Corticosteroid and calcineurin inhibitor sparing regimens in kidney transplantation

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Corticosteroids and the nephrotoxicity of calcineurin inhibitors (CNIs) may increase recipients’ morbidity and mortality in the long run. The purpose of the current report is to review emerging data on corticosteroid and CNI sparing modalities and to identify deficiencies in the available evidence.

ABSTRACT

Corticosteroids are a cornerstone of immunosuppressive regimens. Chronic corticosteroid therapy, however, is complicated by hyperglycemia, osteoporosis, exacerbation of hypertension, impaired wound healing and cataracts. Improvements in short-term allograft survival have created an impetus to reduce steroid exposure. The approach used by most centers is to give high-dose corticosteroids intraoperatively followed by a taper in the ensuing months, with indefinite continuation of low-dose prednisone. An alternative is to withdraw corticosteroids at a specified time post-transplant or avoid their use altogether. The major randomized controlled trials (RCTs) in this area have predominantly focused on the timing of withdrawal.

INTRODUCTION

In the past three decades, the field of kidney transplantation has seen significant advances in early graft and patient survival. However, the adverse metabolic profile from chronic use of corticosteroids and the nephrotoxicity of calcineurin inhibitors (CNIs) may increase recipients’ morbidity and mortality in the long run. The purpose of the current report is to review emerging data on corticosteroid and CNI sparing modalities and to identify deficiencies in the available evidence.
Withdrawal of corticosteroids months after transplantation was examined in an RCT in which patients on therapy with cyclosporine, mycophenolate mofetil (MMF) and prednisone were randomized at 3 months post-transplant to taper corticosteroids over 8 weeks or continue prednisone at 10 mg/day [1]. Patients in the corticosteroid withdrawal group had a significantly higher rate of biopsy-proven acute rejection (BPAR), prompting cessation of patient enrollment after 266 patients had entered the study. The Kaplan–Meier estimate of cumulative incidence of BPAR at 1 year was 4.9% in the maintenance arm and 22.4% in the withdrawal group (P = 0.001). There was no difference in graft loss or patient survival at 1 year of follow-up. Patients in the withdrawal group had significantly lower total cholesterol and a decreased need for antihypertensive medications at 6 months.

The strategy of corticosteroid withdrawal 3–6 months after transplantation was further evaluated in a meta-analysis which pooled 1519 patients from six trials [2]. The follow-up period ranged from 3 to 24 months. There was no difference in mortality or allograft loss, but acute rejection occurred more frequently in the corticosteroid withdrawal group (RR = 2.28; P < 0.001). This association held true regardless of whether tacrolimus or cyclosporine was used. Cholesterol was significantly lower in the withdrawal group, but other metabolic effects were not assessed.

The availability of potent induction agents has raised the question of whether very early corticosteroid withdrawal or avoidance is a feasible strategy. In a trial of corticosteroid avoidance, 551 transplant patients on a regimen of tacrolimus and MMF were randomized to daclizumab induction with corticosteroid avoidance or a standard continuous corticosteroid regimen [3]. At 6 months of follow-up, there was no difference in mortality, allograft loss or acute rejection. New-onset diabetes occurred significantly more often in the group receiving corticosteroids (5.4%) than in the corticosteroid avoidance arm (0.4%). Furthermore, the mean cholesterol increased and the bone density decreased significantly in patients assigned to receive corticosteroids.

In the most rigorous trial evaluating early corticosteroid withdrawal, 397 patients receiving antibody induction therapy, tacrolimus, MMF and initial corticosteroid therapy were randomized at Day 7 to receive chronic corticosteroid therapy tapered to 5 mg/day over 6 months or placebo (no corticosteroids) [4]. At 5 years, there was no difference in mortality, graft survival or graft function. Acute rejection occurred more commonly in the placebo group, while the group receiving chronic corticosteroids had significantly greater weight gain and insulin use. Interestingly, biopsies done for allograft dysfunction demonstrated higher rates of chronic allograft nephropathy in the placebo group (9.9 versus 4.1%, P = 0.008), suggesting that there may be a long-term benefit of chronic low-dose corticosteroid therapy in preventing chronic allograft nephropathy.

The strategy of corticosteroid avoidance has also been evaluated in the pediatric population, where growth retardation is an additional consequence of long-term corticosteroids. In a multicenter RCT, 131 children (age 0–21) were randomized in a 1:1 fashion to a corticosteroid-based regimen with standard daclizumab induction or complete corticosteroid avoidance with extended daclizumab therapy for 6 months post-transplant [5]. Patients in both groups were treated with tacrolimus and MMF in a similar fashion. At 3 years of follow-up, there was no difference in mortality, acute rejection or allograft loss between the groups. Linear growth was similar in both arms, but in the subgroup aged <5 years linear growth was significantly greater in the corticosteroid avoidance arm. Furthermore, blood pressure and cholesterol were significantly higher in patients assigned to the standard corticosteroid regimen.

A recent meta-analysis compared avoidance or early withdrawal with standard chronic corticosteroid therapy from a pooled analysis of 1934 patients from nine RCTs [6]. With the exception of one trial, all patients received induction therapy. Among patients treated with avoidance or early withdrawal, there was an increase in the incidence of acute rejection with cyclosporine use, but not when tacrolimus was the maintenance CNI. Diabetes was more frequent in the chronic corticosteroid group only when cyclosporine was used. There were no differences in graft loss, mortality, cholesterol or blood pressure.

Taken together, the evidence suggests that there is an increase in the incidence of acute rejection regardless of whether corticosteroids are avoided, or withdrawn days to months after transplantation. The episodes of rejection are predominantly Banff grade 1 and have not been conclusively demonstrated to result in graft loss or worsened kidney function. However, most trials have a follow-up duration of only 6–12 months. The 5-year study by Woodle et al. [4] showed that despite an increased rate of acute rejection with corticosteroid withdrawal, there was no downstream increase in allograft loss or attenuation in the estimated glomerular filtration rate (eGFR).

RCTs have also demonstrated clear benefits associated with corticosteroid withdrawal, including decreased need for antihypertensive medications, improved glycemic control and decreased cholesterol. Due to the short duration of follow-up, it is unclear whether these metabolic improvements will lead to improved long-term outcomes. The question has also been raised whether the low maintenance doses of corticosteroids used in transplant regimens have clinically significant effects. Current evidence is not sufficient to clearly inform whether the potential deleterious effects of acute rejection or the adverse metabolic effects of chronic corticosteroid therapy are more detrimental to the kidney transplant patient over the long-term.

Belatacept is a second-generation cytotoxic T lymphocyte associated antigen 4 (CTLA-4) immunoglobulin, which blocks the co-stimulatory pathway of T-cell activation. This fusion protein consists of a modified extracellular domain of CTLA-4 and the constant-region fragment (Fc) domain of human IgG1 [7]. Belatacept binds avidly to its ligands, CD80 and CD86, on the surface of antigen-presenting cells (APCs), blocking Signal 2 in the T-cell activation pathway (Figure 1A and B) [8]. Other effects include impairment of signaling
pathways and cytokine production, culminating in decreased T-cell activation and proliferation and promotion of T-cell apoptosis [9].

Belatacept has been promoted as a CNI-sparing agent because of its apparent lack of nephrotoxicity and seemingly benign metabolic profile. As a result, there is some interest in

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using this intravenous product as a de novo maintenance immunosuppressive agent. The supportive evidence, as reviewed below, comes from non-inferiority trials of relatively short duration and small sample size [10, 11].

Vincenti et al. [10] reported the results of a multicenter randomized, Phase II study comparing belatacept versus cyclosporine with the primary outcome of acute rejection at 6 months. The study population consisted of 173 kidney transplant recipients, 90% of whom were considered to be at low immunologic risk, and all participants received induction therapy, MMF and corticosteroids. The study groups included a more intensive belatacept group, less intensive belatacept group and a cyclosporine-treated group. The intensive belatacept regimen consisted of a longer duration of administration and more frequent dosing (Table 1). Belatacept was non-inferior at preventing acute rejection at 6 months, with rejection occurring in 7, 6 and 8% in the more intensive belatacept, less intensive belatacept and cyclosporine groups, respectively. There were no episodes of acute rejection from 6 to 12 months in any group. Both belatacept groups showed a higher directly measured and eGFR than the cyclosporine group. The cyclosporine-treated patients demonstrated an increased incidence of chronic allograft nephropathy; 44 compared with 29% for the more intensive belatacept group and 20% for the less intensive belatacept group. A 5-year efficacy and safety study was continued with 128 self-selected recipients. At the end of follow-up, belatacept continued to preserve the eGFR up to 5 years, although it resulted in more episodes of BPAR [10].

The BENEFIT (Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial) is a 3-year, Phase III study that assessed 666 standard criteria kidney transplant recipients treated with a more intensive or less intensive belatacept-based therapy versus cyclosporine [12]. At 12 months, both belatacept regimens were non-inferior to cyclosporine when comparing death or graft loss. Fewer patients in the belatacept groups had renal impairment (measured GFR <60 mL/min/1.73 m² or a decrease in measured GFR ≥10 mL/min/1.73 m²) compared with the cyclosporine arm (55 and 54 versus 78%; P ≤ 0.001 more intensive or less intensive belatacept versus cyclosporine). The incidence of chronic allograft nephropathy was also lower in both belatacept arms compared with the cyclosporine arm (18 and 24 versus 32%). However, the incidence of BPAR was increased in the belatacept groups compared with cyclosporine-treated patients (22 and 17 versus 7%), and the more

### Table 1. Immunosuppressive regimens in belatacept trials

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**Immunosuppressive regimens in kidney transplantation**
intensive belatacept group was considered inferior to cyclosporine. Belatacept-treated patients had more BANF IIB rejections, especially in the more intensive group. Despite these findings, follow-up data from 3 years [13] reported similar graft survival across the groups, and the mean eGFR at 3 years was significantly higher in the belatacept arms compared with the cyclosporine-treated group. Thus, the BENEFIT trial showed that compared with the cyclosporine arm, belatacept-treated patients had more frequent and more severe episodes of acute rejection, but at 3 years their eGFR was more preserved. Importantly, the more intensive arm was inferior to cyclosporine.

The BENEFIT-EXT study is a 3-year counterpart Phase III study of BENEFIT, including 595 expanded criteria donors and high immunologic risk patients [11]. When evaluated for the composite end point of patient and graft survival, the belatacept groups were not inferior compared with cyclosporine. Patients receiving cyclosporine developed renal impairment (84.8%) more frequently than those treated with belatacept (more intensive belatacept, 70.5%; less intensive belatacept, 76.5%). The prevalence of biopsy-proven chronic allograft nephropathy was similar between groups. Acute rejection was comparable in all arms, and the non-inferiority criteria were met. As in BENEFIT, there were more episodes of BANF IIB rejection in the more intensive belatacept group. Follow-up data showed that the proportion of patients surviving with a functioning graft at 3 years was similar between groups, but the eGFR was lower in the cyclosporine arm compared with the belatacept arms [14].

The sum of this evidence suggests that lower intensity belatacept treatment is equivalent to cyclosporine for de novo immunosuppression in low- and high-risk immunologic patients for rates of survival and acute rejection, while seemingly superior in preserving kidney function.

Metabolic factors were also evaluated in these studies. Post-transplant diabetes was significantly more common in the cyclosporine-treated patients compared with those receiving belatacept [10, 11], although other studies did not obtain similar findings [12, 15, 16]. Blood pressure was slightly lower in the belatacept groups according to a pooled safety profile [17]. The primary safety risk for belatacept-based therapies is post-transplant lymphoproliferative disorder, especially affecting the central nervous system, with the highest risk reported in patients who are Epstein-Barr virus negative at baseline.

MAMMALIAN TARGET OF RAPAMYCIN INHIBITORS

Inhibitors of the mammalian target of rapamycin (mTORI), sirolimus and everolimus, also have been promoted as CNI-sparing agents. Like tacrolimus, mTORI engage the intracellular immunophillin FK binding protein 12, but the receptor-ligand complex subsequently binds and inhibits mTOR, a serine/threonine kinase involved in the regulation of cell growth and metabolism (Figure 2A and B). Below, we review the evidence for two main strategies for mTORI use in kidney transplantation: (i) as de novo therapy; and (ii) as a substitution during CNI withdrawal months to years after transplantation.

Early studies using mTORI as de novo therapy were promising. In the first pilot study addressing this approach, 83 patients were randomized to receive sirolimus or cyclosporine, with both groups receiving azathioprine (AZA) and corticosteroids [18]. At 12 months, eGFR was significantly higher in the sirolimus arm, with no difference in mortality, acute rejection or allograft loss. In a similar trial published the following year, 78 patients were randomized to receive cyclosporine or sirolimus along with MMF and corticosteroids [19]. Again, at 12 months the eGFR was superior in patients receiving sirolimus, with no difference in mortality or allograft outcomes. Subsequent studies, however, have raised concerns that sirolimus may be inferior to CNIs in terms of allograft and patient survival.

In the ELITE-Symphony study, 1645 kidney allograft recipients were randomized to receive corticosteroids and one of four de novo regimens: standard dose cyclosporine and MMF; low-dose cyclosporine and MMF with daclizumab induction; low-dose tacrolimus and MMF with daclizumab induction; low-dose sirolimus and MMF with daclizumab induction [20]. At 12 months, the eGFR was highest in the low-dose tacrolimus arm and lowest in the sirolimus arm. Acute rejection was significantly more common in the sirolimus group compared with all other groups, with the largest difference between the sirolimus and tacrolimus arms (35.3 versus 11.3%; P < 0.001). Furthermore, allograft survival was lowest in patients receiving sirolimus, especially compared with patients receiving tacrolimus.

The increased rate of acute rejection associated with de novo use of mTORI was also evident in the ORION study [21]. In this trial, 443 kidney allograft recipients were assigned to one of three groups: sirolimus plus tacrolimus, with tacrolimus discontinuation at 13 weeks; sirolimus plus MMF and tacrolimus plus MMF. The study sponsor removed patients receiving de novo sirolimus from assigned therapy due to a high rate of BPAR within the first 6 months (25.7% in Group 2 versus 6.5% in Group 3; P < 0.001). Corroborating evidence comes from a recent meta-analysis of 2688 patients from 16 RCTs comparing mTORI with CNI-based regimens for initial immunosuppression. The use of an mTORI as de novo therapy was associated with an increased rate of death-censored graft failure (OR 1.59; P = 0.009) [22].

In a recent large UNOS-based observational study of 139 370 kidney transplant patients, de novo use of mTORI was associated with increased allograft loss and mortality throughout 8 years of longitudinal follow-up (Figure 3) [23]. The higher incidence of allograft loss is not entirely unexpected, given the increased rate of acute rejection seen with mTORI in the aforementioned RCTs, and the known association of acute rejection with allograft loss [24]. Interestingly, mortality did not correlate with acute rejection, suggesting a mechanism independent of effect on allograft function. This phenomenon was also observed in a prior observational investigation of Hungarian allograft recipients, in which mTORIs were associated with increased mortality, but not
worse allograft outcomes [25]. It is possible that alternative pleiotropic effects of mTORI, including a propensity for hyperlipidemia, led to increased mortality. Further studies are needed to firmly establish this association and the responsible mechanism. A final concern with using mTORI as de novo therapy is its effect on wound healing. In an RCT, sirolimus was associated with a significantly higher rate of post-operative wound complications than tacrolimus [26].

A second approach used in an attempt to improve allograft outcomes is the initiation of an mTORI during CNI
withdrawal. The goal of this strategy is to obtain the benefits of early CNI-based immunosuppression, while foregoing chronic CNI nephrotoxicity. This approach was first addressed in the CONVERT trial, in which patients initiated on an initial CNI-based regimen (along with prednisone and either MMF or AZA) within the last 6–120 months were randomized to exchange the CNI for sirolimus, or continue their current regimen [27]. Patients were prospectively stratified into two groups based on the eGFR: eGFR 20–40 mL/min versus >40 mL/min. Enrollment in the group with an eGFR of 20–40 mL/min was halted early after 8 of 48 patients in the sirolimus arm and 0 of 25 patients in the CNI arm reached the primary safety outcome of BPAR, graft loss or death. In the group with an eGFR of >40 mL/min, there was no difference in eGFR, acute rejection or mortality in the intention to treat analysis. Proteinuria increased significantly in the sirolimus arm, a phenomenon that has been described in other investigations [28]. These findings suggest that mTORIs may not be safe in patients with poor baseline kidney function and in those with significant proteinuria.

Proponents of a CNI withdrawal strategy hypothesized that in the CONVERT trial, substitution of mTORI for CNI occurred after too much allograft dysfunction had accrued for any benefit to be appreciated. This led to a number of trials investigating earlier conversion. In the Spare the Nephron study, kidney transplant recipients started on a CNI-based regimen within the preceding 30–180 days were randomized to continue their current regimen or exchange...
the CNI for sirolimus [29]. At 1 year, the mean percentage change in directly measured GFR was greater in the sirolimus arm (24.4 versus 5.2%; P = 0.054), but this benefit was no longer evident at 2 years. There was no difference in mortality, allograft loss or acute rejection.

The ORION study included an arm in which patients were initiated on both sirolimus and tacrolimus, with tacrolimus discontinuation at 13 weeks. Compared with the group on a standard CNI-based regimen, there was no difference in eGFR, mortality or allograft loss. Of note, significantly more adverse events leading to withdrawal of therapy occurred in patients receiving sirolimus. The ZEUS study assessed the efficacy of exchanging a CNI for everolimus at 4 to 5 months after receipt of an allograft [30]. At 12 months post-transplantation, there was a statistically significant difference in the mean eGFR of 9.8 mL/min/1.73 m² in favor of everolimus. Notably, there was a significantly increased rate of BPAR in the CNI arm prior to randomization. After randomization, BPAR occurred more often in the everolimus arm (10 versus 3%; P = 0.04).

The evidence suggests that in patients without markedly compromised kidney function or proteinuria, conversion from a CNI to an mTORI may preserve GFR to a small degree, but offers no definitive benefit on the hard outcomes of mortality or allograft loss. It should be noted that in each trial discussed, adverse events leading to discontinuation of therapy were more common in patients receiving sirolimus. Given the short follow-up time in these studies, the aforementioned concern of increased mortality with long-term mTORI therapy remains relevant.

The mTORIs are attractive options in certain patients because of their antineoplastic properties [31]. In a recent RCT, 120 kidney transplant patients with a prior history of post-transplant cutaneous squamous cell carcinoma on a CNI were randomized to continue their current regimen or substitute sirolimus for the CNI [32]. Over 2 years of follow-up, patients receiving sirolimus had a significant delay in the median time to recurrent squamous cell carcinoma (7 versus 15 months; P = 0.02). A large multivariate analysis suggested that the use of mTORI are also associated with a decreased rate of non-cutaneous malignancy [33]. These findings have not been seen in all studies, however, with a large retrospective cohort study demonstrating a significantly increased risk of post-transplant lymphoproliferative disorders associated with mTORI use [34].

Finally, whereas CNIs are most commonly associated with hypertension, tremor, insulin resistance and gastrointestinal complaints, mTORIs can cause anemia, thrombocytopenia, leukopenia, hyperlipidemia, interstitial pneumonitis, proteinuria and poor wound healing.

**CONCLUSION**

Despite marked advances in kidney transplantation, current immunosuppressive regimens continue to jeopardize long-term allograft and patient survival. Corticosteroid withdrawal protocols promise to be an attractive option given the improved metabolic profile reported with their use. Indeed, some transplant centers in the USA have adopted corticosteroid-sparing or minimizing approaches, though many US centers continue to use low-dose corticosteroids indefinitely [35]. However, it remains uncertain whether achieved benefits in improved blood pressure, cholesterol, glycemia and bone density will surpass potential detrimental effects from increased acute rejection.

CNI nephrotoxicity has stimulated an ongoing search for alternate immunosuppressive agents to enhance allograft and patient longevity. mTORIs were proposed as a possible substitution, but the evidence suggests their use for de novo immunosuppression increases the risk for acute rejection, allograft failure and death. As a result, the use of these agents in the immediate post-transplant setting has diminished [23]. mTORIs are still used as a possible replacement for CNIs in patients with decreased GFR secondary to CNI nephrotoxicity, though the evidence in support of this approach remains unconvincing. In contrast, in patients with recurrent cutaneous squamous cell carcinoma, the use of mTORI has been proven to be beneficial.

Another promising approach to combat CNI nephrotoxicity has been suggested in small short-term studies of belatacept, which showed that this agent is non-inferior to cyclosporine for de novo use in stable patients. Nevertheless, the role for belatacept in kidney transplantation requires further study.

In sum, we continue to face a great deal of uncertainty concerning the optimal evidence-proven strategy for long-term immunosuppression after kidney transplantation. RCTs of larger size and longer duration are needed to fill this gap. The use of large observational studies could also be helpful when RCTs are not available.

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**CONFLICT OF INTEREST STATEMENT**

None declared.

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