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REVIEW ARTICLE

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Maximizing the clinical outcome with mTOR inhibitors in the renal transplant recipient: defining the role of calcineurin inhibitors

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Abstract The synergistic action of mTOR inhibitors and calcineurin inhibitors (CNIs) provide a rationale for combination therapy, with the potential for CNI-dose reduction and corresponding clinical benefits. CNI therapy is necessary in the early post-transplant phase to deliver sufficient immunosuppressive potency, but use of standard-dose cyclosporine (CsA) with either sirolimus or everolimus has been associated with inferior renal function. Withdrawal of CsA from an mTOR-based regimen reduces renal toxicity, but this may be achieved at the price of increased late rejection and sirolimus-related adverse events. Use of a concentration-controlled mTOR inhibitor with low-exposure CsA seems to be effective in preventing rejection with good renal function. Currently, routine withdrawal of CNIs from an mTOR-inhibitor based regimen, or substitution of an mTOR inhibitor for a CNI, is not justified except in patients who experience toxicity (particularly nephrotoxicity) and who do not respond to CNI dose optimization.

Keywords Sirolimus · Everolimus · Cyclosporin A · mTOR inhibitor · Calcineurin inhibitor · Rejection

Introduction

The recent expansion in immunosuppressive agents licensed for use in transplant recipients has dramatically increased the number of potential drug combinations available to the clinician. The challenge today is to identify regimens that maintain high levels of rejection prophylaxis while reducing short-term and long-term toxicity—both regarding the optimal combination of agents and the optimal dosing strategy for each drug in the de novo and maintenance phases. This task is, of course, complicated by the marked differences in risk profile between transplant patients, and variation in patients' pharmacokinetic response to the same dose of the drug.

There has been a growing interest in the possibility of eliminating or reducing exposure to calcineurin inhibitors (CNIs). When CNI-minimization was investigated in de novo patients receiving mycophenolate mofetil (MMF), complete avoidance of cyclosporine (CsA) resulted in an unacceptable rate of rejection [1]. Protocol-driven withdrawal of CsA in MMF-treated maintenance renal patients was associated with a reduction in toxicity, however at the cost of an increase in late acute rejection rates [2], which is a highly unfavourable prognostic indicator for graft loss [3]. However, in MMF-treated patients with chronic allograft nephropathy, elimination of CsA has shown a clinical benefit [4], and use of MMF facilitates reduction of exposure to calcineurin inhibitors in maintenance of kidney transplant patients [5]. This experience suggests that attempts to withdraw calcineurin inhibitors must be approached with caution and assessed in various types of patients.

The introduction of mTOR inhibitors (sirolimus, everolimus), also known as target of rapamycin (TOR) inhibitors, has since led researchers to examine the use of CNI-free or CNI-sparing regimens in patients receiving

this new class of drugs. mTOR inhibitors block growth factor-mediated proliferation of T cells, B cells and vascular smooth muscle cells [6, 7, 8, 9], thus acting on a later stage of the cellular response than CNIs. Moreover, mTOR inhibitors exert their effect on both haematopoietic and non-haematopoietic cells. The synergistic actions of mTOR inhibitors and CNIs provide a rationale for combination therapy with the potential of reducing the dose of CNI. Animal models have shown that concomitant use of an mTOR inhibitor and CsA has CsA-sparing effects without loss of immunosuppressive potency [10, 11, 12, 13], and in vivo evidence has shown that everolimus enhances the immunosuppressive effects of CsA and steroids on lymphocyte proliferation [9].

This article reviews the currently available evidence on the benefits and risks of CNI avoidance or withdrawal in renal transplant patients receiving an mTOR inhibitor, and assesses alternative clinical strategies that aim to maintain efficacy while reducing the known toxicities associated with CNIs and mTOR inhibitors.

mTOR inhibitors as primary immunosuppression in de novo patient

Two European Phase II trials of de novo kidney transplant patients using sirolimus in a CNI-free regimen showed that relatively high concentrations of sirolimus were required to achieve satisfactory rejection rates [14, 15]. The required level of exposure (30 ng/ml, tapered to 15 ng/ml) significantly increased the risk of thrombocytopenia (37–45%) compared to the CsA-containing groups. The risk of hyperlipidaemia, leucopenia and pneumonia was also higher in sirolimus than in CsA and reached significance in one trial [14]. These results strongly indicated that use of a calcineurin inhibitor is required in the early post-transplant phase, and perhaps indefinitely, to achieve effective rejection prophylaxis without undue toxicity. The European licence for sirolimus requires concomitant use of CsA during the initial post-transplant phase [16]; in the USA it is recommended to use sirolimus in combination with CsA and steroids [17].

mTOR inhibitors and CNIs: the early experience

Subsequent trials have generally used sirolimus or everolimus in combination with standard-dose CsA and steroids, often with fixed dosage of the mTOR inhibitor [18, 19]. An international Phase III study of 576 de novo renal transplant patients which compared sirolimus 2 mg/day and 5 mg/day to placebo, reported a significant benefit when used in combination with full-dose CsA and steroids, but significantly worse renal function at 6 months [18]. This finding was confirmed in the Phase III US study which compared sirolimus to azathioprine, again with standard dosage of CsA and steroids [19]. A similar effect on renal function was reported in comparative trials of the mTOR inhibitor everolimus versus mycophenolate mofetil, when given with standard-dose CsA and steroids [20, 21]. Follow-up data beyond 12 months with both sirolimus [22] and everolimus [23] showed that renal function stabilized after one year, but remained higher than in comparator groups. Additionally, the increased lipid concentrations seen in the mTOR inhibitor cohorts after transplantation persisted beyond the first year after transplantation [22, 23].

Potential management strategies using mTOR inhibitors

Concerns about the safety profile of regimens comprising an mTOR inhibitor with standard-dose CNI have prompted investigators to consider alternative strategies for the use of mTOR inhibitors that avoid the toxicity reported in these early trials.

Two strategies have been examined. Both are based on the assumption that concurrent CNI therapy is required during the first few months after transplantation, given the poor safety results achieved in CNI-free mTOR-inhibitor regimens in de novo patients [14]. The first strategy is to taper the dose of CNI after the initial post-transplantation period, with the aim of complete elimination. The second strategy seeks to modify the dose of CNI and mTOR inhibitor to achieve an appropriate level of immunosuppression with the two agents working synergistically.

Elimination of CNI with mTOR-inhibitor immunosuppression

Two randomized, prospective, open-label studies compared the efficacy and safety of an mTOR inhibitor (in both cases, sirolimus) in combination with CsA and steroids with a protocol, whereby the CsA dose was tapered from the end of the third month after transplantation and then eliminated entirely [24, 25]. Both trials used standard dosage of CsA, as the finding of impaired renal function with sirolimus and standard-dose CsA were not available at the time (however, trough levels of CsA were lower than in previous studies).

In the first Phase II study [24], 246 renal transplant recipients were randomized to sirolimus 2 mg/day with a

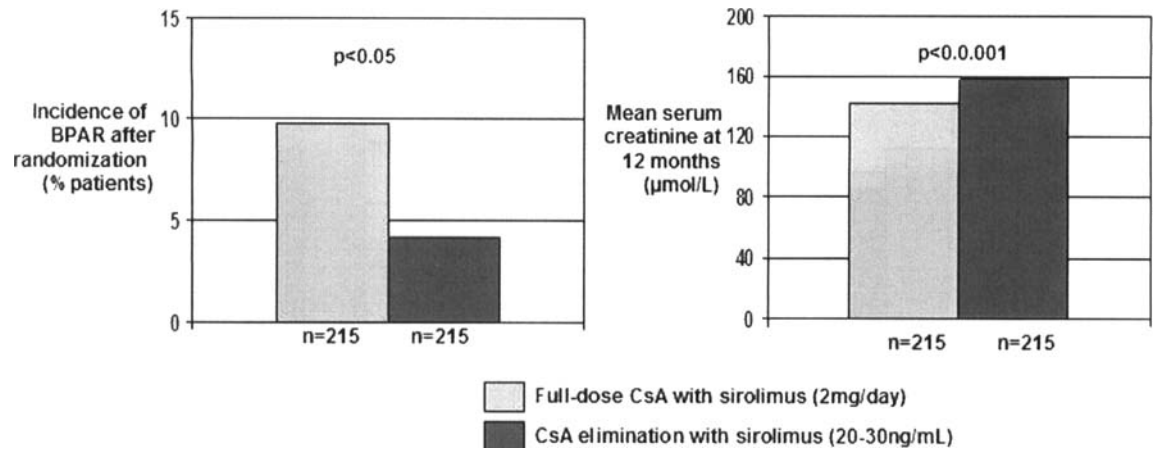

Fig. 1 Biopsy-proven acute rejection (*BPAR*) and mean serum creatinine level in 525 de novo renal transplant patients receiving sirolimus, full-dose CsA microemulsion and steroids, randomized at 3 months to either continuation of CsA or to elimination of CsA with sirolimus dose adjusted to maintain trough levels of 20–30 ng/ml [25]

full-dose CsA, or to sirolimus 10–20 mg/day with reduced-dose CsA, tapered and eliminated after 3 months, if no rejection had occurred in the previous 3 weeks. Patients with delayed graft function were excluded unless renal function improved sufficiently to allow them to receive cyclosporine by day 7. All patients received steroids. Rejection rates at 1 year were similar in both groups, as were patient and graft survival rates. In the intent-to-treat population, mean serum creatinine was significantly lower at month 6 in the cyclosporine-withdrawal group (140 µmol/l vs 170 µmol/l, $P < 0.01$), although the difference was not significant at month 12. Thrombocytopenia, diarrhoea, hypokalaemia and abnormal liver dysfunction were more common in the cyclosporine-withdrawal group, but hypertension, oedema, hypomagnesaemia and dyspnoea occurred less frequently.

In a Phase III study [25, 26], carried out in Europe, Canada and Australia, 525 de novo renal transplant patients received sirolimus (> 5 ng/ml), CsA microemulsion (200–400 ng/ml, tapered to 75–200 ng/ml after 3 months) and steroids. At month 3, patients considered to be at high risk were excluded (exclusion criteria comprised severe acute rejection, vascular rejection, serum creatinine > 400 µmol/l, or inadequate renal function to support CsA elimination). The remaining 430 patients were randomized to remain on CsA with sirolimus (> 5 ng/ml) and steroids, or to a gradual decrease in the dose and elimination of CsA over 4 to 6 weeks, with sirolimus dose adjusted to maintain trough levels of 20 to 30 ng/ml. After randomization, there were significantly more cases of acute rejection in patients randomized to CsA withdrawal than in those randomized to CsA continuation (10% vs 4%, $P < 0.05$), with a trend to higher rejection rates over the entire 12 months of the study in the CsA-withdrawal group (20% vs 14%, $P = 0.09$) [25]. After the first year post-transplantation, there were no rejections in the CsA-withdrawal group, but two in the CsA-continuation group [26]. At 1 year, renal function was significantly better after CsA withdrawal (serum creatinine 142 µg/ml vs 158 µg/ml, $P < 0.001$; calculated glomerular filtration rate (GFR) 63 ml/min vs 57 ml/min, $P < 0.001$; Fig. 1). Among patients in whom CsA was withdrawn, thrombocytopenia, hypokalaemia and abnormal liver function were significantly more common, whereas hypertension, CsA-related nephrotoxicity and hyperuricaemia were less common. Results from this open-label trial of 2 years reported no difference in patient survival, graft survival, discontinuation or the overall rate of biopsy-proven acute rejection between the two treatment groups [26]. Serum creatinine was significantly lower in the CsA-withdrawal group (128 vs 167 µmol/l, $P < 0.001$), and the incidence of adverse occurrences including hypertension, abnormal graft function, creatinine increase and malignancy were less frequent in this cohort. Thrombocytopenia, hypokalaemia, abnormal liver function tests and other conditions were reported more frequently [26]. An open-label single-group study of 54 patients with mild to moderate renal dysfunction in whom CsA was withdrawn over the course of 1 week and sirolimus therapy commenced, also reported improved renal function (GFR at 6 months 39.4 ml/min vs 35.0 ml/min at baseline, $P = 0.014$), with one mild rejection episode and two patients returning to dialysis [27]. An increase in serum creatinine occurred in 9% of patients and proteinuria in 5.5%.

These trials excluded patients at high risk of rejection due to a recent previous rejection episode [24, 25]; no study has yet assessed the effect of CsA elimination with an mTOR inhibitor in these at-risk patients, but it is possible that continuing calcineurin inhibitor therapy will prove to be necessary in this group.

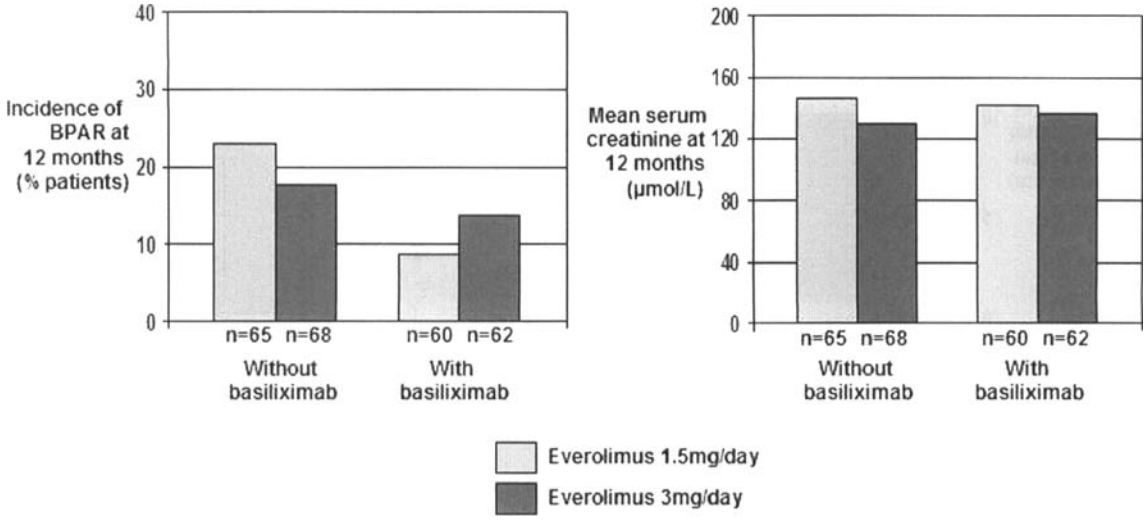

Fig. 2 Incidence of biopsy-proven acute rejection (*BPAR*) and mean serum creatinine in de novo renal transplant patients receiving everolimus 1.5 or 3 mg/day in combination with low-exposure CsA microemulsion (C_2 monitoring) and corticosteroids with [34] or without [35] basiliximab

Low-dose CsA in combination with an mTOR inhibitor

Evidence of impaired renal function with full-dose CsA regimens and an mTOR inhibitor led researchers to consider the use of reduced-dose CsA. An open-label study of 111 de novo renal transplant patients compared outcomes attained with everolimus 3 mg/day at full-dose (C_0 target 150–300 ng/ml to day 60, then 125–250 ng/ml thereafter) to the outcome attained at reduced-dose CsA (C_0 target 75–125 ng/ml to day 60, 50–100 ng/ml thereafter), plus basiliximab and steroids [28]. Renal function was superior with a reduced dose of CsA (as measured by creatinine clearance: 62.1 ml/min vs 51.4 ml/min in the full-dose CsA group at 12 months, $P < 0.05$), despite a low rate of acute rejection (7%).

Two prospective, multicentre studies have since been undertaken in which an mTOR inhibitor (everolimus) was administered in combination with low-dose CsA therapy and steroids [29]. These used C_2 monitoring of CsA-ME, as evidence has shown that it provides a more sensitive guide to CsA exposure than conventional trough level monitoring [30, 31, 32]. In the first of these, 122 de novo renal transplant patients received everolimus 1.5 mg/day or 3 mg/day, with the dose then adjusted according to blood concentration using a CsA C_2 target level of 1200 ng/ml decreasing to 400 ng/ml after 3 months; mean C_0 values at 6 months were 82 ng/ml and 83 ng/ml in the 1.5 mg/day and 3 mg/day groups, respectively. At 6 months, the incidence of biopsy-proven acute rejection was 18% with everolimus 1.5 mg/day and 15% with 3 mg/day. Renal function was good: mean serum creatinine was 146 µmol/l with 1.5 mg/day and 131 µmol/l with 3 mg/day (Fig. 2). The second study [29] used a similar protocol, adding basiliximab, and implemented lower CsA C_2 target levels. In this study, the rejection rate at 6 months was 15% with everolimus at 1.5 mg/day and 9% with a dose of 3 mg/day (Fig. 2). Mean creatinine levels were 142 µmol/l and 137 µmol/l, respectively. There was no difference in the amount of adverse events between the 1.5 mg/day group and the 3 mg/day group in either study.

To date, no trial has directly compared continuation of low-exposure CsA with low-exposure mTOR inhibitor versus standard-dose mTOR inhibitor and CsA withdrawal. One randomized prospective study assessed the effect of CsA withdrawal at 6 months versus low-exposure CsA (50–100 ng/ml) in combination with sirolimus [33] in renal transplant patients, but exposure to sirolimus was the same in both groups (8–16 ng/ml), the total level of immunosuppression being higher in the CsA-continuation group. As would be expected, renal function was lower in the CsA-continuation group (calculated GFR 57 ml/min vs 65 ml/min at 6 months, $P = 0.03$), a difference that was sustained at 1 year [34]. Only four episodes of rejection were reported after randomization: one in the CsA-continuation group and three in the CsA-elimination group. Notably, 35% of 133 patients were not randomized, mostly due to acute rejection or adverse events, so the randomized participants were at relatively low risk of late rejection.

Addition of IL-2 receptor antagonist

Experience using everolimus with reduced-dose CsA has emphasized the potential benefit of including an IL-2 receptor antagonist within a regimen containing an mTOR inhibitor. In patients receiving everolimus with basiliximab, CsA C_2 target levels were lower than that of

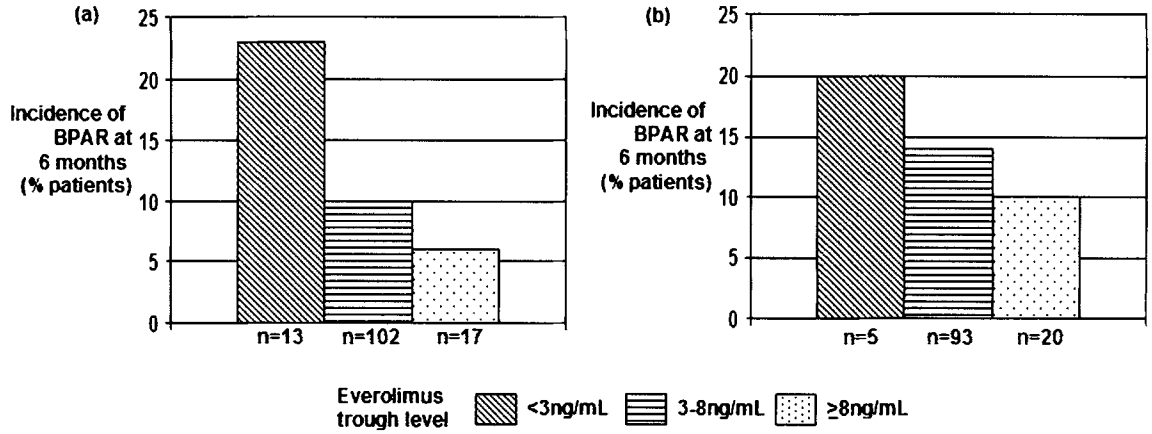

Fig. 3a, b Incidence of biopsy-proven acute rejection (*BPAR*) in de novo renal transplant patients, stratified according to trough blood level of everolimus at 6 months. The initial dose of everolimus was 1.5 or 3 mg/day, adjusted to maintain trough level > 3 ng/ml. All patients received low-exposure CsA microemulsion (C_2 monitoring) and corticosteroids, either (**a**) without basiliximab or (**b**) with basiliximab [41]

a parallel study which adopted a similar protocol but without an IL-2 receptor antagonist [29]. Nevertheless, the primary combined efficacy end-point of biopsy-proven acute rejection, graft loss, death or lost to follow-up was lower in the basiliximab-containing trial in patients receiving 1.5 mg/day everolimus: 15% compared to 28%. Mean creatinine levels were also lower in the basiliximab patients given 1.5 mg/day everolimus (137 μmol/l vs 147 μmol/l), which might be expected in view of the lower CsA exposure levels adopted.

The additional benefits observed with an IL-2 receptor antagonist in combination with reduced CNI exposure and an mTOR inhibitor may be explained by more than one factor: a reduction in calcineurin/calmodulin activity with a decrease in IL-2 production [35, 36]; complete blockade of the IL-2 receptor; and/or mTOR-inhibitor mediated blockade of non-IL-2 cytokine signals thought to become activated once the main IL-2 proliferation pathway becomes blocked, such as IL-15 and IL-7 [37], complementing the effect of the CNI and IL-2 receptor antagonist.

Therapeutic drug monitoring of mTOR inhibitors

Trough levels of everolimus have overlapped considerably in patients receiving either 1.5 mg/day or 3 mg/day with a full dose of CsA [38], indicating that drug absorption varies considerably between patients. In contrast, there was a significant ($P=0.03$) relationship between freedom from rejection and trough levels of sirolimus, ranging from 68% with trough levels up to 3.4 ng/ml to 91% above 8.7 ng/ml [39]. This relationship was confirmed in an analysis of patients receiving everolimus in combination with reduced-dose, C_2-monitored CsA, with or without an IL-2 receptor antagonist [40], which showed that biopsy-proven rejection was less common in patients with everolimus trough levels of 3–8 ng/ml than in those below 3 ng/ml (Fig. 3).

CNI elimination with mTOR inhibitors in chronic CNI-related nephrotoxicity

Elimination or minimization of CNI exposure is of particular interest in patients experiencing chronic CNI-related nephrotoxicity. Ensuring that the patient is not overexposed to CNI inhibitor is an appropriate first step; but if nephrotoxicity persists, a change in regimen is probably needed. Early evidence suggests that switching to an mTOR inhibitor may be effective. A study on 59 renal transplant patients with biopsy-confirmed signs of CNI-related toxicity in whom sirolimus was initiated (target trough level 8–12 ng/ml) and the dose of CsA or tacrolimus reduced by 50% and then withdrawn entirely over the next 1 to 2 months, showed that renal function stabilized or improved in 27 patients (46%) over the following 12 months [41]. The authors proposed that low proteinuria may be a useful marker to identify which patients with chronic nephrotoxicity might benefit from CNI withdrawal.

Conclusion

No single immunosuppressive regimen is optimal for all renal transplant patients, and use of an mTOR inhibitor with elimination of CNI during the maintenance phase is only one option that should be considered on an individual basis. Based on current evidence, it is not justified to routinely eliminate CNIs from an mTOR inhibitor-based regimen after the first few months after transplantation. For the majority of patients, it would seem reasonable to ensure that CNI exposure is not excessive [42] and to monitor for signs of CNI-related toxicity that

could indicate the need to further reduce exposure. However, in those patients for whom chronic CNI toxicity (particularly nephrotoxicity) does not resolve with appropriate dose reduction, reducing the target level of exposure to the CNI with concomitant addition of an mTOR inhibitor would seem a reasonable strategy. The data available currently suggest that patients may benefit from the synergistic actions of a CNI and mTOR inhibitor, combining effective prevention of rejection with a good safety profile. Withdrawal of CNI therapy could then be considered if the new regimen does not appear to resolve the decline in graft function, if this appears necessary to avert graft loss. This should be approached with particular caution in patients who have experienced a severe rejection episode, for whom it seems likely that a CNI will be required indefinitely.

The difficulty facing the clinician is that there is currently no effective way of identifying in advance patients with a predilection to CNI-induced toxicity and who will not respond to dose optimisation. In the future, research into genetic polymorphisms for immunologic and physiologic reactions to drugs will hopefully allow us to predict responses prior to initiation of immunosuppressive therapy.

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