Minimizing Immunosuppression, an Alternative Approach to Reducing Side Effects: Objectives and Interim Result

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Exceptionally low acute rejection rates and excellent graft survival can be achieved with cyclosporine and tacrolimus (CNI)-based immunosuppressive protocols that incorporate antiproliferative immunosuppressants and corticosteroids. However, despite short-term success, long-term attrition of graft function and side effects of immunosuppressive agents continue to be significant problems, leaving clinicians looking for possible interventions. CNI nephrotoxicity is but one of numerous factors that may contribute to long-term damage in transplant kidneys. Metabolic, cosmetic, and neuropsychiatric complications of steroids affect quality of life after transplantation. Newer immunosuppressive agents such as mycophenolate mofetil and sirolimus (Rapa) have raised the possibility of withdrawing or avoiding CNIs or steroids altogether. In this report we review studies that address either CNI or steroid minimization strategies and discuss their risks versus benefits. Given the accumulated experience to date, in our opinion the use of CNIs and steroids as part of immunosuppressive regimens remains the proven standard of care for renal transplant patients. The long-term safety and efficacy of CNI and steroid minimization strategies needs to be further validated in controlled clinical trials with adequate long-term follow-up.


Renal transplantation, currently the established treatment of choice for individuals with end-stage renal disease, does not merely enhance the quality of life but actually confers a significant survival advantage over dialysis (1). Most notable among the many factors that contributed to the preeminence of renal transplantation as the established clinical modality in the management of end-stage renal disease is the low rate of acute rejection routinely observed with modern immunosuppressive regimens. In recent years, clinical focus has shifted from a primary emphasis on prevention of acute rejection early after transplantation to the durable maintenance of long-term graft survival and mitigation of side effects associated with immunosuppressive regimens. Unfortunately, however, despite the attainment of excellent short-term graft survival and low acute rejection rates, equivalent improvements in long-term graft survival have not occurred (2).

Immunosuppressants used in organ transplantation may exhibit organ-specific and/or systemic toxicities (3). Among the many agents in current use, calcineurin inhibitors (CNI) (cyclosporine (CsA) and tacrolimus (TAC)) and corticosteroids are commonly indicted culprits in the causation of many clinically relevant undesired side effects that occur despite successful transplantation. In an effort to minimize or avoid these toxicities, attention has been directed toward avoiding, withdrawing or minimizing exposure to corticosteroids and CNIs.

In this report we review the rationale for the development of corticosteroid and CNI avoidance, minimization, or withdrawal in renal transplantation. Key studies that have used various approaches to achieve these ends are summarized and discussed.

Achieving Balance between Efficacy and Toxicity

Shortly after the introduction of CsA in 1984, both acute and chronic toxic effects attributable to CsA became increasingly apparent. The acute toxicities of CNIs include hypertension, renal dysfunction, and neurological disturbances such as tremors and seizures (4,5). Whereas the pathological lesions of CNI toxicity are well described, CsA acts directly on the renal vasculature producing afferent arteriolar constriction, which may manifest clinically as reversible concentration dependent fluctuations in glomerular perfusion and consequently rise serum creatinine levels, a phenomenon not necessarily a manifestation of irreversible nephrotoxicity (4).

CNI have also been implicated in the pathogenesis of posttransplant diabetes mellitus, hypertension, hyperlipidemia, and cosmetic stigmata (6,7). Although the CNIs have often been discussed as a class, differences between CsA and TAC became evident shortly after the introduction of TAC in the mid 1990s. Whereas hypertension, hyperlipidemia, and cosmetic side effects such as hirsutism are more common with CsA, impaired glucose tolerance, neurotoxicity, and alopecia are more common with TAC. Some clinicians also feel that TAC may exhibit less nephrotoxicity; supporting this opinion are studies where pathological evidence of decreased fibrogenicity were noted with TAC (8,9). However, such evidence remains controversial as other studies have not reported any differences in profibrogenic effects of CsA and TAC at either the renal or molecular level, and the effects of adjunctive therapies cannot be separated easily from the primary effects of CsA or TAC (8,10).

Nankivell et al. demonstrated anatomic lesions (vasculopathy,
interstitial fibrosis, glomerulosclerosis), which they attributed to CNI effects in serial protocol biopsies of kidney allografts (6). These lesions increased in prevalence over time in the lifespan of an allograft (6). However, lesions of vascular sclerosis, interstitial fibrosis, and importantly in this observational series, the cumulative incidence of subclinical rejection were significantly greater in patients on CsA and azathioprine (AZA) compared with those on TAC and mycophenolate mofetil (MMF) (8). The fact that immunological factors remain important in the pathogenesis of the attrition of renal allograft function over time is illustrated in a recent study of protocol biopsies in TAC- and MMF-treated renal transplant recipients in whom the occurrence of rejection and low TAC exposure were independent risk factors for the development of chronic pathological lesions in allografts (11). Thus the exact and exclusive contribution of CNI alone to the development of chronic pathological lesions in the renal allograft, and, more relevantly, their role as predominant contributors to failure of the renal allograft over time is not necessarily as unequivocal as has been portrayed.

Corticosteroids have been an integral component of immunosuppressive regimens in renal transplantation for >50 yr. Corticosteroids are associated with myriad complications. These include the development of obesity, hypertension, glucose intolerance, hyperlipidemia, osteoporosis, avascular necrosis, impaired linear growth (children), glaucoma, cataracts, myopathy, Cushingoid habitus, and neuropsychiatric complications after transplantation (3). These complications of steroid therapy can be devastating in their adverse impact on the quality of life after transplantation. There is thus a desire both in patients and transplant physicians to explore strategies to avoid or minimize the complications of steroid therapy. The fact that avoiding steroids in renal transplantation is making greater inroads into the mainstream of routine clinical practice is underscored by the fact that 23 percent of first renal transplants in 2004 were discharged after transplantation without steroids as opposed to 5 percent in 2000 (12).

In recent years, strategies aimed at minimizing, eliminating, or avoiding exposure to corticosteroids and CNI involve the use of regimens that incorporate more potent modern immunosuppressants such as MMF and sirolimus. When elimination, avoidance, or minimization of either CNI or corticosteroids is attempted, the potential risk of side effects of these agents should be balanced against the ever-present risk of acute rejection (13,14). The concerns regarding acute rejection assume particular importance in high-risk populations such as black patients and sensitized recipients.

Rationale Underlying Steroid and CNI Withdrawal/Avoidance Regimens
In most steroid minimization regimens, to maintain immunological efficacy, treatment with an antiproliferative agent and a CNI is maintained after stoppage of corticosteroids to provide sufficient rejection prophylaxis. Likewise, CNI withdrawal/ avoidance regimens continue steroids and one or more antiproliferative agents after elimination of the CNI. Antibody induction has also been used to minimize rejection risk in both steroid and CNI withdrawal/avoidance and will be discussed along with the individual studies.

MMF, an antiproliferative agent when used with CNI and corticosteroids, affords excellent protection from acute rejection with no accompanying intrinsic nephrotoxicity (15,16). In combination with a CNI, MMF is associated with a decreased relative risk of graft failure independent of its effects on acute rejection as opposed to AZA (17). MMF also provides significant protection against long-term deterioration of renal allograft function and prophylaxis against late rejection [mt]1 yr after transplantation (16,18). Notably, leucopenia, anemia, and gastrointestinal side effects are common with MMF (19). However, MMF is devoid of any intrinsic nephrotoxic, diabetogenic, hyperlipidemic, or hypertensive effects (20). Given the salutary effects of MMF on acute rejection, it is a reasonable expectation that MMF could potentially permit minimization or withdrawal of CNIs or steroids and thereby ameliorate or avoid the nephrotoxic effects of CNI.

The second class of antiproliferatives that have been used to attempt CNI or steroid withdrawal/avoidance are inhibitors of mammalian targets of rapamycin (sirolimus (Rapa) and everolimus), which block proliferation signals provided by T cell growth factors to T cells (21). For a brief period of time, Rapa was used in combination with CNIs, initially CsA and then TAC. The synergistic immunosuppression provided by the CsA/Rapa combination afforded superior acute-rejection prophylaxis compared with the then standard regimen of CsA, AZA, and corticosteroids (22). The storied benefits of mammalian target of rapamycin inhibitors were many and included the ability of sirolimus (Rapa) to inhibit smooth muscle proliferation, inhibit antibody synthesis, and promote tolerant immune responses (23). Rapa has also been shown to be tolerogenic in experimental models (24). However, to date, these benefits remain largely speculative.

In early studies serum creatinine levels were higher in CsA/ Rapa/prednisone-treated patients compared with those on CsA/AZA/prednisone, findings attributed at that time to the effects of full dose CsA (25). Subsequently, in both prospective clinical trials and retrospective analyses, Rapa in combination with CNIs has been associated with inferior graft survival and renal function compared with CsA or TAC with MMF and corticosteroids in kidney transplantation likely due to the potentiation of CNI nephrotoxicity by Rapa (21,26–30). Thus, focus has shifted to investigating the use of Rapa with other immunosuppressive agents such as MMF and/or corticosteroids with the ultimate aim of withdrawing or avoiding CNIs altogether in transplantation (27–29,31).

Clinical Experience: Corticosteroid Withdrawal and Avoidance
Corticosteroid Withdraw
The introduction of cyclosporine in the 1980s prompted numerous studies that examined effects of steroid withdrawal in stable renal transplant recipients (32–34). Beneficial impact of steroid withdrawal was noted on BP, glycemic control, and lipid profiles in some of these studies (35–37). An immediate penalty of acute rejection was incurred (33,34). However, a
deleterious impact of steroid withdrawal on short-term graft survival was not always observed, which may partly be a function of both limited follow-up and small numbers of patients enrolled in these studies. Most of these studies also examined steroid withdrawal in predominantly white subjects (33,34). In the largest randomized trial that examined steroid withdrawal with >5 yr of follow-up in CsA-treated patients, Sinclair noted that deleterious impact of steroid withdrawal on graft survival was noted only after >5 yr of follow-up. This study did have some limitations with regard to widespread applicability of the data because cyclosporine monotherapy was used with patients whose steroids were withdrawn as well as the fact that the deleterious effects of steroid withdrawal primarily occurred in subjects with cadaveric transplants or those with repeat transplants (38).

The high incidence of acute rejection with steroid withdrawal in the context of CsA-based triple therapy with AZA is a recurring theme that detracted from overall enthusiasm for widespread application of this strategy. The introduction of MMF in the mid-1990s was associated with a halving of then prevalent acute rejection rates. This reduction of acute rejection with MMF spawned renewed interest in steroid withdrawal. Initial studies of steroid withdrawal from regimens containing CsA and MMF observed a significant increase in acute rejection with steroid withdrawal despite the use of CsA with MMF with acceptable 1-yr graft survival. These small studies reported follow-up of ≤1 yr, and antibody induction therapy was not applied uniformly (39,40).

In a large, European, multicenter trial, a total of 500 recipients were randomized to either a standard steroid regimen or a low-dose steroid regimen followed by steroid withdrawal at 3 mo posttransplant. The 1-yr biopsy-proven acute rejection rate was 25% with steroid withdrawal versus 15% in the standard steroid group (P < 0.001). However, most of the rejection episodes had predated the steroid withdrawal, making comparisons between the intervention and control arms rather difficult. One-year graft survival rates were not different between the two arms; again, this is a probable reflection of relative short follow-up. Systolic and diastolic BP, triglycerides, cholesterol, and bone mineralization were all favorably affected by steroid withdrawal (41). Ahsan et al. reported a multicenter, randomized, double-blind, placebo-controlled study of corticosteroid withdrawal in subjects on CsA, MMF, and prednisone (42). This study planned a total enrollment of 500 subjects. Despite the use of MMF, the overall, cumulative, biopsy-proven, 1-yr acute rejection incidence was 22.4% with steroid withdrawal (versus 4.9% percent in the group on steroid maintenance; P = 0.0007). However, no detrimental effects were noted on 1-yr graft survival. The cumulative incidence of rejection or treatment failure within 1 yr posttransplant was significantly higher in blacks (39.8%) versus non-blacks (16.0%) (P < 0.001) regardless of assigned treatment group; the overall enrollment of blacks, however, was only 16% of the total. The relative hazard (withdrawal of steroids versus maintenance) for acute rejection was 2.0 for non-blacks and 7.0 for blacks (42). Because of the fivefold increase in acute rejection rates with steroid withdrawal in this study, the study was halted early when only 266 patients were enrolled. It should be noted that this study, in contrast to the European multicenter trial, included only subjects that did not have any episodes of rejection in the first 3 months posttransplant; thus, inference of a temporal association between steroid withdrawal and rejection becomes plausible (42). Both of the multicenter trials summarized above did not employ antibody induction. In contrast, in a single-center, uncontrolled, European study of 34 consecutive patients, Budde et al. noted that with CsA/MMF maintenance, steroids could be withdrawn after the first year without any rejection episodes in 1 yr of follow-up (43). Whether their results reflect the effect of inadequate follow-up and relative racial homogeneity is unclear, and the absence of a control group limits our ability to draw any more inferences about the safety and efficacy of the regimen used (43).

Lauaad et al. (44) reported long-term outcomes in 223 consecutive renal transplant recipients treated at a MMF or AZA and corticosteroids. Steroids were stopped within 1 yr (range: 3 to 11.7 mo) after transplantation. The 15-yr actuarial graft survival was 83.9%. In multivariate analysis, young recipients (age < 35 yr) and those not on MMF were at significantly higher risk for graft loss. These findings do fit into the overall theme of rejection risk after steroid withdrawal in that young recipients with vigorous immune responses would mount a significant alloimmune response and that the greater immunological efficacy of MMF could be expected to provide protection from acute rejection after steroid withdrawal. Such findings are also of more than passing interest in that the case for steroid withdrawal is often made in a more compelling manner in the younger patient in the interest of preserving normal skeletal growth.

**Steroid Withdrawal in Blacks**

Hricik et al. conducted an uncontrolled prospective study in 30 black kidney transplant recipients whose steroid therapy was withdrawn between 3 and 5 mo after transplantation (45). Maintenance immunosuppression after steroid withdrawal consisted of TAC and sirolimus (Rapa); antibody induction therapy was not used. Patients were deemed eligible for steroid withdrawal from the third month posttransplant onward if they had no prior episode of biopsy-proven acute rejection. Patients were excluded from steroid withdrawal for renal insufficiency, recent significant increase in creatinine, or significant proteinuria. After a mean follow-up of 14 ± 7 mo, biopsy-proven acute rejection occurred in only 2 of 30 patients after the withdrawal of steroids (45). Long-term outcomes of patients who were treated with this protocol were recently reported (46). In all, 47 black kidney transplant recipients were enrolled in an uncontrolled trial where they were treated with TAC, sirolimus, and corticosteroids without induction therapy. Outcomes were compared between the patients who underwent steroid withdrawal (n = 32) and those who were ineligible for steroid withdrawal (n = 15). Over a follow-up period averaging about 4 yr, 13 of 32 (41%) patients in the steroid withdrawal group experienced acute rejection and only 13 (41%) of the group remained free of steroids. The majority of rejection episodes were associated with noncompliance. Grant loss occurred
in 8 of 32 patients (25%) in the steroid withdrawal group and in 5 of 15 (33%) patients in the group not eligible for steroid withdrawal, a difference that does not approach statistical significance. With regard to allograft function, serum creatinine rose from 1.4 ± 0.41 mg/dl to 2.45 ± 1.7 mg/dl (P = 0.0004) in the steroid withdrawal group and from 2.1 ± 0.45 to 2.62 ± 1.2 mg/dl (P = NS) in the patients who did not undergo steroid withdrawal. Notably, in the 13 patients who remained steroid-free at the time of reporting, serum creatinine had risen from 1.28 ± 0.37 mg/dl before steroid withdrawal to 1.64 ± 0.54 mg/dl at the last-follow-up (46).

This study underscores the negative impact of acute rejection and/or noncompliance on long-term graft function in blacks undergoing steroid withdrawal. That graft function worsened over time even in those patients who had no acute rejection episodes is a definite cause for concern. These results are probably even more significant considering that the comparator to steroid withdrawal in this study comprised subjects deemed ineligible for steroid withdrawal on the basis of criteria that arguably could themselves pose risk for graft loss. Furthermore, given what we now know of the synergistic nephrotoxicity of the TAC-Rapa combination, it is quite possible that the deterioration of graft function in patients remaining free of steroids could well reflect the toxicity of the regimen per se.

Given the lackluster experience with steroid withdrawal in renal transplantation, steroid withdrawal is now being gradually supplanted by regimens that eliminate corticosteroids within the first week posttransplantation. These regimens are collectively referred to as steroid minimization or avoidance regimens, and some investigators have used totally steroid-free regimens as well with success. The key elements of such regimens include antibody induction (antithymocyte globulin and/or IL-2 receptor antibody), triple therapy with corticosteroids, a CNI, and an antiproliferative agent such as Rapa or MMF followed by rapid withdrawal of steroids within the first week posttransplant. The underlying rationale is that the increased, up-front, immunological protection afforded by the antibody induction therapy will mitigate the potential increased rejection risk with rapid withdrawal of steroids.

Corticosteroid Avoidance

A number of studies have been conducted in North American centers in both adults and children and in patients with simultaneous kidney and pancreas transplant recipients who have reported short-term efficacy and safety of rapid withdrawal of corticosteroids after transplantation (47-56). Although excellent 1-yr graft and patient survivals have been reported in each of these studies, it is noteworthy that rejection rates are for the most part higher with steroid elimination versus controls on steroids.

Matas et al. (57) reported on the 5-yr follow-up of the prednisone-free regimen at their center. A total of 589 kidney transplant recipients at their institution were treated with their protocol, in which prednisone was discontinued by day 6. Intraoperative, prerulefusion, rabbit antithymocyte globulin was used as induction. Prednisone was discontinued by day 6 posttransplant and maintenance immunosuppression was either CsA and MMF or TAC and Rapa. This steroid avoidance cohort was compared with a historical cohort consisting of first and second living and deceased donor transplants treated with polyclonal antibody induction, CsA and AZA, or MMF along with maintenance doses of prednisone. At the time of reporting, only 27 recipients had accrued ≥5 yr of actual follow-up, and, accordingly, actuarial survival figures were reported. At 5 yr, actuarial graft survival was 84%, patient survival was 91%, death-censored graft survival was 92%, and acute and chronic rejection-free survival were 84% and 87%, respectively. Overall, 86% of the kidney recipients remained free of prednisone at the time of their report. The serum creatinine levels were remarkably stable, averaging 1.6 ± 0.6 mg/dl at 1-yr posttransplant and 1.7 ± 0.8 mg/dl at 5 yr posttransplant (P = NS). Some of the key limitations to this study that the authors acknowledged included the use of historic controls, actuarial 5-yr survival figures as opposed to actual 5-yr outcomes, and the lack of protocol biopsies to exclude the possibility of ongoing subclinical rejection despite the apparent stability of renal function. The population in this study was predominantly white and the majority receiving living donor kidneys. Thus, the overall propensity to risk of acute rejection was low in this study, and the historical control group did include some subjects on AZA from an era with higher baseline acute rejection rates. Although, in a subset of this study, Khwaja et al. (50) did report that this regimen could have applicability in higher-risk recipients such as blacks and sensitized recipients, the overall number of subjects (n = 79), particularly blacks (n = 6), was small and only 3-yr actuarial graft survival was reported.

Another significant clinical question that is open in the context of steroid avoidance protocols is whether those patients experiencing acute rejection when on a steroid avoidance regimen should receive maintenance steroids after an episode of acute rejection. Recently published data from the University of Minnesota experience certainly suggest that patients experiencing an episode of acute rejection may benefit both in terms of graft survival and prevention of a subsequent episode of acute rejection with the continuation of steroids after the first rejection episode (58).

Other single-center studies have noted that steroid withdrawal could be performed under induction therapy with either daclizumab or antithymocyte globulin in high-risk subjects including sensitized and black subjects (59,60). Although thymoglobulin significantly reduced acute rejection rates, 1-yr graft survival was reported at 88% and overall rejection rates approached 40%; both figures should arouse concern in the current era (59,60).

Kumar et al. reported a randomized controlled steroid avoidance trial where steroids were discontinued within 5 to 7 d posttransplantation or tapered to 5 mg/d by 1 mo posttransplantation in a group of 77 patients that included blacks (62%) and cadaveric kidney recipients (82%) receiving cyclosporine, MMF, and basiliximab induction (62). They reported excellent graft and patient survival with this protocol, with protocol biopsies up to 2 yr showing no increase in subclinical rejection, chronic allograft nephropathy, or interstitial fibrosis in the steroid avoidance group. Blacks were slightly more likely to ex-
hibit subclinical acute rejection, albeit not approaching statistical significance, and chronic allograft nephropathy was not noted more commonly in blacks. It is of interest that, in this study, the authors treated all episodes of subclinical rejection with pulse corticosteroids. There was a trend to greater degrees of glucose intolerance in the group receiving steroids. Interestingly, weight gain was identical between the steroid avoidance and steroid maintenance groups (62).

Kaufman et al. have examined the use of the TAC/Rapa and the TAC/MMF combination in steroid avoidance protocols for kidney and kidney/pancreas transplant recipients with either alemtuzumab or basiliximab induction (47,63,64). Woodle et al. noted in a multicenter pilot study of early steroid withdrawal in 77 low-risk kidney transplant recipients with TAC/Rapa and antithymocyte globulin induction that the 1-yr biopsy-proven acute rejection rate was 13% and presumptive acute rejection was 10.5% with 100% 1-yr graft and patient survival (56). In an uncontrolled, single-center study involving an inner city population with a high percentage of blacks, Haririan et al. report excellent short-term outcomes with early steroid withdrawal using antithymocyte globulin induction, TAC, and Rapa or MMF (65). Although excellent short-term safety in terms of acute rejection risk and graft survival has been reported as initial outcomes in such studies, as longer follow-up is accrued, it appears that a trend to greater attrition of kidney allograft survival exists with the TAC/Rapa combination (66). Whether this reflects the synergistic nephrotoxicity of the TAC/Rapa combination or the expression of ongoing smoldering rejection is unclear.

Woodle et al. recently reported 4-yr results from an ongoing, randomized, double-blind, placebo-controlled study comparing early corticosteroid elimination to chronic corticosteroid maintenance in renal transplant recipients (67). This study remains blinded to date with planned follow-up to 5 yr. In this study, corticosteroid withdrawal on day 7 (n = 191) is being compared with chronic steroid maintenance (n = 195). All patients received TAC and MMF for maintenance immunosuppression. Induction treatment was either rabbit antithymocyte globulin (used in more than two-thirds of recipients in both arms) or IL-2 receptor antibody. The primary end point was treatment failure, defined as a composite of death, graft loss, or severe acute rejection (requiring antibody treatment or Banff 97>2A) after transplant. At 4 yr, no significant differences were noted between the steroid cessation and steroid maintenance groups with regard to the primary end point (steroid maintenance, 12.3%; steroid cessation, 16.8%), death, or death-censored graft loss. A trend toward increased biopsy-proven acute rejection was evident (steroid maintenance, 10.8%; steroid cessation, 17.3%; P = 0.08). Importantly, severe rejection (>Banff 2A (Banff 97)) was present in 2.6% of steroid maintenance patients versus 5.8% in the steroid withdrawal group. Of particular concern, for cause biopsies obtained ≥1 mo posttransplant showed a significant increase (steroid maintenance 4.1%; steroid cessation, 8.9%; P = 0.03) in features of chronic allograft nephropathy (Banff 97). Systolic and diastolic BP were not significantly different between the two treatment groups. Importantly, mean weight gain was almost identical with an average of 7.8 kg in the steroid maintenance group and 7.6 kg in the steroid cessation group. Triglycerides declined significantly and HDL cholesterol was lower with steroid avoidance, although the difference was not statistically significant. The incidence of posttransplant diabetes requiring insulin was lower with steroid withdrawal (steroid maintenance, 11.3%; steroid cessation, 3.6%; P = 0.03). Bone disorders (avascular necrosis and fractures) were reduced by almost two thirds (steroid maintenance, 9.7%, steroid cessation, 3.7%; P = 0.02) (67).

These results are somewhat sobering in that some of the major anticipated benefits of steroid avoidance include mitigation of weight gain and hypertension after transplant. That there was no significant change in these clinically relevant end points and a rather concerning absolute increase in chronic allograft nephropathy of 4.8% is notable (67,68).

Steroid-Free Immunosuppression

Birkeland evaluated the use of a steroid-free immunosuppressive protocol at their center in 100 consecutive first and second transplants performed at their institution between 1996 and 1999 (69). No corticosteroids were used, all patients received 10 d of induction with antithymocyte globulin, and maintenance immunosuppression consisted of CsA and MMF. In up to 4.5 yr of reported follow-up, 4-yr graft survival was 82% and the overall acute rejection rate was 13%. All rejection episodes responded to corticosteroids and the majority of acute rejections occurred early (<3 mo) in the posttransplant period. These results are impressive, but it does need to be kept in mind that they are derived from a relatively homogeneous, largely white population without a control group, and results could be expected to vary in populations at higher immunologic risk (69).

Rostaing et al. studied 538 renal transplant recipients in a multicenter, open-label, parallel group study in which patients were randomized 1:1 to receive daclizumab induction, tacrolimus and MMF, or TAC, MMF, and steroids (70). The primary end point was biopsy-proven acute rejection at 6 mo. The incidence of acute rejection was 16.5% in both groups. Graft and patient survival were identical between the two groups. Steroid-free immunosuppression was also associated with a significant decrease in the incidence of new-onset diabetes requiring insulin treatment. However, promising as these results are, it would be premature to extrapolate these excellent short-term results as harbingers of long-term safety or efficacy (70).

A more recent example of corticosteroid-free immunosuppression is provided by the FREEDOM trial, which had its 1-yr results reported in 2006 (71). In this prospective, multicenter, open-label trial that lasted 12 mo, de novo adult renal transplant recipients were randomized 1:1 to receive daclizumab induction, tacrolimus and MMF, or TAC, MMF, and steroids (70). The primary end point was biopsy-proven acute rejection at 6 mo. The incidence of acute rejection was 16.5% in both groups. Graft and patient survival were identical between the two groups. Steroid-free immunosuppression was also associated with a significant decrease in the incidence of new-onset diabetes requiring insulin treatment. However, promising as these results are, it would be premature to extrapolate these excellent short-term results as harbingers of long-term safety or efficacy (70).
12-mo GFR values were comparable across all groups (no steroids, 64 mL/min; rapid discontinuation, 62.6 mL/min; standard steroids, 63.4 mL/min). However, biopsy-proven acute rejections occurred in 31.5% of patients in the no-steroid group versus 14.7% in the standard steroid group (P = 0.0004). Rejections were also more frequent in the rapid steroid withdrawal group at 26.4% (P = 0.046 versus standard steroids). The principal appeal of this study lies in the fact that rapid discontinuation of steroids was compared with steroid-free immunosuppression and standard-dose steroids in the same trial. However, although the GFR values and graft and patient survival were similar across all groups at month 12, the two-fold increase in acute rejections is rather sobering and certainly long-term follow-up needs to be accrued before this strategy can be widely recommended.

Steroid Minimization: Discussion
The main impetus to do away with or minimize the use of corticosteroids in transplantation stems from the desire to forestall or mitigate the many complications associated with corticosteroids. These complications, as alluded to earlier, can be disabling in their impact on the quality of life and functional status of the kidney transplant recipient and by no means can be dismissed as trivial. Steroid withdrawal has gone through several permutations, and the advent of newer immunosuppressive medications and regimens has seen renewed attempts at steroid withdrawal, all coming to similar conclusions of a higher postwithdrawal acute rejection rate and, in some studies where long enough follow-up was available, worse graft survival as well. Subsequently researchers found renewed enthusiasm in steroid-sparing protocols based on the idea that early rapid withdrawal might have a different impact on acute rejection. In fact, it has been postulated that the mechanistic explanation underlying the increased rejection risk with steroid withdrawal may stem from upregulation of chemokine receptors that accompanies the decreased chemokine synthesis mediated by steroids (68). Thus, withdrawal of steroids may increase the synthesis of chemokines in the setting of upregulated chemokine receptors that accompanies the decreased chemokine synthesis mediated by steroids (68). Thus, withdrawal of steroids may increase the synthesis of chemokines in the setting of upregulated chemokine receptor expression, thereby triggering acute rejection. Looking at the sum of clinical data accumulated with rapid steroid elimination, it does not look like this theoretical advantage has translated into a resolution of the higher risk of rejection that goes with the steroid-free regimens. The best evidence thus far comes from the double-blind rapid steroid elimination trial where doubled acute rejection rates at 3 yr posttransplant were noted (67). This study, reported by Woodle, documented excellent renal function and excellent graft survival in both the study group and the control arm, but one certainly would question how much follow-up would be needed to see a difference in these parameters in this low-risk population. In fact, at 4 yr there was a significant increase in CAN in the steroid-free group (67). So, overall the early steroid withdrawal data looks very similar to late steroid withdrawal with the only difference being in the timing of the increased rejection rates in the steroid-free arms. The best evidence for the merits and potential risks of early steroid withdrawal come from Woodle and from Matas et al. because of the extensive follow-up of 4 yr and 5 yr, respectively (67,72). Paradoxically, the excellent results of these studies are also their principal drawback because much longer follow-up might be needed to show safety in terms of graft and patient survival. The significance of long-term follow-up becomes even more relevant when one considers the results of the Canadian Multicenter Study of Steroid Withdrawal, in which changes in graft survival were not evident until 5 yr posttransplant. Steroids do have antiinflammatory effects, and thus it is quite possible that they may mitigate interstitial scarring in the long term. In that regard, one single-center study examining serial protocol biopsies does suggest that interstitial scarring may be more frequent with steroid avoidance (73).

Certainly, data from certain studies that explore steroid avoidance strategies in largely white patients does suggest the feasibility of this approach, but an increase rate of acute rejections can be anticipated with this approach with unknown long-term consequences. However, when it comes to long-term follow-up data in higher-risk populations such as blacks, the data are rather more sobering in terms of risk of attrition of renal function, late acute rejection, and graft loss. Studies that explore steroid withdrawal have demonstrated beneficial impact on posttransplant lipid profiles, BP, bone loss, fractures, diabetes, and avascular necrosis. On the other hand, in the largest trial comparing low-dose steroids (5 mg prednisone/d) with steroid avoidance in de novo renal transplant recipients on TAC/MMF maintenance therapy, there was no significant difference in weight gain or BP and only a marginal metabolic benefit when compared with the arguably low-dose steroid maintenance arm. This information is important when considering the risk–benefit profile of rapid steroid discontinuation protocols and because these are the side effects that drive patients to opt for and physicians to promote rapid steroid discontinuation (67).

CNI Withdrawal/Minimization
MMF-Based CNI Withdrawal in Patients with Stable Renal Function
Early studies of CsA withdrawal in regimens involving AZA and corticosteroids showed rather disappointing results with increased risk for acute rejection and uncertain effects on long-term graft survival (74,75). De novo use of MMF with corticosteroids with the view of avoiding CNIs has also provided disappointing results primarily as a result of unacceptably high acute rejection rates (76). These observations have been confirmed in a more recent study that studied MMF with corticosteroids in a CNI-free regimen with daclizumab induction. Despite the use of induction treatment and restriction of enrollment to HLA-DR–matched panel reactive antibody-negative first transplants, the rejection rates were unacceptably high at 70% (77).

In a prospective study, 64 renal transplant recipients with stable renal graft function on a maintenance CsA/prednisone regimen were randomized to conversion to either MMF or AZA and then underwent CsA withdrawal. The incidence of acute rejection was strikingly higher in patients randomized to AZA (AZA, 36.7%; MMF, 11.8%; P = 0.04) (40).
Several prospective controlled trials have subsequently investigated the impact of MMF regimens after CsA withdrawal. In a randomized multicenter trial involving 170 patients on CsA/steroid maintenance regimen with or without AZA at 12 to 30 mo posttransplant, MMF was added on for patients on dual therapy or MMF replaced AZA over a 3-mo run-in; patients on triple therapy with MMF/CsA/prednisone were directly randomized. Patients were randomized to one of two treatment arms: MMF/prednisone where CsA was tapered off, or MMF/CsA/prednisone (78). With CsA withdrawal, renal function improved and serum cholesterol levels decreased significantly. However, a moderate but statistically significant increase in acute rejection at 6 mo occurred in the CsA withdrawal group versus controls (10.6% versus 2.4%, respectively; \( P = 0.03 \)) (78). A total of 151 of these patients were then followed for an additional 4 yr; the 5-yr patient and graft survival rates were 93% and 88%, respectively, for the MMF group and 95% and 92%, respectively, for the CsA/MMF/prednisone group. Unfortunately, acute rejection episodes increased to 10% in the CsA withdrawal group versus 1% in the control group (\( P = 0.0029 \)). During follow-up, 7 MMF patients experienced acute rejection episodes compared with 1 CsA-MMF patient (\( P = 0.0283 \)). The rate of graft loss caused by acute rejection was significantly higher with the withdrawal of CsA (CsA withdrawal, 19%; CsA maintenance 5%; \( P = 0.01 \)) (79).

Recently, the Cyclosporine Avoidance Eliminates Serious Adverse Renal Toxicity (CAESAR) trial investigated the safety and efficacy of maintaining recipients on CsA for an abbreviated course (no longer than 6 mo) or in reduced doses with the primary aim of preserving renal function (78). In this 12-mo, prospective, randomized, open-label, multicenter, parallel group study, 536 recipients of first kidney transplants were randomized 1:1:1 to low-dose CsA/MMF/prednisone (target trough level of 50 to 100 mg/ml for 12 mo), standard-dose CsA (target trough level of 150 to 300 mg/ml up to month 4 and then 100 to 200 mg/ml thereafter)/MMF/prednisone, or CsA withdrawal (CsA taper starting at month 4 posttransplant and completed by month 6 posttransplant; remaining only on MMF and prednisone). Thus this study compared both CNI avoidance and a low-dose CNI strategy to standard CsA therapy. Patients in the low-dose CsA and CsA withdrawal arms received IL-2 receptor blockade (daclizumab) induction to provide protection against acute rejection. The primary end point was measured GFR at 12 mo. Each of the three regimens was well tolerated. Measured GFR at 12 mo was not statistically different among the three groups. However, biopsy-proven acute rejection rates were significantly higher in the CsA withdrawal group (38%) than in either the low-dose CsA (25.4%), or standard-dose CsA arms (27.5%) (\( P < 0.05 \)). With regard to rejections overall (clinically suspected, treated, or biopsy-proven), the proportion was significantly greater with CsA withdrawal (44.1%) versus low-dose CsA (30.1%) (odds ratio, 1.94; 95% CI, 1.23 to 3.06; \( P = 0.015 \)) and standard-dose CsA (34.7%) (odds ratio, 1.52; 95% CI, 0.96 to 2.39; \( P = 0.071 \)). The authors also noted that although the overall numbers were small, repeat episodes of acute rejection were more common in the CsA withdrawal arm (80). In post hoc analyses, calculated creatinine clearances were lower in rejec-

tors in all three treatment arms. With regard to other parameters of interest that could reflect the extrarenal toxicities of CsA, such as BP or hyperlipidemia, no significant differences were observed between the groups. The most fitting unifying explanation for these findings of the CAESAR study is that any potential advantage in terms of maintaining a better GFR through CsA elimination was likely annulled by the deleterious impact on allograft function of the higher rejection rate with CsA withdrawal.

Taken together, the studies summarized above underscore the cardinal limitation to CsA withdrawal in patients who have stable allograft function: Increased risk of acute rejection episodes (78,80). Because rejection episodes can adversely affect both the ambient level of graft function and long-term graft survival, extreme caution in patient selection and follow-up is advised when attempting these strategies (80).

**CsA Withdrawal in Patients with Deteriorating Graft Function**

Thus far, we have reviewed studies that focus on subjects with stable allograft function. However, because CNIs do have both acute and chronic deleterious effects on allograft function, which could either directly cause graft dysfunction or compound preexisting renal insufficiency, interventions directed on patients with deteriorating renal function are of more immediate clinical relevance. Also, the risk–benefit ratio changes when attempting CNI withdrawal in patients with deteriorating renal function versus stable patients. In patients with deteriorating renal function, graft failure might be imminent and any risk of the approach employed to attenuate the progressive loss of renal function is more acceptable when compared with a stable patient with an outlook of ≥10 yr of stable renal function.

Substitution of AZA with MMF and subsequent withdrawal of CsA in subjects with known deterioration of renal function or biopsy-proven chronic allograft nephropathy was accompanied by both improvement in renal function and minimal increase in acute rejection risk over a follow-up periods averaging 25 mo (81,82).

Weir et al. reported an observational cohort study where 105 renal transplant recipients with impaired kidney function (baseline creatinine of approximately 3 mg/dl or biopsy proven CAN) either had their CNI dose reduced or discontinued altogether while remaining on MMF and corticosteroids for maintenance immunosuppression (83). This protocol was applied on average 29 mo after transplantation and follow-up after initiation of the protocol varied between 41 and 75 mo. There were 24 graft failures (24 of 64; 37.5%) in the reduced CsA group, 9 in the reduced TAC group (9 of 28; 32%), and only one graft loss (1 of 13; 7.7%) in the CNI withdrawal group. The incidence of acute rejection did not differ significantly among the groups, occurring only in 6 out of the 105 patients, all of whom responded to pulse steroid therapy. These results are encouraging; however, based solely on these findings, a generalization of these results in attesting to the safety and efficacy of CNI withdrawal in all recipients with impaired graft function cannot be made because of the inevitable selection biases that could operate in any nonrandomized study (83).
In a randomized clinical trial reported by Dudley et al. (MMF Creeping Creatinine Study Group), 143 patients who had significant deterioration in renal function (by serial reciprocal values of serum creatinine) >6 mo posttransplantation were either maintained on their CsA-based immunosuppressive regimen or withdrawn from CsA and maintained on only MMF and corticosteroids (84). Significant improvement in renal function occurred in patients maintained only on MMF and prednisone compared with those continued on CsA. Most remarkably, acute rejection did not increase after withdrawal of CsA (84). This study suggests that, in renal transplant patients with worsening renal function, CsA withdrawal with the addition of MMF confers significantly better renal function and possibly improved graft survival compared with CsA maintenance therapy. In a smaller randomized trial reported by Suwelack et al. (85), MMF was used with or without CNI withdrawal in long-term renal transplant recipients who had biopsy-proven chronic allograft nephropathy, and progressive deterioration of renal function calculated creatinine clearance and BP measurements improved significantly in patients who underwent withdrawal of CsA or TAC compared with those that remained on CsA (or TAC)/MMF/prednisone. Notably, no acute rejections were noted for up to 35 wk of follow-up (85). The absence of acute rejection in this study could represent both small sample size and a relatively short follow-up period. Interestingly, in the reference study, reduction of CsA by 50% led to an increase in creatinine clearance by approximately 11% during 2 yr of investigation without an increase in biopsy-proven acute rejection, demonstrating that complete elimination of CsA is not always necessary to accrue beneficial impact on graft function. Whether the improved creatinine clearance with CsA dose reduction in this study was reflective of hemodynamic effects of CsA dose reduction is unclear. It should be noted that, in the CAESAR study, the continued maintenance of low-dose CsA protected against acute rejection and the Symphony study (see below) does suggest that renal function is superior with the Tac/MMF/steroid combination compared with the CsA/MMF/steroid combination (86,87).

In summary, MMF-based CNI-sparing studies in patients with chronic graft dysfunction show some potential for a beneficial impact on renal function and possibly delaying graft failure. Whether the improvement in renal function is solely reflective of the effects of CsA withdrawal versus the independent salutary effects of MMF is uncertain.

CNI Withdrawal with Rapa/Prednisone
In a phase II study and a subsequent, larger, phase III trial, renal transplant patients were randomized at 3 mo to discontinue CsA from their Rapa/CsA/prednisone regimen, which resulted in significantly better renal function at 6, 9, and 12 mo in the CNI withdrawal group (88). The largest randomized prospective study investigating this approach is the Rapamune Maintenance Regimen (RMR) trial, in which, at 3 mo posttransplant, patients were randomized from triple therapy with Rapa/CsA/corticosteroids to either continue that regimen unchanged or to a CsA withdrawal group with higher targeted SRL levels. Overall graft survival after 48 mo was significantly better in the Rapa/corticosteroid arm as compared with the triple therapy control arm, as was death with a functioning graft (84.2% (triple therapy) versus 91.5% (Rapa/prednisone); \( P = 0.024 \)) and death-censored graft survival (90.6% (triple therapy) versus 96.1% (Rapa/Prednisone); \( P = 0.026 \)). Also, the calculated GFR was significantly higher with the withdrawal of CsA (54.5 ml/min (triple therapy) versus 68.6 ml/min (Rapa/prednisone); \( P < 0.001 \)). The incidence of biopsy-proven acute rejection was similar in the CsA maintenance (6.5%) and withdrawal group (10.2%) (\( P = 0.223 \)). As one may expect, more acute rejections occurred in the CNI withdrawal group 3 to 6 mo into the study (89,90). Analysis of protocol biopsies at 36 mo revealed significantly lower chronic allograft damage index, tubular atrophy, and inflammation in the Rapa/corticosteroid group (91). However, as discussed earlier, it may take >4 yr of follow-up to get a true appreciation of the adverse impact of rejection episodes on long-term graft survival.

In summary, MMF-based CNI-sparing studies in patients with chronic graft dysfunction show some potential for a beneficial impact on renal function and possibly delaying graft failure. Whether the improvement in renal function is solely reflective of the effects of CsA withdrawal versus the independent salutary effects of MMF is uncertain.

CNI Withdrawal with Rapa/MMF/Prednisone
The ongoing Spare-The-Nephron Trial is investigating the substitution of a CNI with Rapa in stable renal transplant recipients on CNI, MMF, and prednisone. Of 340 recipients on MMF, CsA, or TAC and prednisone, 254 were randomized 30 to 180 d posttransplantation to discontinue their CNI and switch to an MMF/RAPA/prednisone regimen or to continue their current immunosuppressive regimen (CNI/MMF/prednisone). The primary end point of this trial is the percentage change in measured GFR 12 mo after randomization. In a preliminary report, iothalamate GFR values increased by approximately 20% from baseline in the MMF/RAPA group, whereas those remaining on MMF/CNI only exhibited a 4.4% increase (including individuals taking TAC) (94).

CNI Avoidance
CNI Avoidance with Rapa/MMF/Prednisone
A few clinical trials have explored the possibility of CNI avoidance in an attempt to altogether avoid potential toxic effects of CNIs. In these trials patients were randomized to receive either Rapa or CsA, in combination with AZA and steroids or MMF and steroids; follow-up was 2 yr. Calculated GFR values were
significantly higher in Rapa- versus CsA-treated patients (95–97). After these trials, other prospective trials have evaluated the outcome of Rapa/MMF/prednisone on graft survival with a view to mitigating immunological graft loss while avoiding CNI nephrotoxicity.

Flechner et al. (97) conducted a prospective study where 61 de novo renal transplant recipients receiving basiliximab for induction, MMF 2 g/d, and corticosteroids were randomized to either Rapa (n = 31) or CsA (n = 30). The primary goal of this study was to compare the efficacy of Rapa/MMF/prednisone with a CsA/MMF/prednisone regimen as reflected in the incidence of acute rejection rates and renal function over 1 yr. Patient and graft survival rates along with acute rejection incidence were not significantly different between the CsA- and Rapa-treated groups at both 6 and 12 mo (98). At 1 yr, the authors noted both lack of deterioration of renal function and less histological evidence for chronic renal injury by protocol biopsy in the Rapa/MMF/prednisone group with comparable acute rejection rates and excellent short-term allograft and patient survival (98,99).

More recently, Larson et al. conducted a prospective trial in which de novo renal transplant recipients were randomized to Rapa/MMF/prednisone (n = 81) or TAC/MMF/prednisone (n = 84); follow-up ranged from 13 to 47 mo (100). Graft function was comparable in the two groups at 1 and 2 yr. At the end of the study, protocol biopsies revealed no pathological difference in interstitial, tubular, or glomerular findings between the two groups; however, there existed a higher incidence of chronic vascular changes with the TAC group as compared with those on Rapa (43% versus 26%; P = 0.03). Also, minimal variations in renal function existed between the two groups. In fact, glomerular filtration decreased slightly over 1 yr in the TAC/MMF group, with a greater decline observed in the Rapa/MMF group. However, at 1 to 2 yr there was no significant difference in mean GFR between the two groups. Acute rejection rates were comparable (100). These results are encouraging; however, the trend toward nonimprovement of GFR at 1 yr in the Rapa/MMF group in this study is against the prevailing dogma that CNI-free immunosuppression is synonymous with improved renal function. Thus, it is difficult to forecast long-term impact of these short-term results on the continued maintenance of renal function in recipients on Rapa/MMF/prednisone.

At this juncture, it is worth contrasting the differences in renal function noted with the Rapa/MMF regimen by Larson et al. (99) with that reported by Flechner et al. (97) The CsA/MMF comparator in the study of Flechner et al. could well have tilted their results toward inferior renal function as studies do suggest that the CsA/MMF combination may be associated with slightly inferior allograft function compared with the TAC/MMF combination (101).

It should also be noted that each of the clinical trials alluded to above have limitations in terms of the number of patients enrolled and the accrued follow-up time. These constraints limit the widespread application of data from these studies to analyses directed at end points such as graft and patient survival, which demand a greater number of subjects to afford sufficient statistical power to detect small differences in graft and patient survival. In that regard, analysis of large transplant databases such as the Scientific Registry of Renal Transplant Recipients (SRTR) becomes relevant (102).

With a view to evaluate outcomes with Rapa/MMF in renal transplantation, a comparison of that regimen with other commonly used regimens in renal transplantation was performed using data reported to the SRTR database between 2000 and 2005. In deceased donor transplant recipients, Rapa/MMF versus TAC/MMF or CsA/MMF at 6 mo posttransplantation was associated with a significantly lower graft survival at 5 yr posttransplantation (64%, 78%, 78%, respectively). Rapa/MMF was associated with a 75% increased risk for patient death (adjusted hazard ratio = 1.75; 95% CI, 1.53 to 2.00; P < 0.01) relative to the TAC/MMF discharge regimen. Among both living and deceased donor transplants, 6-mo acute rejection rates were highest for individuals on the Rapa/MMF regimen (16.4% in living donor transplants and 15.8% in the deceased donor transplants) as compared with CsA or TAC/MMF and CsA or TAC/Rapa (approximately 10%) (30). Thus, the Rapa/MMF regimen, in the context of clinical practice, appeared to be associated with inferior outcomes compared with other commonly used maintenance regimens in kidney transplantation. The inferior graft survival noted in the Rapa/MMF group most likely reflects varying contributions of higher acute rejection rates and the overall poor tolerability of the regimen. Importantly, interpretation of the results of this retrospective study should necessarily be tempered by the following caveats (103). First, such data reflects the use of particular drug combinations in the relatively uncontrolled setting of clinical practice as opposed to a clinical trial conducted in a carefully predefined population. Second, bias in the selection of immunosuppressive agents and the exact reasons for regimen selection are not available in the database. For instance, it is entirely possible that higher-risk transplants selectively received Rapa/MMF or that this regimen was used preferentially for kidneys perceived to be at higher risk for nephrotoxic insults, such as kidneys from older or extended criteria donors. In that regard, multivariate statistical analysis does correct for some but not all of the selection biases using such measures as on-treatment analysis of outcomes and analysis of outcomes across all patient subgroups. Last, the SRTR database does not contain any dosing or drug concentration data that can help interpret the effects of drug doses and exposure on transplant outcomes. Thus, any associations derived in such analyses should only be applied to the pattern of clinical use of particular drug combinations during the historic timeframes analyzed. Therefore, to establish causal relationships between a regimen and an outcome, one must necessarily integrate results of retrospective studies with results from randomized clinical trials.

The recently reported Symphony study was designed to evaluate low toxicity immunosuppressive regimes that could potentially both preserve adequate renal allograft function and achieve excellent graft survival. In the Symphony trial, standard-dose CsA-based regimens were compared with low-dose CsA, TAC, or Rapa in combination with MMF, daclizumab, and corticosteroids in renal transplantation. At 1 yr, biopsy-proven
acute rejection in Rapa/MMF patients was 33% versus 11% with TAC/MMF (P < 0.01) and 22% with CsA/MMF. The calculated GFR was 57.3 ml/min with Rapa/MMF versus 65.4 ml/min with TAC/MMF (P < 0.0001). Last, 1-yr graft survival was significantly inferior in Rapa/MMF patients (TAC/MMF, 94%; Rapa/MMF, 89%; P = 0.017) (87).

The Symphony study, taken together with the preceding summary of the SRTR analysis, does suggest that the Rapa/MMF immunosuppressive regimen, when used in de novo renal transplant recipients, falls short of preserving renal allograft function and improving graft survival, most probably reflecting inadequate acute rejection prophylaxis of Rapa/MMF in the de novo setting.

CNI Avoidance with Belatacept/MMF

The CNI and steroid minimization protocols discussed here have all been investigated in the context of US Food and Drug Administration (FDA) approval of immunosuppressive medications. New immunosuppressive medications in development often are also tested with either the intent of avoiding steroids or CNIs or both. Recently, a novel approach to CNI avoidance was pursued in a multinational, multicenter, randomized trial using belatacept (LEA29Y), an agent not yet approved by the FDA and currently in phase II trials in the United States. Belatacept is a selective costimulation blocker that blocks to surface costimulatory molecules (CD80 and CD86) of antigen-presenting cells, thereby inhibiting T cell activation. Belatacept is devoid of intrinsic nephrotoxicity. In a phase II trial in recipients of first renal transplants, different doses of belatacept administered along with MMF and steroids were compared with a control group receiving CsA/MMF/prednisone. Similar 6-mo acute rejection rates were observed between the belatacept and CsA groups (7% for intensive belatacept and 6% for less intensive belatacept versus 8% for CsA). At 1 yr, GFR was significantly higher with belatacept than with CsA, and CAN was less commonly noted in protocol biopsy in belatacept-treated patients (belatacept, 29%; CsA 44%; P < 0.05). Favorable trends with regard to cardiovascular risk factors such as BP, total cholesterol, and non-HDL cholesterol were also noted with belatacept (104). Thus far these promising preliminary results with belatacept suggest its safety and efficacy in de novo renal transplant recipients. However, these results do need to be validated in a phase III trial.

Calcineurin Inhibitor Avoidance: Discussion

The primary impetus to eliminate CNIs from immunosuppressive protocols in kidney transplantation has stemmed from concerns about their intrinsic nephrotoxic effects. Granted, CNIs may be associated with functional and morphological manifestations that accompany progressive allograft failure (4,6). However, one must also keep in mind that the best outcomes to date in renal transplantation have been realized in the CNI era. Certainly, studies reported by Nankivell et al., which show evidence of anatomical lesions consistent with a CNI effect in serial protocol biopsies of kidney allografts, offer a point of concern (8). However, by the same token, such studies are observational and therefore do not establish these CNI-related lesions as the immediate and predominant cause of progressive renal dysfunction. In a recent report, Nankivell et al. have shown that lesions with morphology similar to CNI toxicity are less common in MMF-treated subjects receiving CsA and corticosteroids as opposed to those on AZA in a CsA-based triple therapy regimen (8). As may be noted in a previous publication from this group, the cumulative burden of subclinical rejection was also more common in AZA-treated patients (6,105). Recently published results of protocol biopsies obtained from renal transplant recipients on TAC/MMF and steroids demonstrate that the primary determinants of chronic pathological lesions in the renal allograft were low tacrolimus exposure and subclinical acute rejections. This important insight redirects our attention to immunological mediators of chronic allograft injury (11). Therefore, we submit that attribution of all vascular and fibrotic lesions in an allograft biopsy entirely to CNI nephrotoxicity is too simplistic and probably incorrect. Fibrointimal changes in the vasculature and fibrotic/atrophic changes in the tubulointerstitial compartment may be secondary to nonspecific pathological manifestations of repair after injury by the alloimmune, metabolic, or the toxic effects of a drug (106,107). Importantly, observational studies such as those of Nankivell et al (8) do not actually test the hypothesis that graft function, histology, and survival would be superior had the treatment regimen been a CNI-free regimen. These questions can only be answered in adequately powered, prospective randomized controlled trials.

With regard to nephrotoxicity, all CNIs are probably not alike, and therefore CNI avoidance or withdrawal studies can have a different meaning for regimens containing different CNIs. Certainly, clinical experience and data from prospective, retrospective, and histological studies support the notion that TAC may be associated with less nephrotoxicity than CsA (9,87,108). Therefore, when renal function is the primary end point, CNI withdrawal studies can seem more successful with CsA versus TAC. From an empiric standpoint, removal of a CNI and especially CsA from immunosuppressive regimens usually results in lower creatinine levels. This may be interpreted by the transplant physician as a manifestation of improved renal function. However, this improvement in the creatinine probably signifies nothing more than an intrarenal hemodynamic effect. In fact the removal of the CsA constrictor effect on the afferent arteriole causes an acute increase in GFR. One must be cautious in not being lulled into complacency based on this phenomenon because this might not necessarily have an impact on preexisting histological lesions that can continue to progress over time; additionally, the decreased levels of immunosuppression may manifest many months later as overt rejection or, even worse, as subclinical rejection not readily apparent on cursory and sporadic follow-up of serum creatinine levels. Also to be noted from the practical standpoint is that any patient on a minimization regimen (whether it is steroid or CNI minimization) that encounters even the most transient interruption of their dosing, be it because of intercurrent illness or frank non-compliance, is at a much greater risk for an acute rejection episode. Furthermore, the incidence of acute rejection rates upon withdrawal of CNIs or steroids is not negligibly small;
Unfortunately, effects of such rejection episodes on attrition of graft function and in turn patient survival still remain largely unknown. In addition, even although the incremental rates of acute rejection in many CNI and steroid withdrawal studies are small, the underlying risk might be underappreciated because acute rejection might be underdiagnosed when biopsies are performed only for cause. The higher rates of clinically overt acute rejections might be a marker of a much greater increase in subclinical rejections that ultimately could have a significant impact on long-term graft survival.

To a large extent, transplant physicians now practice in an era where very low acute rejection rates are the norm with standard immunosuppression (30). On the other hand, such rejection episodes as manifested in the recent era are less likely to respond to treatment and have a far greater deleterious impact on long-term graft survival (2).

Even with very low acute rejection rates, long-term results have not significantly changed and long-term CNI toxicity could be certainly one of the reasons. On the other hand, there are several other very visible and recently emerging pathologies that hamper long-term success after kidney transplantation. The very sophisticated immunosuppressive armamentarium that has allowed for very low acute rejection rates has also brought to the fore new, and more numerous, long-term complications like BK virus nephropathy, other opportunistic infections, and malignancies (109,110).

The large-scale applicability of de novo CNI-free immunosuppression with Rapa/MMF has also been put into question by recent clinical trials and registry data. The failure of the combination of Rapa/MMF to provide a safe platform for CNI avoidance might be in part related to the poor tolerability of this regimen with potentially additive or even synergistic mechanisms underlying the overall toxicity of this regimen. Leukopenia and diarrhea are rate-limiting toxicities for both Rapa and MMF. Rapa has also been associated with proteinuria, pneumonitis, and renal insufficiency in both native and transplant kidneys with ongoing injury. This lack of tolerability with certain immunosuppressive regimens used for CNI avoidance can trigger suboptimal compliance, breakdown in immunosuppression, and ultimately decreased patient and allograft survival. Thus, with the currently available armamentarium, the goal of avoiding CNIs altogether is not a casual exercise.

**Summary and Conclusions**

Immunosuppressive medications are associated with toxicities related directly to the immunosuppressive effects. These toxicities or side effects are similar for different agents, and they are associated with secondary toxicities not related to the primary therapeutic actions of the drug, which usually are quite unique for the compound. Immunosuppressive minimization strategies try to address both these toxicities. By reducing immunosuppression, side effects related to overimmunosuppression can arguably be efficiently prevented, and at the same time dose-dependent side effects can be expected to improve. On the other hand, because the intrinsic immunosuppressive requirements for each donor recipient pair are unknown, any minimization strategy has a potential risk for underimmunosuppression and consequently acute rejection and potentially premature graft loss and death. Immunosuppression minimization efforts that are in the clinical mainstream are focused on either corticosteroid or CNI avoidance. CNI-Free regimens were developed and promoted with the overarching goal of improving graft function and ultimately long-term graft survival. However, results to date have indicated varying efficacy, and studies with long-term follow up are not available. Especially in de novo renal transplant recipients, studies indicate less than acceptable outcomes when using de novo CNI-free immunosuppression with currently FDA-approved agents. When considering CNI minimization and/or withdrawal strategies, it is important to assess the risks and benefits for each individual patient. In patients with advanced chronic allograft dysfunction, the potential downside of reducing or withdrawing CNIs is probably significantly less compared with patients with excellent and stable renal function. In patients facing imminent allograft failure, anything to delay the process and gain time is likely to be a significant success. Regimens that minimize CNIs in patients with stable allograft function have been justified on the basis of the expectation that the immediate risk of acute rejection is an acceptable price to pay for the ultimate gain in renal function. However, this line of thought is largely conjectural and not borne out by the evidence thus far.

The use of therapeutic drug monitoring for mycophenolic acid could potentially gain importance because CNI withdrawal and avoidance is becoming more common (111). More sophisticated pharmacokinetic and pharmacodynamic monitoring for CNIs might also allow for safely reducing exposure in the future. Currently there are no reliable tests to quantify the amount of immunosuppression administered cumulatively or even for single drugs, and there are no tests to assess how much immunosuppression each individual donor-recipient pair might need to avoid rejection. Pharmacokinetic monitoring and dosing strategies currently used in transplantation are derived from population data. It is very difficult to apply the therapeutic threshold derived from populations to the individual patient.

All minimization strategies are accompanied by the risk for acute rejection and overall inadequate immune response prophylaxis and its potential adverse impact on graft survival. The lack of ability to measure immunosuppression required by and administered to the individual patient is the real Achilles’ heel of immunosuppression individualization. With the way that they are currently developed, immunosuppressive minimization strategies always carry a finite risk of harm to a fraction of the population while potentially benefiting, to a less certain extent, another fraction. The ongoing challenge for the transplant professionals remains choosing the best therapy for each individual patient.

**Disclosures**

None.

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