Chronic Calcineurin Inhibitor Nephrotoxicity: Reflections on an Evolving Paradigm

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Use of the calcineurin inhibitors (CNI) cyclosporine and tacrolimus has revolutionized solid organ transplantation. For more than 30 yr, the transplant community has dealt with nephrotoxicity attributed to these agents. Acute renal vasoconstriction (as described by many investigators, including John Curtis and colleagues) is the unequivocal consequence of their use; chronic CNI nephropathy, although indistinct in terms of histology and pathophysiology, has become accepted as a major cause of late kidney allograft failure. This article examines clinical, laboratory, and histologic findings that evolved into a paradigm that was never fully consistent with observed outcomes and new evidence that may offer an alternative interpretation for adverse events that are attributed to CNI nephrotoxicity in kidney transplant recipients.

The introduction of cyclosporine was a watershed event in the history of transplantation. Not only did it dramatically improve outcomes for renal allograft recipients, but also, for the first time, transplantation of hearts, livers, and pancreata became successful enough to justify incorporation into routine clinical practice. Coincident with these successes, however, emerged reports of the dark side of cyclosporine use: nephrotoxicity. Calne et al. (1), in their initial human experience with the drug (at dosages of 15 to 25 mg/kg per d, as monotherapy), noted six of 15 patients to have “primary anuria,” with decreased renal function in the others. The response to this initial report was so dismal as to almost halt development of the agent (2). Subsequently, successful administration of cyclosporine in kidney transplantation (using varying dosages and combinations of immunosuppressants in Canada, Denver, Houston, Boston, and Minneapolis) led to its approval by the US Food and Drug Administration in December 1983 (3–7). Even as American transplanters were learning to use the new drug, another report emerged, from Myers et al. (8) at Stanford, documenting two cases of end-stage kidney disease in cardiac transplant recipients who were taking cyclosporine. Almost immediately, clinical thinking and practice changed: Because our most effective immunosuppressant was also nephrotoxic, a (the?) primary concern in using cyclosporine must be to reduce its impact on kidney function, particularly what was termed “chronic nephropathy” (9). Now, a quarter of a century later, cyclosporine and its newer counterpart, tacrolimus, remain our most effective and widely used immunosuppressants; we continue to deal with nephrotoxicity, struggling to find acceptable alternatives. All along the way, there have been skeptics, those who questioned the link between acute and chronic nephrotoxicity, especially in kidney transplantation. Emerging data may now support an alternative view, one with the potential to change how we use these agents.

Initial Descriptions of Cyclosporine Nephrotoxicity

Early preclinical studies in animals made no note of nephrotoxicity; however, the first report by Calne et al. (1) of cyclosporine administration to kidney transplant recipients documented early impairment of renal function, particularly after an initial dose of 25 mg/kg per d. By the second Cambridge report, use of lower cyclosporine dosages and forced hydration seemed to reduce the complication, and a hint of reversibility was noted when the drug was discontinued (10). Not long afterward, a study from Oxford reported that renal function could be “normalized,” with substantially less rejection, in kidney transplant recipients who converted from cyclosporine to azathioprine-based immunosuppression after 90 d (9). As in subsequent studies, histologic examination of kidneys from these patients revealed rather nonspecific changes of interstitial fibrosis, tubular vacuolization, glomerulosclerosis, and vascular hyaline arteriopathy. Notably, in the Oxford study, these changes were less profound in cyclosporine-treated patients than in control recipients who never took the drug; each of the histologic findings was also potentially attributable to other insults to the allograft.

It was the seminal observation of Myers et al. (8,11) of chronic renal impairment in cardiac transplant patients that inspired the term “chronic nephropathy.” Early reports revealed striking changes of interstitial fibrosis, tubular vacuolization, glomerulosclerosis, and vascular hyaline arteriopathy. Notably, in the Oxford study, these changes were less profound in cyclosporine-treated patients than in control recipients who never took the drug; each of the histologic findings was also potentially attributable to other insults to the allograft.
sion, dramatically impaired renal function (indicated by parameters including inulin and para-amino-hippuran clearance, renal plasma flow, renal vascular resistance, and urinary albumin excretion), and three of 37 heart transplant recipients progressed to ESRD. The accompanying histologic changes in the 15 patients who underwent kidney biopsy were similarly diverse, with variable degrees of glomerulosclerosis, tubular atrophy/interstitial fibrosis, arteriolar hyalinosis, and “cyclosporine-associated arteriolopathy.” It is interesting that in the patients who underwent serial physiologic examination, mean arterial pressure, GFR, renal plasma flow, and renal vascular resistance did not deteriorate further during 1 to 3 yr, although urinary albumin excretion did increase. In the six patients with sequential biopsies, only glomerulosclerosis was consistently worse over time.

To duplicate cyclosporine-induced impairment of kidney function in animals, primarily rodents, required very large dosages of cyclosporine, sodium depletion, or both (12–14). In these models, the predominant findings were two-fold: an intense, reversible, arteriolar vasoconstriction and interstitial fibrosis with tubular atrophy. The former was thought to predispose to the latter, the link being the distinctive lesion of arteriolar hyalinosis with ischemic glomerular collapse (13) (Figure 1). Thus, a paradigm based on clinical and laboratory observations emerged: two basic syndromes of cyclosporine nephrotoxicity that evolve in tandem, with reversible vasoconstriction responsible for hypertension and compromised GFR that, over time, led inalterably to chronic kidney disease (CKD) or renal allograft failure. Although understanding of pathogenic mechanisms has evolved over time (incorporating direct tubular effects, abnormal renin-angiotensin homeostasis, reactive oxygen species, induced apoptosis, and TGF-β as potential mediators), its basic implication has not: Long-term use of CNI-based therapy induces progressive injury to the kidney (15).

The widespread acceptance of this paradigm has played an enormous role in the evolution of transplant immunosuppression, including the quarter-century-old multiplicity of attempts to reduce nephrotoxicity by reducing intensity or duration of exposure to cyclosporine. These include simple dosage reduction, addition of azathioprine and prednisone to facilitate CNI dosage reduction (16), use of antibody induction to delay CNI administration (17), conversion to non–CNI-based therapy at a defined point after transplantation (18,19), and drug development programs (belatacept, CP690550, among others) focused on CNI avoidance (20–22). Even the ascendance of tacrolimus in clinical practice may be at least partially attributable to the widely held perception that its use prevents rejection with less adverse impact on BP and renal function than occurs with cyclosporine (23). By 2003, it was possible to conclude, as did Nankivell et al. (24) from Westmeade, that in kidney transplantation, “Calcineurin inhibitor nephrotoxicity was the chief cause of late histologic injury and ongoing decline in renal function.” In extrarenal transplantation, others concluded that “the predominant cause of [kidney disease] is the long-term use of calcineurin inhibitors” (25).

**Alternatives to an Incomplete Paradigm**

Why, then, do we remain dependent on CNI-based immunosuppression? Might things be more complicated than we have assumed? The work of Curtis and colleagues contributed significantly to our understanding of cyclosporine nephrotoxicity in humans. Having previously developed a model to study hypertension in kidney transplant recipients (documenting the primacy of the kidney in influencing BP responses after kidney transplantation), this group went on to define the renal effects of cyclosporine in their patients (26,27). A landmark article in 1986 confirmed the impact of cyclosporine on BP, renal plasma flow, and GFR that others had noted, but with a different perspective: These changes had a strong hemodynamic component and were reversible with discontinuation of the drug (28). Additional studies documented preservation of tubular function, reversibility of hemodynamic effects with calcium channel blockers, and stability of GFR over time, all supporting the concept of a functional, not structural, derangement as the primary cyclosporine-induced abnormality in kidney transplantation (29–32) (Figure 2). Subsequently, Curtis went so far as to question the relationship between the reversible entity that he had observed and the concept of irreversible consequences of CNI use: “Impaired renal function with cyclosporine appears to be relatively stable. If the drug dosage is maintained in the face of severely impaired function, serum creatinine does not rapidly increase as it would with continued dosage of...other tubular toxins” (33).

Several other discrepancies emerge when trying to link the widely documented phenomenon of cyclosporine-induced vasoconstriction with its presumed correlate of irreversible fibrosis and atrophy. The first is the undeniable improvement in allograft outcomes that has occurred under CNI-based therapy, even as the field has witnessed significant aging of the donor.

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**Figure 1.** (Left) Scanning electron micrograph of an afferent arteriole (AA) and glomerular tuft from a control animal. (Right) From a similar animal after 14 d of cyclosporine treatment. Reprinted from English J, Evan A, Houghton DC, Bennett WM: Cyclosporine-induced acute renal dysfunction in the rat: Evidence of arteriolar vasoconstriction with preservation of tubular function. *Transplantation* 44(1): 135–141, 1987 (reference 13), with permission.
and recipient populations, less MHC similarity between donor and recipient, and, in kidney transplantation, commonplace use of kidneys with preexisting injury (34,35). Although some studies have indeed documented excellent outcomes with CNI-free immunosuppression, CNI-based protocols have been shown over and over again in clinical trials to result in renal function at least as stable as proposed alternatives and graft survival equivalent or superior to those available with any other option, as shown in the Symphony (Efficacy Limiting Toxicity Elimination [ELITE]-Symphony) trial, the CAESAR (Cyclosporine Avoidance Eliminates Serious Adverse Renal toxicity) trial, the ORION (Optimizing Renal Transplant Immunosuppression to Overcome Nephrotoxicity) trial, and numerous single-center studies (36–39). Even the aforementioned Westmeade study, despite its emphasis on fibrosis and atrophy, documented excellent graft survival with remarkable preservation of GFR at 10 yr after transplantation (24).

Second, numerous studies have shown intervention to change the clinical course and histology of CNI nephrotoxicity. Although admittedly controversial, it is widely accepted that tacrolimus may be less nephrotoxic than cyclosporine, on the basis of preservation of renal function and attenuation of histologic changes (primarily fibrosis and atrophy) on protocol biopsies (40,41). Both of these findings, however, accompany the clinical observation of less immunologic insult (i.e., fewer rejection episodes and less subclinical rejection) with tacrolimus-based therapies (42). Subsequently, the Westmeade group documented the addition of mycophenolate to cyclosporine-based immunosuppression not only to reduce adverse immunologic events but also to diminish the lesions thought to be the *sine qua non* of CNI nephrotoxicity: arteriolar hyalinosis and striped interstitial fibrosis (43). Indeed, several series have documented much greater stability of renal function, despite ongoing use of CNI-based therapy, in the current era (35,44). The reversibility and relative stability of renal dysfunction that can occur after CNI withdrawal (as in the Spare-the-Nephron trial, among others), as long as rejection does not supervene, also argues against the concept of irreversible chronic nephrotoxicity (45).

The histologic lesions that are thought to be most specific for CNI nephrotoxicity (striped interstitial fibrosis and arterial hyalinosis) have always been, in reality, rather nonspecific, with great heterogeneity in diagnostic criteria from study to study. A recent review documented seven different histologic findings suggestive of chronic CNI injury (15). Our understanding of the pathogenesis of these lesions is changing rapidly as new tools become available. Lerut et al. (46) examined late biopsies in compliant and noncompliant kidney recipients. As might be expected, the noncompliant patients demonstrated more inflammatory changes but were also found to have more interstitial fibrosis and identical degrees of arteriolar hyalinosis than the compliant patients. In kidney transplantation, it is now becoming apparent that the presence of fibrosis and atrophy may not predispose to graft failure; a more critical variable is evidence of ongoing inflammation (47,48). In a recent report from the Deterioration of Kidney Allograft Function study group (49), 60% of patients with allograft dysfunction 7 yr after transplantation had donor-specific antibody, C4d staining, or both. Many of these patients had a histologic diagnosis of CNI toxicity, and in the absence of inflammation, donor-specific antibody, or C4d staining, the prognosis was excellent.

It seems increasingly clear that at least some of the chronic changes that are attributed to CNI nephrotoxicity in kidney transplant recipients are, in reality, the consequence of previously unrecognized immunologic injury. The most compelling evidence, though, for a direct nephrotoxic effect of cyclosporine derives from its use in extrarenal transplantation and autoimmune disease (50–52). In many of these studies, data are compromised by the same limitations that are evident in the kidney transplant literature: heterogeneity in diagnostic criteria and histologic confirmation, variable evidence of progression, and other nonspecific factors. It may also be true that some portion of the renal failure that is attributed to CNI toxicity outside of kidney transplantation may be the result of other factors, including significant undiagnosed CKD at the time of transplantation. Liver recipients are among the most likely to develop renal insufficiency after transplantation. Curtis’s University of Alabama at Birmingham group performed protocol kidney biopsies in 30 patients who had hepatitis C and normal renal function and underwent liver transplantation (53). Twenty-five (83%) had significant preexisting glomerular pathology. Likewise, 15 to 40% of patients who underwent cardiac transplantation had significantly impaired kidney function at the time of transplantation, with only incomplete resolution in many after successful transplantation with or without CNI-based therapy, indicating that other mechanisms may be operative (54). Even so, given the 15 to 20% incidence of CKD attributed to CNI use outside of kidney transplantation (24), it is difficult to extend these observations to support the conclusion that CNI nephrotoxicity is the major cause of late kidney allograft failure.

**Conclusions**

To suggest the CNIs cyclosporine and tacrolimus are not in any manner associated with chronic nephrotoxicity is ludicrous; the experience of all involved in transplantation indicates otherwise. The consistent observation of Curtis and other investigators that these agents caused renal vasoconstriction...
and that functional nephrotoxicity was, in many cases, reversible on CNI withdrawal is unquestionably of profound significance. It is unfortunate, however, that these findings have evolved into the dogma that CNI toxicity is a major (or the major) cause of late kidney allograft failure. In the presence of “creatinine creep” (slow decline in GFR), our most common response is to reduce the dosage of our most effective immunosuppressant, perhaps precisely the wrong intervention. In our obsession with developing CNI-free immunosuppression, we may have missed the opportunity to incorporate promising new agents into the therapeutic armamentarium had they only been tested as adjuncts to rather than replacements for cyclosporine or tacrolimus. Until we are better able to understand and manipulate immunologic responses to allografts, we remain dependent on effective immunosuppression to extend the lives of our patients. For three decades, despite enormous efforts otherwise, our reliance on CNIs persists. Better understanding of mechanisms of long-term renal allograft injury may allow us to perfect our use of these revolutionary drugs and, in so doing, better deal with their consequences.

Disclosures
None.

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