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# Combination of a Calcineurin Inhibitor and a Mammalian Target of Rapamycin Inhibitor: Not So Nephrotoxic As We Thought?

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## Abstract

***Early experimental studies demonstrated that the combination of calcineurin inhibitors and mammalian target of rapamycin inhibitors is potentially nephrotoxic. After almost 20 years of clinical experience using this drug combination, no one would argue that this is also true in clinical transplantation. The complex synergistic drug interaction between calcineurin inhibitors and mammalian target of rapamycin inhibitors is still not completely known and has limited the clinical use of this combination. Several uncertainties still exist regarding the influence of calcineurin inhibitor and mammalian target of rapamycin inhibitor combinations on the recovery from ischemia/reperfusion injury, on the level and stability of allograft function, and on the incidence and severity of proteinuria. Furthermore, it is also not known whether these effects can be mitigated by changing dosing strategies.***

***Recent clinical data suggest that, compared to standard calcineurin inhibitor blood concentrations combined with mycophenolate, a reduction of 50-80% in calcineurin inhibitor blood concentrations in combination with mammalian target of rapamycin inhibitors can produce a comparable incidence of delayed graft function, renal function, and proteinuria. The evidences also indicate that levels of allograft function appear to be more related to calcineurin inhibitor blood concentration, while the incidence and magnitude of proteinuria appear to be associated with mammalian target of rapamycin inhibitor blood concentrations.***

***Because calcineurin inhibitors are still the most effective drugs to suppress alloreactive memory/effector T-cells and have synergistic effects when combined with mammalian target of rapamycin inhibitors, this drug combination may be used in a broader kidney transplant population compared to calcineurin inhibitor avoidance or withdrawal strategies, which are mostly used in low-risk patients. Nevertheless, long-term trials comparing calcineurin inhibitors (reduced blood concentrations) and mammalian target of rapamycin inhibitors, with early conversion from calcineurin inhibitors to mammalian target of rapamycin inhibitors and an***

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***adequate current control regimen, are warranted to further explore the safety and tolerability as well as the impact of these regimens on the rate of decline in renal function, histology, and patient and graft survivals.*** **(Trends in Transplant. 2011;5:49-56)**

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**Key words**

***Calcineurin inhibitor. Mammalian target of rapamycin inhibitor. Cyclosporine. Tacrolimus. Sirolimus. Everolimus. Nephrotoxicity.***

# Introduction

In 1991 Whiting, et al. showed in rats that concomitant treatment of sirolimus (SRL) and cyclosporine (CsA) for 14 days exacerbated CsA-induced reduction in creatinine clearance and N-acetyl-β-D-glucosaminidase enzymuria. Clearance of $^{51}$Cr ethylenediamine tetra acetic acid was not affected by SRL treatment alone, but was reduced by 28% in animals treated with CsA and by 61% in those animals treated with CsA and SRL. The magnitude of those changes already suggested a synergistic effect[1]. In 1996, Andoh, et al. examined the chronic effects of 28 days of treatment with CsA and SRL on renal structure and function in a rat model of chronic CsA nephropathy. Sirolimus at a subtherapeutic dose worsened glucose metabolism and potentiated chronic nephrotoxicity induced by CsA. The conclusion was that the synergistic effects of the combination of CsA and SRL could be potentially nephrotoxic and that clinical combinations of CsA and SRL should be tested carefully for chronic nephrotoxicity[2].

At that time it was not known whether these and many more experimental findings could be extrapolated to clinical settings. In fact, initial trials in humans were unable to capture this synergistic nephrotoxic effect. Doses of SRL up to 6 mg/m$^2$ for 14 days did not influence the glomerular filtration rate (GFR) of stable kidney transplant patients receiving cyclosporine and steroids[3]. Nevertheless, four large, open-label, prospective and controlled phase III trials in *de novo* kidney transplant recipients demonstrated that administration of SRL or everolimus (EVR) in combination with standard doses of CsA resulted in inferior allograft function compared to CsA in combination with placebo[4], azathioprine[5] or mycophenolate[6,7]. Interestingly, in these studies it was not possible to detect significant differences in CsA blood concentration comparing those patients receiving or not mammalian target of rapamycin inhibitors (mTORi). Soon after, SRL was combined with tacrolimus (TAC), even though these two drugs share the same intracellular binding protein, FKBP12[8]. While this drug combination was effective for the prevention of acute rejection, similar nephrotoxic effects were observed when SRL was combined with CsA[9-11]. After more than 15 years of clinical experience using calcineurin inhibitors (CNI) in combination with mTORi, no one would argue that this drug combination is potentially nephrotoxic when used in organ transplant recipients[12]. The question is whether we can mitigate this effect by changing dosing strategies.

The use of CNI may lead to a variety of acute and chronic histological changes, which are not drug specific and usually very difficult to distinguish from other causes of injury[13]. The complex synergistic drug interaction between CNI and mTORi is still not completely known and this has limited the clinical use of

this drug combination. It is believed that pharmacokinetic and pharmacodynamic interactions are involved and that the major effect is observed in the tissue compartment rather than in the blood[13,14]. At the biochemical level, CNI toxicity is believed to be due to drug-induced mitochondrial dysfunction, with mTORi enhancing the negative effects of CNI on cell energy metabolism[15].

There are at least three potential nephrotoxic clinical events under investigation in *de novo* kidney transplant recipients receiving CNI and mTORi immunosuppressive regimens. Several uncertainties still exist regarding the influence of CNI and mTORi combinations on recovery from ischemia/reperfusion injury, on the level and stability of allograft function, and on the incidence and severity of proteinuria.

## Recovery from ischemia/ reperfusion injury

The use of mTORi immediately after kidney transplantation has been limited by data indicating that the antiproliferative effects of these immunosuppressive agents may delay recovery from ischemia/reperfusion injury and proper wound healing. In animal models, recovery from renal ischemia/reperfusion injury may be aggravated by the antiproliferative effect of mTORi on renal tubular cells[16]. Reports from single-center studies indicate that SRL is associated with an increased incidence and/or duration of delayed graft function, but contrasting results have been observed in multicenter randomized clinical trials[17]. In a recent multicenter prospective study the incidence of delayed graft function in patients receiving EVR (0.75 or 1.5 mg twice daily) combined with reduced CsA concentrations was similar to that observed in those patients receiving enteric-coated mycophenolate sodium (10.2 vs. 10.4 vs. 9.2%) combined with standard CsA trough blood concentrations, respectively[18]. Furthermore, in a prospective kidney transplant study including patients at higher risk of developing delayed graft function who were receiving CsA, corticosteroids, and IL-2 receptor antagonist antibody induction, a similar low rate of delayed graft function was observed comparing patients with immediate (day 1) or delayed (six weeks) introduction of EVR (24.6 vs. 24.3%). Additionally, the incidence of slow graft function (38.5 and 47.2%; NS), the rate of recovery of renal function and the achieved GFR at three months (52.7 ± 20.4 vs. 48.8 ± 19.6 ml/min/1.73 $m^2$) were not different comparing patients with immediate or delayed introduction of EVR[19].

## Prevention and preservation of allograft function

Several clinical trials have investigated the combination of mTORi with empirical reductions in the doses or concentrations of CNI. Not surprisingly, while maintaining the efficacy for the prevention of acute rejection, these drug combinations were associated with preserved renal function. Dose/concentration reductions ranging from 50 to 80% have been investigated and all were associated with improved renal function and maintained efficacy.

## Combination of calcineurin inhibitor and sirolimus

In a single-center study, 408 renal recipients treated *de novo* with CsA and SRL received high (> 5; n = 91), medium (2.5-5.0) or low (< 2.5 mg/kg/day; n = 192) CsA doses together with induction antibody among 5% (high dose), 48% (medium dose) and 68% (low dose) of subjects, respectively. Mean CsA $C_2$ blood concentrations were 725, 400, and 306 ng/ml. Mean SRL trough blood concentrations were kept between 10-15 ng/ml during the early phase and between 8-12 ng/ml

during maintenance treatment. There were no differences in the incidence of acute rejection, graft loss, or death. Mean four-year GFR by modification of diet in renal disease (MDRD) formula were 48.4, 54.1, and 64.8 ml/min/1.73 $m^2$ ($p = 0.002$). Significant GFR predictors were CsA dose ($p = 0.015$) and younger donor age ($p < 0.001$). The authors concluded that 80% reduction in *de novo* CsA blood concentration with antibody induction improved renal function at four years compared with 50 or 66% reductions[20].

In another prospective study, 150 kidney transplants recipients were randomized to receive TAC/SRL (n = 50), TAC/MMF (n = 50), or CsA/SRL (n = 50). There were no differences in mean TAC trough blood concentration at one (8.60 ± 0.59 vs. 7.67 ± 0.41 ng/ml) and three (7.33 ± 0.52 vs. 6.25 ± 0.43 ng/ml) years comparing patients receiving mycophenolate mofetil (MMF) or SRL. Mean CsA trough blood concentrations were 162.1 ± 8.7 and 134.9 ± 7.5 ng/ml at one and three years. Mean SRL concentrations ranged from 5-8 ng/ml in all groups during the three-year follow up. At three years there were no differences in patient (90 vs. 92 vs. 96%) or graft (82 vs. 88 vs. 88%) survival. Patients receiving TAC/MMF tended to show lower incidence of biopsy-confirmed acute rejection (26 vs. 10 vs. 20%; $p = 0.07$). Mean Cockroft-Gault calculated creatinine clearance was statistically higher among patients receiving TAC/MMF compared only to CsA/SRL (72.8 ± 4.3 vs. 72.1 ± 4.1 vs. 61.8 ± 3.8 ml/min; $p = 0.04$)[21]. Although TAC concentrations were sufficiently low to preserve allograft function in patients receiving SRL compared to MMF, this was not the case in the CsA group where relatively high trough blood concentrations, according to current knowledge, were observed at up to three years of follow-up.

In a prospective, multicenter, open-label study, 207 kidney transplant recipients receiving CsA/SRL and prednisone were randomized to undergo CsA minimization or elimination beginning at week 13 after transplantation. At 12 months, there were no differences in renal function (61.08 vs. 65.24 ml/min; $p = 0.132$), incidence of biopsy-confirmed acute rejection (14.3 vs. 22.5%; $p = 0.152$), and patient (89.5 vs. 92.2%; $p = 0.632$) or graft (87.6 vs. 88.2%; $p = 0.999$) survival comparing both groups. A caveat to this study was that enrollment did not reach the anticipated sample size of 280 patients required to detect differences in renal function at one year[22].

A single-center retrospective study examined the outcomes of 518 consecutive first renal transplants treated with TAC/SRL (n = 307) or TAC/MMF (n = 211) with prednisone. Outcomes were analyzed by era of transplant (2000-2002 vs. 2003-2006) where, in most recent cohorts, elimination of the SRL loading dose and reduction in TAC target trough blood concentrations were implemented. Comparable graft and patient survival between TAC/SRL and TAC/MMF were observed in the most recent cohorts (2003-2006), confirmed following multivariable analysis controlling for donor and recipient factors. Although a decreased in mean TAC trough blood concentrations was observed comparing 2000-2002 to 2003-2006 cohorts of patients receiving SRL (9.1 vs. 6.7 ng/ml), there were no differences in TAC trough blood concentrations comparing patients receiving SRL or MMF in the 2003-2006 cohorts (6.7 vs. 6.8 ng/ml). This is perhaps the reason that a lower one-year GFR (57.6 vs. 63.1 ml/min; $p = 0.008$) was still noted in the TAC/SRL cohort[23].

## Combination of calcineurin inhibitor and everolimus

Several studies have been investigating the use of EVR in combination with CsA[24-26]. First attempts were to define the ideal concentrations of CsA in combination with EVR. More recently, more attention has been given also to the ideal therapeutic concentration of EVR.

A recent study compared the use of EVR 0.75 mg twice daily targeting EVR trough blood concentration between 3-8 ng/ml, and 1.5 mg twice daily targeting EVR trough blood concentration between 6-12 ng/ml combined with progressive reduction in CsA blood concentration. These two regimens were compared to a control arm where patients received 720 mg twice daily of mycophenolate sodium (MPS) in combination with doses of CsA to maintain standard trough blood concentrations. Patients also received basiliximab and corticosteroids. At 12 months, a lower proportion of patients were still receiving EVR compared to MPS (70 vs. 65.9 vs. 78.3%). The most frequent reason for drug discontinuation was an adverse event (18.1 vs. 20.4 vs. 9.4%). Mean EVR concentrations were 5.4 ± 2.2 and 7.8 ± 3.1 ng/ml, respectively. Mean CsA concentrations were 60% lower in patients receiving EVR compared to MPS (55 ± 39 vs. 49 ± 26 vs. 136 ± 55 ng/ml). Both regimens containing EVR were non-inferior to MPS regimens for the composite efficacy failure primary endpoint (25.3 vs. 21.9 vs. 24.2%, respectively). There were also no differences in the incidence of first treated biopsy confirmed acute rejection rate (16.2 vs. 13.3 vs. 17%). Mean calculated GFR (MDRD) with last-observation-carried-forward analyses was non-inferior in EVR groups compared to MPS (54.6 vs. 51.3 vs. 52.2 ml/min/1.73 $m^2$)[18]. Between month 12 and 24, the proportions of patients discontinuing EVR or MPS were similar (4.3 vs. 5.0 vs. 5.4%), mostly due to adverse events. At month 24 there were still no differences in the incidence of the composite primary endpoint (27.1 vs. 21.5 vs. 25.3%), in the incidence of first treated biopsy confirmed acute rejection (17.3 vs. 13.6 vs. 18.1%), the rates of graft loss (5.8 vs. 6.1 vs. 4.0%) or death (3.2 vs. 3.6 vs. 2.9%). Mean EVR trough blood concentrations were 5.8 ± 2.5 and 8.0 ± 3.7 ng/ml, respectively. Mean CsA trough blood concentrations were still 60% lower in patients receiving EVR compared to MPS (52 ± 51 vs. 50.3 ± 42 vs. 135 ± 64 ng/ml). Mean calculated GFR (MDRD) with last-observation-carried-forward analyses was still non-inferior in EVR groups compared to MPS (56.7 ± 20.5 vs. 54.2 ± 18.9 vs. 53.8 ± 20.7 ml/min/1.73 $m^2$)[27].

Two studies investigated the use of EVR in combination with TAC. The first exploratory study compared the use of standard (8-11 ng/ml) and reduced (4-7 ng/ml) TAC trough blood concentrations in combination with EVR (0.75 mg twice daily) adjusted to obtain EVR trough blood concentrations between 3-12 ng/ml. All patients received basiliximab induction and steroids. At six months, mean EVR (5.2 ± 2.2 vs. 5.2 ± 2.3 ng/ml) and TAC (7.1 ± 5.3 vs. 7.2 ± 2.5 ng/ml) trough blood concentrations were not different in both groups. There were no differences in the incidence of biopsy confirmed acute rejection (14% in both groups) or in renal function (75.3 ± 16.6 vs. 72.5 ± 15.2 ml/min using the Nankivell formula)[28].

To investigate the potential benefit of further reductions in TAC exposure, a 12-month, prospective, multicenter study was conducted. In this study, patients received basiliximab induction, EVR 1.5 mg twice daily adjusted to maintain trough blood concentrations between 3-8 ng/ml, and low-dose TAC adjusted to maintain trough blood concentrations between 4-7 ng/ml. At three months, patients were randomized to undergo (very low TAC) or not (low TAC) further reduction in TAC dose to maintain trough blood concentrations between 1.5-3 ng/ml. At 12 months, mean TAC trough blood concentrations were 3.4 ± 1.4 and 5.5 ± 2.0 ng/ml and mean EVR blood concentrations were 5.5 ± 2.7 and 5.8 ± 2.6 ng/ml. Unexpectedly, the incidence of biopsy proven acute rejection was higher in the very low TAC group during the first three months (18.7 vs. 7.7%; p = 0.0138) where TAC trough blood concentrations were comparable between the two groups. Between four and 12 months, both groups showed similar incidence of biopsy proven

acute rejection (2.7 vs. 1.1%, respectively; p = 0.165). A slightly superior renal function was achieved in patients of the very low TAC group (57.1 ± 19.5 vs. 51.7 ± 20 ml/min/1.73m$^2$ using the MDRD formula)[29].

Although these studies indicate that the combination of EVR and reduced TAC trough blood concentrations is effective and associated with preserved and stable renal function, the lack of an active and adequate comparator group, perhaps using low-exposure TAC and MMF/MPS, and long-term follow-up, preclude any robust risk/benefit evaluation at this point.

## Development of proteinuria

Recent studies have shown that in patients receiving CNI and mTORi combination, the incidence and magnitude of proteinuria is associated with blood concentrations of mTORi. The inhibitors of mTOR may alter the behavior and integrity of glomerular podocytes. The use of these drugs immediately after kidney transplantation or as a conversion strategy decreased the expression of nephrin within glomeruli, a critical component of the glomerular slit-diaphragm, and increased proteinuria in some but not all patients. This effect was not observed in biopsies from control transplant patients not treated with mTOR inhibitors. Whether there is a direct correlation between mTOR concentrations, decreased expression of nephrin, and proteinuria is not known[30]. Compared with a CsA-based immunosuppression regimen, a SRL-based regimen is associated with *de novo* low-grade glomerular proteinuria, increased excretion of markers associated with tubular damage, and evidence of tubular damage on kidney biopsy[31].

The incidence of proteinuria in patients receiving EVR 0.75 mg or 1.5 mg twice daily and reduced CsA blood concentration was compared with that observed in patients receiving 720 mg twice daily of mycophenolate sodium and standard CsA trough blood concentrations. At 12 months, the mean urinary protein:creatinine ratio was higher in the high-EVR concentration group (35.6 ± 66.3 vs. 61.4 ± 165.2 vs. 31.1 ± 68.7 mg/g). A higher proportion of patients receiving EVR showed sub-nephrotic or nephrotic range proteinuria (≥ 300 mg/g) compared to MPS (25.6 vs. 28.1 vs. 14.7%)[18]. At 24 months, the mean urinary protein:creatinine ratio was higher in EVR groups (43.8 ± 73.5 vs. 47.4 ± 82.4 vs. 20.3 ± 27.2 mg/g)[27]. In the study where EVR was combined with low or very low dose of TAC trough blood concentrations, no differences in mean urinary protein concentrations were observed (0.24 vs. 0.27 g/l, respectively)[29].

## Summary, limitations and future directions

The accumulated clinical data suggests that by adjusting the doses of CNI and mTORi we may be able to mitigate the risk of nephrotoxicity associated with this regimen, namely, delayed recovery from ischemia/reperfusion injury, level of allograft function, and incidence and severity of proteinuria.

There are still many aspects that need to be further explored. First, does the fact that patients receiving CNI and mTORi show similar renal function to those receiving CNI and mycophenolate during the first years after kidney transplantation mean that the CNI and mTORi combination is not so nephrotoxic? Second, is the evolution of renal function stable over time in patients receiving mTORi and reduced CNI concentrations? Third, because CNI blood concentrations in these patients are very low, could these patients be withdrawn from CNI? These questions are perhaps more difficult to answer at this point, mainly due to the lack of prospective long-term comparative studies.

Comparative studies thus far have been able to produce short-term (1-3 years) similar renal function comparing patients receiving MMF or mTORi. The rate of renal function decline and the severity of tissue lesions have decreased with the use of more recent immunosuppressive strategies[32,33]. There are no prospective studies, however, evaluating long-term renal function decline with modern use of CNI combined with mTORi or mycophenolate.

The currently used CNI blood concentrations in patients receiving mTORi raise concerns on whether these low concentrations are in fact therapeutic. Data from several clinical trials, however, indicate that CNI withdrawal in patients receiving mTORi has been associated with a higher incidence of rejection compared to those maintained on both drugs, especially in patients with higher immunological risk[34,35]. Because CNI still are the most effective drugs to suppress alloreactive memory/effector T-cells[36] and have synergistic effects combined with mTORi, this drug combination may be used in a broader kidney transplant population. Avoiding or withdrawing CNI, although associated with improvement in renal function, is limited to a relatively small cohort of low-risk patients, is often associated with an increased risk of rejection and graft failure, and even more often, with a high rate of side effects, perhaps due to overlapping adverse reactions of MMF and SRL in the absence of the CNI[37]. Long-term trials comparing CNI (reduced blood concentrations) and mTORi with early conversion from CNI to mTORi are warranted.

Finally, the evidences indicate that the incidence and magnitude of proteinuria in *de novo* kidney transplant recipients appear to be associated with mTORi blood concentrations. More understanding of the pathophysiology of this relationship and of the natural history of proteinuria and its impact on in long-term renal function, structure, and graft survival is necessary to assure the potential long-term benefits of this immunosuppressive regimen.

## Disclosure

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