How should the immunosuppressive regimen be managed in patients with established chronic allograft failure?

Gabriel M. Danovitch
Division of Nephrology, UCLA School of Medicine, Los Angeles, California, USA

The transplant literature is replete with recommendations regarding the choice of immunosuppressive medications for the prevention and treatment of acute rejection, and, with somewhat less conviction, for long-term maintenance immunosuppression [1]. The question posed in the title, however, has been given minimal attention. It is of great practical importance, and it is one of the most frequent questions posed to me by my nephrology colleagues responsible for the long-term care transplant of recipients. The discussion that follows will relate principally to the immunosuppressive management of the failing kidney transplant. The broader diagnostic and management issues have been reviewed extensively elsewhere.

QUESTIONS TO ADDRESS BEFORE MANIPULATING IMMUNOSUPPRESSION

The question of adjusting the immunosuppressive regimen for patients with chronic allograft dysfunction may often be the first that is asked of me by my colleagues, but it is not necessarily the best question to ask. Chronic allograft failure is essentially a specialized form of chronic renal failure and should be approached with a similar philosophy. Pre-renal and post-renal reversible causes must be ruled out, the volume status must be optimized, and the medication regimen critically assessed. In most patients, the diagnosis will be confirmed by biopsy which also serves to uncover the cases of recurrent or de novo glomerulonephritis that may account for up to 5% of long-term graft losses. A biopsy also permits a diagnosis of less common but critical-to-diagnose causes of graft failure such as post-transplant lymphoma and polyoma virus nephropathy [8]. Recent changes in immunosuppressive drug formulations (e.g., from Sandimmune cyclosporine to Neoral cyclosporine) may cause graft dysfunction, as may the addition to the medication regimen of drugs that interact with the hepatic metabolism of the CIs [9].

WHAT IS THE APPROPRIATE DOSE OF THE CALCINEURIN-INHIBITOR IN ESTABLISHED CHRONIC ALLOGRAFT FAILURE?

Despite nearly 20 years of clinical experience with cyclosporine and 10 years with tacrolimus there are still a paucity of prospective clinical trials comparing various
dose regimens of these drugs for long-term use in well-functioning grafts, let alone in poorly functioning grafts. Most of the standard recommendations for well-functioning grafts are based on retrospective analyses. There is also a considerable, though disputed, body of evidence that it may be safe to discontinue these drugs completely in many patients, though most practitioners seem to have determined that the risk/benefit analysis favors their continuation [1]. The nephrotoxic potential of the CIs is well established and, although their use is conducive to excellent long-term function, some degree of renal dysfunction, both reversible and irreversible, is an inevitable consequence of their administration [7]. In the case of CAN, the situation is particularly paradoxical. Is it logical to continue these drugs, both vasoconstrictors, in the face of fibrosis and vascular hyalinosis for which they may be in varying degrees responsible? On the other hand, should their use be intensified to address any undertreated alloimmune response that the histologic picture may suggest? A theoretical argument could be made for both dose reduction and intensification.

There is no substantive evidence to suggest that CAN will respond favorably to intensification of CI dosage, to exchanging CIs, or to changing formulations of CIs. On the contrary, each of these manipulations may be followed by apparent transient or permanent deterioration of function, presumably as a result of exaggeration of vasoconstriction and nephrotoxicity [9]. There is, however, a body of evidence suggesting that reduction or discontinuation of these drugs may be beneficial and, in this regard, the studies of Weir et al [10, 11] are worthy of particular attention. Starting in 1996, Weir et al [10] began a policy of reducing the CI dose in patients with declining renal function and biopsy proven CAN. So-called immunosuppressive “support” was maintained by addition of mycophenolate mofetil (MMF) or by increasing its dose. Early observations demonstrated a short-term benefit in the rate of loss of renal function the authors suggested was caused by a release of CI induced vasoconstriction. The long-term impact of this policy was then evaluated in a cohort of 118 patients followed over a period of approximately 2 years [11]. Once again, MMF was continued or added together with low-dose steroids. The decision to discontinue the CI rather than reduce its dose (typically to approximately 50% of its initial value) was made in only 18 patients in somewhat arbitrary manner based on HLA matching and the degree of renal dysfunction. Depending on the technique used to determine the rate of change of renal function following the change in CI dose, more than 90% of the discontinued group and 40% of the reduced group showed an improvement or at least a lack of deterioration in the rate of decay of renal function. Thirty-three of the patients were biopsied during follow-up to evaluate episodes of graft dysfunction and there were a total of 19 episodes designated as acute rejection that were typically mild or borderline and responsive to a short course of high-dose steroids. No patient was deemed to require re-introduction or escalation of the CI dose. In a follow-up analysis of this data, the authors concluded that cyclosporine withdrawal was the most beneficial policy for the management of CAN (abstract A4816, ASN/ISN World Congress of Nephrology, October 2001). It should be emphasized, however, that the various treatment groups varied in their baseline characteristics and were not prospectively randomized, and that only 13 patients were totally withdrawn from CI drugs. Graetz et al (abstract A4663, ASN/ISN World Congress of Nephrology, October 2001) replaced cyclosporine with MMF in a group of 15 patients with CAN and reported a significant improvement in the serum creatinine level without graft loss or episodes of acute rejection. Similar findings were reported by Filler et al [12] in a small group of pediatric patients with progressive graft dysfunction ascribed to cyclosporine toxicity.

Based on this data, CI dose reduction in CAN appears to be safe and well tolerated and to have a beneficial effect on the rate of deterioration of graft function in a high percentage of patients. Not all patients benefit, however, and the occurrence of episodes of acute rejection indicates that careful follow-up is mandatory. It is also important to note, as emphasized by Kreis et al [13] that functional stability or improvement as judged by the serum creatinine level may not necessarily parallel histologic stability.

**MYCOPHENOLATE MOFETIL FOR CHRONIC REJECTION**

MMF was introduced into clinical transplantation based on its capacity to reduce the incidence of acute rejection in the early post-transplant period [1]. There were also theoretical reasons, based on studies in animal models [14], to anticipate that the drug might serve to prevent or treat clinical CAN. Convincing proof of ability to do so, however, has proved elusive, though the available data is suggestive. In the prospective studies of prophylactic MMF use there was a small but not statistically significant reduction in the rate of graft loss [15]. It should be noted, however, that the studies were not designed or statistically powered to address long-term function [1, 15]. In a large retrospective study, Ojo et al [16] showed that use of MMF at some time during the post-transplant course was associated with a lower incidence of chronic rejection, but the extent of MMF treatment to achieve this effect could not be determined. None of these studies, however, address the issue of whether MMF has a favorable impact on established CAN. In a small, randomized study by Glicklich et al [17], no benefit could be shown for the addition of MMF...
in a group of patients with established CAN on a stable dose of cyclosporine. On the contrary, Maria et al (abstract A4921, ASN/ISN World Congress of Nephrology, October 2001), in a non-randomized study of 18 patients found that the addition of MMF to a stable or reduced dose of cyclosporine led to a stabilization of graft function. In the previously discussed studies of Weir et al [10, 11], it is not clear whether the addition of MMF for immunosuppressive “support” played a part in the beneficial effect of reduction of the CI dose. To answer this important question, the study would need to be repeated with randomization to groups receiving or not receiving MMF. Until these data are available, it would seem reasonable to introduce MMF or continue its administration if the dose of CI is significantly reduced.

RAPAMYCIN FOR CHRONIC REJECTION

The histology of CAN together with work on experimental models of chronic rejection provide a tempting theoretical rationale for the benefits of rapamycin in CAN. These benefits have yet to be proven of clinical value [18]. Rapamycin inhibits growth factor mediated proliferation of cells involved in the pathogenesis of chronic rejection in vitro [19, 20]. In a variety of experimental models, rapamycin reduced intimal hyperplasia resulting from both immune and non-immune injury [18, 21]. The doses of rapamycin used in these studies are, however, considerably greater than those used clinically. Of particular importance rapamycin, in standard clinical dosage, has an immunosuppressive potency approaching that of the CIs, but it is not nephrotoxic when used alone [18].

In a large, multicenter, randomized study, the discontinuation of cyclosporine in stable patients with good graft function receiving rapamycin was shown to be safe and to be associated with significant improvement in graft function [22]. The obvious question, therefore, is whether this benefit can be safely reproduced in patients with impaired graft function and, if so, whether any benefit is transient and likely to be hemodynamic in nature, or long-lasting and likely histologic in nature. Adequate data to answer this question is lacking, though the available preliminary data is encouraging. Dominguez et al [23] switched 12 patients with CAN from CI-based therapy to rapamycin and after 6 months reported a significant decrease in serum creatinine levels (233 ± 34 to 210 ± 56 μmol/L, P < 0.05). Five patients developed pneumonia, however, two with Pneumocystis carinii. The authors recommended the reintroduction of prophylactic antibiotic therapy [23]. Peraldi et al (abstract P063, 18th International Congress of the Transplantation Society, June 2000) in a prospective, non-randomized study of 23 patients with varying degrees of CAN found that graft function improved when rapamycin was substituted for a CI. Eight of the patients, however, developed pneumonitis. Fischereder et al (abstract A4642, ASN/ISN World Congress of Nephrology, October 2001) safely converted 12 patients with impaired graft function from cyclosporine to rapamycin and reported improved graft function without adverse side effects. Macaulay et al (abstract A4755, ASN/ISN World Congress of Nephrology, October 2001) reported that 10 patients with CAN showed improvement of graft function after conversion from a CI to rapamycin. However, Saunders et al (abstract 432, Transplant 2000 Meeting, May 2000) in a study of 30 patients with CAN found no benefit in adding rapamycin to a reduced dose of cyclosporine. In this study, rapamycin was introduced while reducing but not discontinuing the CI dose, and it is possible that the potential benefits of rapamycin were masked by continued CI toxicity [18]. Hyperlipidemia may be exaggerated by the addition of rapamycin and may theoretically be a factor in the perpetuation of CAN [24]. It would seem logical that if the potential benefits of rapamycin in CAN are to be exploited, the drug should be studied in this situation together with discontinuation or drastic dose reduction of the CI.

MANAGEMENT OF CAN WITH A FLUCTUATING CREATININE LEVEL

During the course of CAN, there may be fluctuations in the serum creatinine level whose clinical significance may be difficult to assess. Ideally, a full clinical, ultrasonographic, and histologic evaluation would accompany each of these events, though patients and physicians may be understandably reluctant repeatedly to biopsy patients with established CAN and empiric decisions may be required. With respect to the immunosuppression regimen, care must be taken to ensure patient adherence, lack of which could predispose to superimposed acute rejection episodes. The current availability of multiple, similar but not identical, preparations of cyclosporine requires that inquiry be made of the patient to determine if a new formulation had been prescribed with a potentially different pharmacologic profile. It may be tempting to treat otherwise unexplained episodes of rising creatinine levels with high doses of corticosteroids, though the improvement in graft function may be transient. Repeated courses of “pulse” steroids for patients with progressive CAN should be avoided, as should the maintenance of high baseline doses [25].

IMMunosuppressive management of the end-stage transplant

The above discussion has related to the management of patients with CAN in whom graft function is still regarded as salvageable. In CAN as in native kidney chronic
renal failure, a point is eventually reached when preparations for end-stage failure must be made. In the case of CAN, the question of how to manage the immunosuppressive regimen in the abandoned graft must be addressed. Ideally, the patient with the failed graft returns to dialysis (or receives another transplant) without the necessity to remove the failed graft which typically becomes small and fibrotic. Once a decision has been made to abandon a graft, it has been my policy to discontinue adjunctive immunosuppressive agents (e.g., azathioprine, MMF) and to maintain low plasma levels of the CI until dialysis commences at which time they are stopped completely over several weeks. If a patient is still receiving corticosteroids, the dose should be minimized and then discontinued slowly over several months because the patient may be adrenally suppressed. During the process of immunosuppressive withdrawal, the failed graft may become a source of constitutional symptoms (swelling, fever, local pain, and hematuria) that require treatment. In this event, a short course of oral or intravenous corticosteroids may reverse the symptoms and signs. The corticosteroid dose, however, should be rapidly returned to its baseline level and, if the clinical manifestations return, then allograft nephrectomy may be required. The corticosteroid dose should not remain elevated, and other immunosuppressive agents should not be reintroduced. Patients are sometimes reluctant to discontinue immunosuppression after returning to dialysis for fear of losing residual graft function and urine output. They should be persuaded that the risks associated with continued immunosuppression while on dialysis are not worth the marginal benefit of the residual function.

2. Consideration should be given to reduction or even discontinuation of CI therapy. Such a therapeutic maneuver requires careful follow-up to screen for episodes of deteriorating graft function.

3. Reduction of CI therapy is generally accompanied by addition of a non-nephrotoxic immunosuppres- satant, though it has not been firmly established that such addition is necessary. There is most experience with MMF in these circumstances, though rapamycin may be an appropriate alternative.

4. Introduction of a new immunosuppressive agent in previously immunosuppressed patients has potentially dangerous consequences. Patients should be monitored carefully, and consideration given to prophylaxis to prevent development of infectious complications.

5. High baseline doses of corticosteroids are not indicated. “Pulse” steroid therapy may be valuable for episodes of deteriorating function, but repeated treatment should be avoided. Ideally, use of pulse steroids in these circumstances should follow histologic confirmation of an element of acute rejection.

6. Since repeated pulse steroid therapy should be avoided, it is rarely indicated to repeatedly biopsy patients with established CAN.

7. If graft function continues to deteriorate despite the above measures, plans should be made to prepare for ESRD treatment options, and immunosuppression should be withdrawn in a stepwise fashion as when dialysis commences.

SUMMARY

The above discussion permits some broad recommendations for immunosuppressive management in established CAN. It must be emphasized, however, that these recommendations are tentative. They are not based on carefully randomized prospective clinical trials, but largely on theoretical considerations, clinical experience, and non-randomized and often small retrospective studies several of which are published only in preliminary form. Patients should be apprised of the quality of the information upon which these treatment decisions are made and should be included in the decision-making process. These recommendations are made on the presumption that reversible causes of chronic graft dysfunction have been ruled out, and that the clinical diagnosis of CAN has been confirmed histologically whenever possible.

1. Intensification of CI dosage or switching from one preparation to another has not been shown to be beneficial and may lead to exaggeration of nephrotoxicity.

REFERENCES


