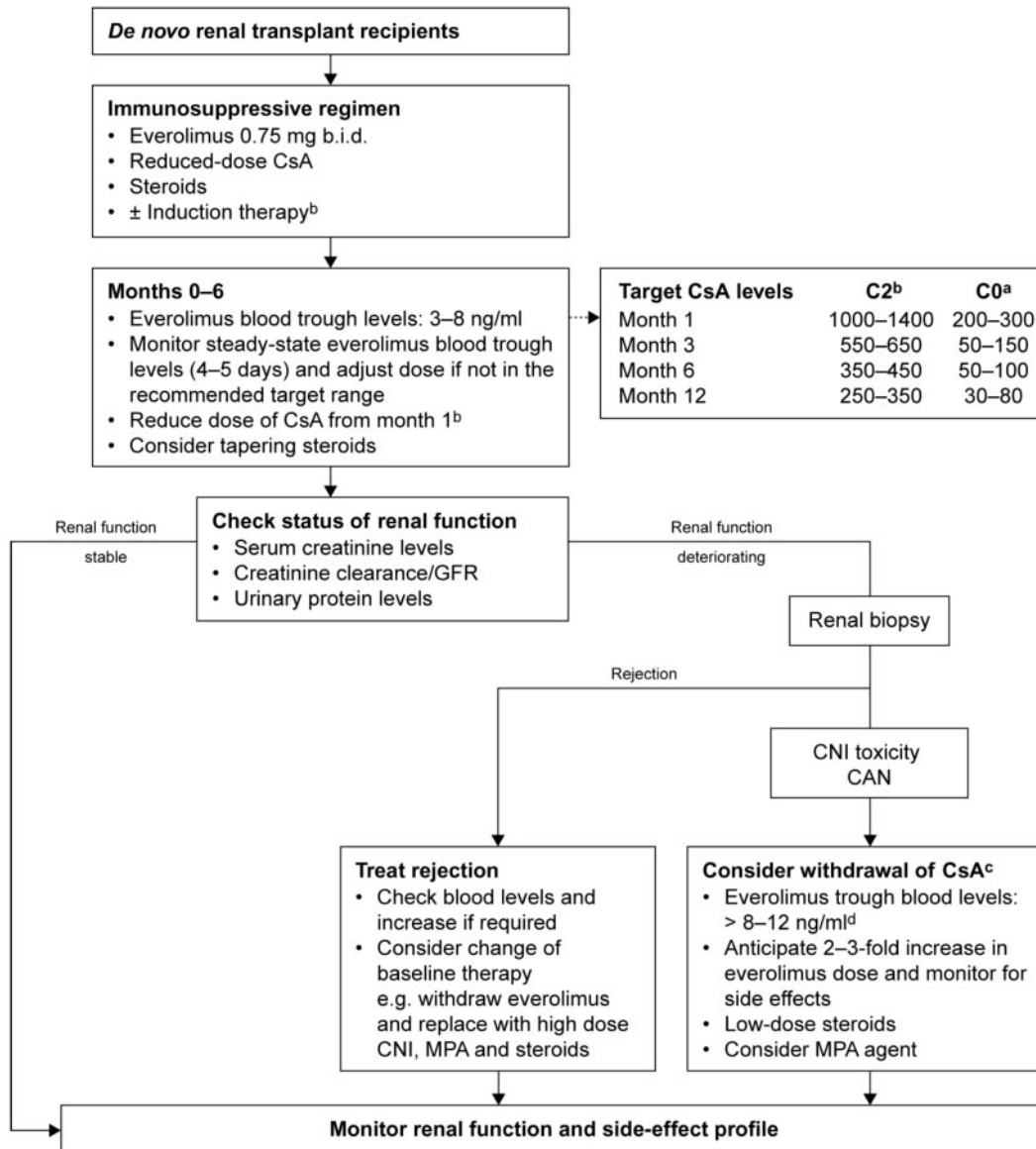


Fig. 1. Treatment guidelines for the use of everolimus in *de novo* renal transplant recipients. Adapted from Pascual *et al.* (2006) [1]; reproduced with permission. ^aEverolimus trough blood levels have been reported to remain stable, with down-titration of ciclosporin (CsA) concentrations, with CsA C0 levels in the range 25–50 ng/ml. ^bWith basiliximab induction therapy, CsA exposure may be minimized further: CsA C2 levels 500–700 ng/ml in weeks 0–8 and 350–450 ng/ml in week 9 to month 12. ^cCsA withdrawal from everolimus-based regimens has not been validated in large clinical trials. ^dThere is limited experience of the use of everolimus above trough blood levels of 12 ng/ml. A single case study reports everolimus trough blood levels above 12 ng/ml after CsA withdrawal. b.i.d., twice a day; CAN, chronic allograft nephropathy; CNI, calcineurin inhibitor; CsA, ciclosporin; GFR, glomerular filtration rate; MPA, mycophenolic acid.

response, and also identified baseline hypertensive therapy and post-conversion serum lactate dehydrogenase (LDH) level as additional independent predictors of treatment response [11]. The data from this study showed that LDH levels at 1 month following conversion to sirolimus were significantly lower in responders than in non-responders (746 ± 422 U/l vs 516 ± 104 U/l, $P = 0.008$). Multivariate analysis confirmed the association of LDH level 1 month post-conversion with improvement in creatinine clearance 6 months post-conversion ($P = 0.0018$) [11].

Management of adverse events

The PSIs/mTOR inhibitors as a class are associated with a number of adverse events, and, in general, these can easily be managed if they occur during treatment. One common adverse event occurring with sirolimus and everolimus treatment is hyperlipidaemia, with increased serum cholesterol and triglyceride levels occurring in 30–50% of the patients [1]. An animal study investigating the mechanism behind everolimus-induced hyperlipidaemia has demonstrated that

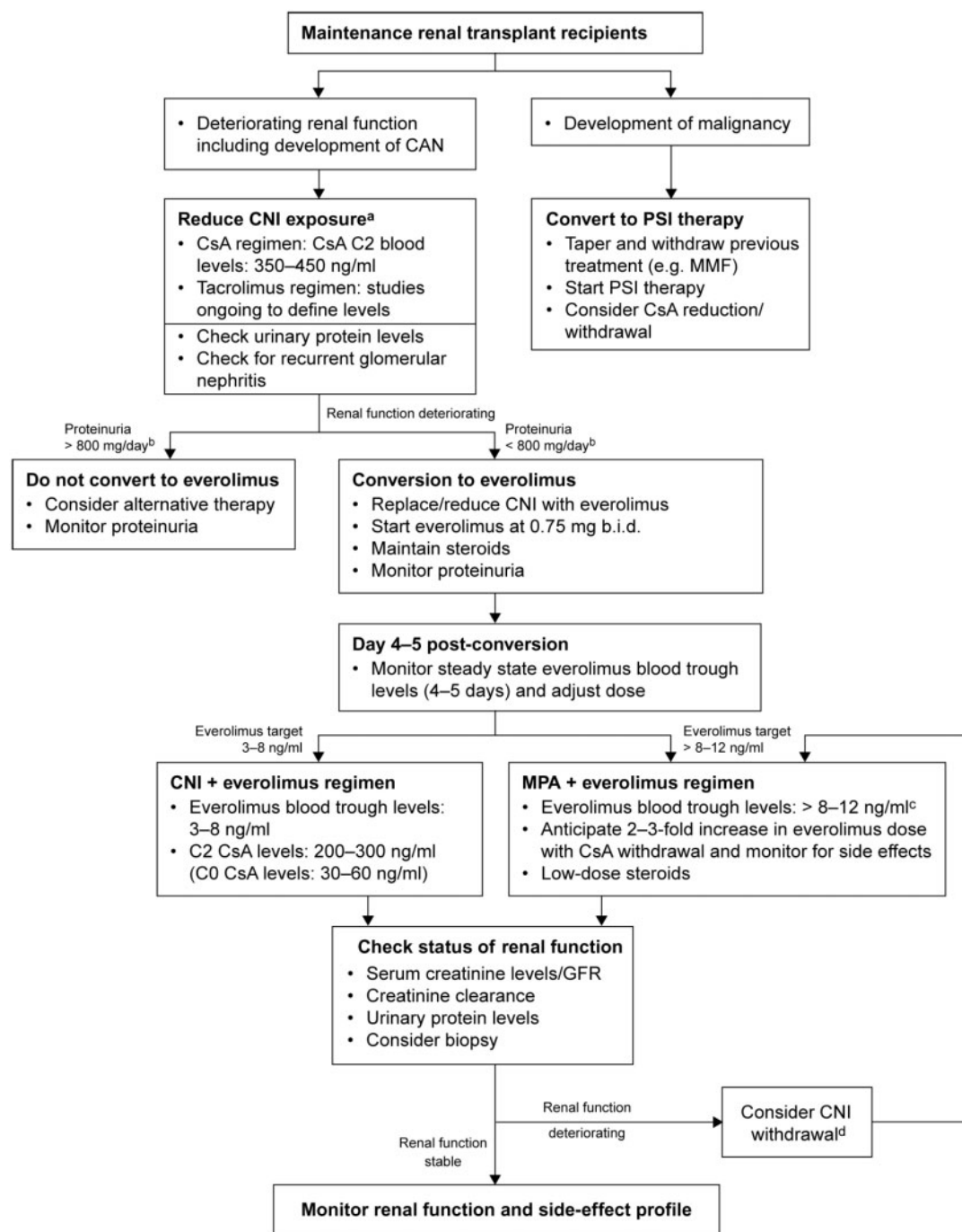


Fig. 2. Treatment guidelines for the use of everolimus in maintenance renal transplant recipients. Adapted from Pascual *et al.* (2006) [1]; reproduced with permission. ^aCNI can be reduced in a stepwise progression of ~25% in each step; however, abrupt cessation of CNI is also used in clinical practice. ^bRange 800–1500 mg/day; published data from one study [11] recommends 800 mg/day as the cut-off point for proteinuria, although an ongoing Phase IV study is assessing 1500 mg/day proteinuria as the cut-off value for conversion to PSI therapy. ^cThere is limited experience of the use of everolimus above trough blood levels of 12 ng/ml. Clinical opinion [1] suggests that lower everolimus blood exposure may allow for increased tolerability. Everolimus trough blood levels of 6–12 ng/ml are currently being evaluated in ongoing Phase IV studies. ^dCsA withdrawal from everolimus-based regimens has not been validated in large clinical trials. b.i.d., twice a day; CAN, chronic allograft nephropathy; CNI, calcineurin inhibitor; CsA, ciclosporin; GFR, glomerular filtration rate; MPA, mycophenolic acid; PSI, proliferation signal inhibitor.

everolimus can cause disruption of cellular lipid homeostasis in mouse peritoneal macrophages at concentrations similar to therapeutic range (0.01 μM), resulting in increased cholesterol esterification and efflux and reduced triglyceride biosynthesis [12].

Dyslipidaemia can be managed with a combination of lifestyle changes and lipid-lowering agents, including statins for hypercholesterolaemia and fibrates for hypertriglyceridaemia, in accordance with published guidelines such as those of the National Kidney

Foundation Kidney Disease Outcomes Quality Initiative [1,13]. Recent data have shown that the combination of everolimus and statin therapy may have additional clinical benefits. The combined use of everolimus and fluvastatin on rat aortic smooth muscle cells was found to result in 8.4 times more antiproliferative activity than that seen with everolimus alone [14]. These findings further support the combined use of everolimus and a lipid-lowering agent such as fluvastatin.

Importantly, any impact of dyslipidaemia on cardiovascular risk is likely to be balanced by the beneficial effects of PSIs. For example, meta-analysis of CNI-sparing regimens has shown that withdrawal of CNIs from sirolimus-based regimens is associated with a significant decrease in the risk of hypertension ($P=0.0006$), with significant reductions in both systolic (-7.02 mmHg) and diastolic (-3.2 mmHg) blood pressure ($P<0.01$) [9]. In clinical trials, sirolimus has been associated with the development of proteinuria (>1000 mg/day) in as many as 28% of patients after switching from CNI [11]. As noted earlier, proteinuria is an important predictor of renal dysfunction following conversion from CNI to a PSI-based regimen [11], and is also a marker of the risk of progressive decline in kidney function [15]. The minimization of proteinuria is, therefore, an important goal in patients with chronic kidney disease, and data on the incidence, mechanism and management of proteinuria in patients receiving everolimus are currently being investigated. The use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is recommended for the treatment of proteinuria in transplant recipients [1]. In addition, the maintenance of everolimus trough levels within the range of 3–8 ng/ml and minimization of CsA dose, instead of a CNI-free regimen, may assist with the prevention and management of proteinuria [1].

An increased incidence of microcytic anaemia has been observed in studies with sirolimus compared with either CsA or MMF [16]. However, in a 12 month comparative study of everolimus and MMF, the incidence of anaemia was similar with both agents (29–34%) [3]. A dose reduction in PSI or MPA-based therapy may be sufficient to resolve anaemia, although severe anaemia should be treated with erythropoietin [1,17].

Sirolimus has been reported to induce pneumonitis following renal transplantation [18,19], with one centre reporting an incidence of 11.0% in patients receiving sirolimus [20]. However, despite numerous published case reports, sirolimus-associated pneumonitis is ill-defined due to the lack of specific diagnosis criteria. Pneumonitis may be causative of pulmonary fibrosis in later stages of the disease. There are no reported cases of pneumonitis in renal transplant recipients receiving immunosuppression with everolimus and low-dose CsA. In clinical trial reports the incidence of pneumonitis is very low, with a total of three patients receiving everolimus reporting the adverse events out of two trials including ~500 patients. Pulmonary fibrosis was

not reported by any of these patients. Pneumonitis may be managed by dose reduction or withdrawal in these patients [21,22].

Other adverse events observed with PSIs that may require minor interventions include lymphocele, which can be treated with povidone iodine or surgical intervention, and wound-healing problems [1,23]. Avoiding a loading dose and maintaining moderate exposure to PSIs will decrease the incidence of such complications [1,24]. In addition, appropriate surgical techniques and special caution with the use of PSIs in patients with obesity or diabetes are also advisable [1].

The future of everolimus

One current topic of debate regarding the use of everolimus in the future is its role as a monotherapy compared with its place in combination regimens. In addition to the interest in CNI-sparing regimens discussed earlier, many physicians also feel that the reduction or withdrawal of corticosteroids has potential benefits in terms of obesity, diabetes mellitus and bone disease. There is, therefore, a clear rationale for reducing the number of agents used in immunosuppressive regimens, as triple therapy (e.g. with a steroid, CNI and MPA-based agent) is now common. In patients at high immunological risk, it is generally felt that a combination therapy will continue to be necessary to prevent acute rejection and graft loss. However, in patients with a lower risk of rejection, CNI- and steroid-sparing therapies using everolimus and sirolimus are likely to play an increasingly important role in the future. Appropriate targeting and monitoring of blood levels will be critical to ensuring that each patient receives the optimal therapy.

Another area in which everolimus is likely to play a key role in future immunosuppressive therapy is in the minimization of cancer risk. Renal transplant recipients are at an increased risk of malignancies, and, whereas the CNIs are associated with tumour promotion, everolimus and sirolimus have a negative effect on the growth of malignant cells [25]. In a multivariate analysis of the Organ Procurement and Transplantation Network database, the incidence of post-transplant malignancies was assessed in 33 249 patients [25]. The results showed that patients receiving sirolimus or everolimus, either alone or in combination with a CNI, had a significantly lower incidence of *de novo* malignancies than patients receiving CNI therapy alone ($P<0.05$).

In the Sirolimus Renal Conversion Trial Study, 830 renal transplant recipients were randomized to either continuing CNI therapy or switching to sirolimus [26]. The results show that the incidence of malignancies was significantly lower in those converted to sirolimus (1.4% vs 5.1%; $P=0.004$). In a further study, patients receiving sirolimus-based therapy after CNI withdrawal had a reduced incidence of both skin and non-skin cancer at 5 years post-transplant and a delayed incidence of first skin cancer [27].

Conclusions

The efficacy of everolimus therapy for immunosuppression in renal transplant recipients has been demonstrated in an extensive clinical trial programme. Notably, the use of everolimus enabled reduced exposure to CsA, resulting in improved renal function with no increase in the risk of acute rejection. Everolimus and sirolimus are associated with a number of adverse events (such as dyslipidaemia or anaemia) that are related to their mode of action as PSIs, and are easily managed.

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