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Calcineurin Inhibitors: Short-Term Friend, Long-Term Foe?

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Although calcineurin inhibitors (CNIs) have significantly improved the outcome for solid-organ transplant recipients, they have drug-specific side effects. One purported side effect is chronic progressive nephrotoxicity, but there are few meaningful data to support this contention. Given that the concern regarding CNI nephrotoxicity limits CNI dosing, and the reduced dosing may impair long-term transplant outcome, it is important to develop studies that accurately determine whether CNIs cause long-term kidney dysfunction.

The introduction of CNIs—initially cyclosporine (CsA)—resulted in significantly decreased acute rejection (AR) rates and significantly better 1-year patient and graft survival for kidney transplant recipients and permitted successful development of liver, heart, lung, and pancreas transplantation. However, both CsA and the second CNI (tacrolimus) have side effects. Given that the binding sites and subsequent metabolism of these two CNIs are different, it is not surprising that some of their side effects overlap; some are drug-specific. Critically, many side effects are related to high drug levels and can be reduced via level reduction. At the same time, there is great individual variability in tolerance to CNIs; that is, some patients have no side effects with high levels and others have side effects with low levels.

Some CNI-related side effects (e.g., hirsutism, alopecia, and gingival hypertrophy) are cosmetic and perhaps could be tolerated by most patients. Others (e.g., hypertension, new-onset diabetes, and hyperlipidemia) have the potential to significantly impact longevity.

One particular concern has been CNI-related nephrotoxicity. For kidney transplant recipients, it has long been recognized that AR episodes were a risk factor for poorer long-term outcome.[1] Yet, although CNI-based immunosuppression lowered AR rates and improved 1-year outcome, rates of graft functional deterioration after the first year remained unchanged. In addition, there have been reports that a significant proportion of patients having non-renal transplants have developed chronic kidney disease (CKD) while taking CNIs. One explanation uniting these observations is that CNIs are associated with *chronic progressive* nephrotoxicity, and this nephrotoxicity causes late graft loss in kidney recipients and CKD in non-renal transplant recipients.

There is no doubt that *acute* CNI nephrotoxicity exists (reviewed in ref. 2). Numerous reports attest to renal dysfunction related to high CNI blood levels, and this toxicity has been associated with specific histological lesions.[2] However, the acute dysfunction is usually reversible when the CNI is withdrawn.[3] In contrast to acute nephrotoxicity, data supporting

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CONFLICT OF INTEREST

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chronic progressive CNI-related nephrotoxicity are less clear.[1,3] Yet because of concern about *progressive* nephrotoxicity, we have spent more than two decades attempting to minimize or eliminate CNIs from our immunosuppression protocols. This has had negative consequences for some of our recipients. First, the diagnosis of "CNI toxicity" in individual patients has led to lowering of CNI doses (and levels); for some, dose reduction resulted in increased immunological activity. Second, we have focused on "CNI nephrotoxicity" instead of studying and minimizing other, more prevalent causes of late dysfunction.

There are numerous problems with the data purported to show progressive CNI nephrotoxicity after kidney transplantation.[1,3] First, there are no prospective randomized studies clearly demonstrating CNI nephrotoxicity to be a predominant cause of late graft dysfunction. Just the opposite is the case: most studies—starting with successful transplants at 1 year—show no improvement in long-term graft survival (or in slope of estimated glomerular filtration rate vs. time) to CNI-free immunosuppression, suggesting that chronic progressive CNI nephrotoxicity is not affecting the grafts. Second, because no clinical or histological parameters are known to be diagnostic of chronic CNI nephrotoxicity,[1] the condition has probably been overdiagnosed. In the absence of a biopsy, kidney transplant recipients developing progressive graft dysfunction (or non-renal transplant recipients developing native kidney dysfunction) are often diagnosed as having CNI nephrotoxicity. Alternatively, if a biopsy shows fibrosis and atrophy, the pathologist, in the absence of any other specific diagnosis, often interprets the biopsy sample as being consistent with CNI nephrotoxicity.

Why, then, has there been this emphasis on CNI-related nephrotoxicity? Major support has come from two areas (neither based on controlled studies). First, as noted above, kidney dysfunction has developed in non-renal transplant patients. As early as 1984, Meyers *et al.* reported that 12-month post-transplant estimated glomerular filtration rate was significantly lower in 17 CsA-immunosuppressed heart transplant recipients than in CNI-free historical controls (reviewed in ref. 1). However, the CsA doses used in that study were extraordinarily high (17 mg/kg/day); even with these doses, the renal function in the majority of patients remained stable. More recently, Ojo *et al.* described the significant cumulative incidence of CKD among 69,000 patients receiving non-renal transplants.[4] Yet, in their multivariate analysis, use of a CNI was not significant. Also of note was that the rate of development of CKD was not related to organ-specific CNI target levels. For example, liver transplant recipients who are targeted for relatively low CNI levels had a much higher rate of CKD over the first 10 years than did lung, heart, or heart-lung transplant recipients (who are targeted for higher levels).

Importantly, recent single-center analyses of heart, liver, and pancreas transplant recipients have noted that CNI use was not a risk factor for CKD (reviewed in ref. 1). In addition, many patients with chronic heart or lung disease or diabetes have significant renal dysfunction at the time they undergo transplant. Liver failure itself is associated with renal dysfunction; in studies in which a kidney biopsy has been done in liver transplant recipients —either at the time of transplant or upon the development of CKD—numerous non-CNI-related diagnoses have been made.[1]

The second body of data supporting progressive nephrotoxicity is from a sequential-biopsy study of 120 CNI-immunosuppressed kidney-pancreas recipients that showed progressive development of glomerulosclerosis, periglomerular fibrosis, and totally sclerosed glomeruli.[5] Of note, the 10-year death-censored graft survival for the patients was 95%; the mean serum creatinine level was 1.6 ± 0.5 mg/dl. Therefore, although histological abnormalities developed, the long-term outcome was excellent. There are numerous problems with the published interpretation of these data. First, the study was not

randomized; all recipients were on CNIs. The development of histological lesions may have been due to CNIs but could have been attributable to other common factors. Second, the median histological follow-up was 3.9 ± 3.3 years; there were relatively few late observations. Third, two-thirds of the fibrosis that was present at 10 years had already appeared by 1 year; there was little progression beyond this point. Fourth, subclinical AR remained a significant clinical problem, occurring in 19.5% of biopsies done 2–5 years post-transplant and 12.3% of biopsies done 6–10 years post-transplant. Thus, it is quite plausible that the development of progressive histological lesions was due to ongoing subclinical AR.

Perhaps the most powerful observation challenging these data comes from a subsequent article by the same group in which they reported on sequential biopsies in a second cohort of recipients taking CNIs,[6] but differing in that mycophenolate mofetil (MMF) replaced azathioprine in the immunosuppressive protocol. The authors noted that MMF-treated recipients had decreased AR and reduced arterial hyalinosis, striped fibrosis, and tubular microcalcification; there was significant minimization of “CNI nephrotoxicity” when MMF was used (in CNI-treated recipients), and the incidence of AR declined.

There are considerable data refuting chronic progressive CNI nephrotoxicity, as outlined below.

1. Numerous studies have not found CNI nephrotoxicity to be a predominant cause of late graft dysfunction or graft loss. We showed that when death with function, technical failure, primary nonfunction, and recurrent disease are censored, actuarial 10-year graft survival for CNI-treated recipients with no rejection was 91% (vs. 45% for those with one or more rejections; $P = 0.001$).[1] CNI toxicity was a rare cause of graft loss in both groups. El-Zoghby *et al.*, in a detailed analysis of 330 graft losses, found that only one case could be attributed to CNI nephrotoxicity.[7] Others have shown no subsequent progressive deterioration of function when transplant biopsies showed only fibrosis and atrophy (and no inflammation).[1]
2. As noted above, in prospective randomized studies of CNI-containing versus CNI-free protocols, there has been no long-term graft survival benefit for the CNI-free groups.
3. Many recipients have stable renal function on long-term CNIs. We reported on 1,263 recipients with graft survival of 1 year or more who remained on CNIs. Mean serum creatinine level and calculated creatinine clearance were stable through 20 years. At least for these patients, there has been no evidence of progressive nephrotoxicity.
4. Perhaps most important is that, just as there are alternative explanations for the majority of CKD in non-renal transplant recipients, there are evolving alternative explanations for most late renal dysfunction after kidney transplantation. First, as described above, AR and subclinical AR have been well established as risk factors for late graft dysfunction and graft loss. But our understanding of AR is evolving. By Banff criteria (a system of scoring kidney transplant biopsies), inflammation in the area of scarring was not scored. Recent studies have documented that inflammation in these areas is associated with poorer short- and long-term outcome.[8] Thus, active inflammation and immune-mediated damage may have been underappreciated and progressive graft dysfunction erroneously attributed to CNIs. Second, sensitive technology has been developed to measure circulating donor-specific human leukocyte antigen antibody (DSA) and to diagnose antibody-mediated rejection. This has led to numerous studies showing an association between DSA and chronic graft loss, and some authors suggest that DSA is responsible for most cases of late graft loss.[1,9]

Thus, there is considerable doubt that CNI toxicity is the major cause of late post-transplant kidney dysfunction. This was clearly demonstrated in the Long-Term Deterioration of Kidney Allograft Function (DeKAF) study, in which recipients whose biopsy specimens were interpreted (by the local pathologist) *as having CNI toxicity*, had *lower* rates of graft failure than those without such a diagnosis; patients whose biopsy specimens were C4d-positive (indicating antibody-mediated rejection) had significantly worse outcomes.[10] New prospective randomized controlled studies are needed to characterize specific causes of dysfunction in both kidney and non-renal transplant recipients.

There are ongoing efforts to develop new immunosuppressive drugs with minimal or no side effects. At the same time, there are attempts to determine whether individualization of immunosuppression (e.g., based on clinical risk factors or single-nucleotide polymorphisms) will allow maximal efficacy with minimal toxicity. CNIs have numerous side effects that justify search for new agents. However, it is not clear that *progressive* renal dysfunction is one of them. It is possible that *chronic progressive* CNI nephrotoxicity exists, but data do not support that it is a predominant cause of late kidney dysfunction after kidney or non-renal transplantation. The majority of transplant recipients have stable renal function with long-term CNI treatment.

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