Renal Function in Patients Receiving Long-Term Cyclosporine Therapy

David H. Van Buren, James F. Burke, and Richard M. Lewis

D.H. Van Buren, Renal Transplantation Division, Vanderbilt University Medical Center, Nashville, TN
J.F. Burke, Division of Nephrology, Thomas Jefferson University Hospital, Philadelphia, PA
R.M. Lewis, Renal Transplantation, Loyola University Medical Center, Maywood, IL


ABSTRACT

The site at which the vasomotor effects of cyclosporine are associated with acute nephrotoxicity appears to be the afferent arteriole. Proposed mechanisms mediating these effects include sympathetic nerve stimulation, disruption of the balance between vasodilating and vasoconstricting prostaglandins, hypersensitivity to vasoactive peptides, and endothelin release. These mechanisms mediate cyclosporine-associated intrarenal vasoconstriction, yet the causal relationship between these changes and the obliterative vasculopathy seen in association with chronic progressive renal allograft dysfunction is uncertain. Histologic findings seen in chronic progressive renal dysfunction are nonspecific and cannot be correlated solely with cyclosporine use. Retrospective studies analyzing both aggregate serial serum creatinine and reciprocal creatinine determinations did not report a pattern of progressive attrition consequent to toxic nephropathy. Prospective studies with serial GFR determinations with various reference substances did not report a pattern of progressive attrition. Both retrospective and prospective studies indicate that the attrition of renal allograft function associated with cyclosporine use reflect the chronic effects of immunologic injury. Renal function in extrarenal transplant recipients immunosuppressed with cyclosporine can be characterized by an initial decline in native renal function followed by subsequent stabilization beyond the first 6 months. There does not appear to be an inordinate rate of progression to ESRD.

Key Words: Renal transplantation, cyclosporine A, GFR, nephrotoxicity

Cyclosporine A (CsA)-based immunosuppression protocols increased 2- and 5-yr renal allograft survival to 80 to 90% and 60 to 70%, respectively (1–3). The efficacy and immunosuppressive specificity of CsA allowed for reduced steroid requirements (4) and a general decline in the rate of infectious complications and other morbidity (5).

Enthusiasm for the beneficial effects of CsA was somewhat tempered after the report of Myers et al. (6), which suggested that long-term CsA use in cardiac transplant recipients led to a progressive nephropathy, resulting in dialysis dependence in 10% of a small cohort of patients treated for more than 1 yr. A longitudinal analysis of the same population revealed no improvement in renal physiologic parameters with CsA dose reduction (7). However, both this study and others documenting severe CsA nephrotoxicity involved protocols using dosages now recognized as excessive. In the first published clinical experience with CsA in renal transplantation, for example, induction doses of up to 25 mg/kg per day (8) were selected on the basis of preclinical canine studies (9).

Although the acute vasomotor effects of CsA have been well documented, its role in the pathogenesis of chronic obliterative vasculopathic renal disease is controversial. Reversible acute renal dysfunction after CsA administration is associated with a reduction in both GFR and RBF (10). The primary site at which CsA acts to increase renal vascular resistance is probably the afferent arteriole (10). Proposed mechanisms (11) mediating these renal hemodynamic changes include sympathetic nerve stimulation, alteration of relative balance between vasodilating and vasoconstricting prostaglandins, increased sensitivity to vasoactive peptides, and endothelin release from endothelial cells.

Moss et al. (12) showed that acute CsA administration experimentally increased afferent renal and genitofemoral nerve activity significantly. Additionally, α-adrenergic blockade and denervation of the kidney have both shown to mitigate CsA-induced intrarenal vasoconstriction (13). CsA decreases prostacyclin synthesis by vascular endothelial cells (14). Although prostaglandin is felt to play a relatively minor role in
resting intrarenal hemodynamics, increased local generation occurs in response to vasoconstrictive stimuli (15). In addition, CsA generates the local release of the vasoconstrictive prostaglandin thromboxane (15). The concomitant reduction in prostacyclin and the enhanced production of thromboxane exacerbate the vasoconstrictive effect. Heightened renal arterial vasoconstrictive responses to endogenous pressors have also been linked with CsA therapy and are associated with acutely increased cytotoxic calcium levels in mesangial and vascular smooth muscle cells (16). This occurs independently of renal innervation. The intrarenal vasomotor effects of CsA may also be mediated by the paracrine vasoconstrictive peptide endothelin (ET-1). ET-1 increases both afferent and efferent glomerular arteriolar resistance (17). The in vitro exposure of human endothelial cells to high concentrations of CsA induced ET-1 release (18). In addition, the administration of high doses of CsA (20 mg/kg) to rats increased circulating ET-1 levels (19). It is unclear, however, whether heightened ET-1 release occurs in association with long-term CsA use. Two clinical studies have shown no correlation between ET-1 plasma levels and the use of CsA in solid organ recipients (20,21). In contrast, Grief et al. demonstrated elevated peak ET-1 levels temporally associated with peak CsA levels (22).

These mechanisms may be particularly important in liver transplant recipients. Cirrhosis with ascites is associated with lower renal perfusion pressures, increased PRA, and reduced effective circulating blood volume (23). Circulating levels of thromboxane are also elevated in patients with severe hepatic disease (24). Textor et al. (25) showed that GFR and RBF fall during the first month after liver transplantation in conjunction with declining thromboxane and prostacyclin production. The ratio of circulating concentrations of thromboxane to prostacyclin remained elevated, however.

To summarize, sympathetic nerve stimulation, prostaglandin imbalance, and hyperresponsiveness to endogenous pressors and endothelin generation may mediate CsA-associated intrarenal vasoconstriction. It has been clearly established that CsA withdrawal increases RBF after conversion to azathioprine-prednisone immunosuppression (26). It is not clear, however, whether persistently elevated renal vascular resistance associated with CsA use is causally related to the obliterative vasculopathy seen in association with chronic progressive renal allograft dysfunction. Routine renal biopsies performed on patients with well-functioning allografts immunosuppressed with CsA have failed to demonstrate vasculopathic abnormalities (27). Interstitial fibrosis, arteriolar hyalnosis, and proximal tubular atrophy have been observed in biopsies from CsA- and prednisone-azathioprine-treated patients. Similarly, an autopsy study of native kidney morphology in a cohort of patients with end-stage cardiomyopathies never treated with CsA documented these same structural changes in 15 of 16 patients (28). As such, these histopathologic findings are nonspecific and cannot be achieved solely with CsA use. These histologic abnormalities were identical to those described in CsA-treated cardiac transplant recipients (7).

Despite the uncertainties vis-a-vis the effect of long-term CsA use on the pathogenesis of microvascular obliterative disease in solid organ allografts, the landmark study of Myers et al. (6) compelled the renal transplant community to address a critical question, namely, is long-term CsA use an independent risk factor for renal allograft loss consequent to a progressive toxic nephropathy? The remainder of this review will summarize clinical studies addressing this question, as well as data assessing the effect of contemporary CsA regimens on long-term native kidney function in extrarenal transplant recipients.

LONG-TERM DATA ON RENAL TRANSPLANTATION

The evolution of renal function in CsA-treated organ transplant recipients has been analyzed in retrospective population studies with follow-up periods of up to 10 yr (29-31). The single-center study reported by Lewis et al. (30) evaluated serial reciprocal creatinine determinations in a cohort of 111 CsA-treated renal transplant recipients with allograft survivals of at least 1 yr and temporal opportunity for 5 yr or more of follow-up. The aggregate rate of decline in allograft function did not differ from that observed in a historical control group receiving prednisone-azathioprine immunosuppressive therapy (30). A retrospective multicenter analysis of 1,415 CsA-treated renal transplant recipients was reported by Burke et al. (31). Mean follow-up was 3 yr, and 361 patients were monitored for 4 yr or longer. At 3 yr, graft survival was 78% and mean serum creatinine was 1.92 mg/dL. Aggregate analysis of serial serum creatinine determinations was not consistent with a pattern of progressive attrition of function consequent to a toxic nephropathy. Moreover, doses of CsA of less than 4 mg/kg per day at 90 days after transplantation were associated with an increased incidence of acute rejection during the subsequent 90 days (10.6 versus 4.7%, \( p = 0.009 \)) (31). Those patients maintained on higher doses of CsA had stable and slightly improved serum creatinine levels at 1 and 3 yr when compared with those maintained with lower levels of CsA (\( p < 0.013 \)) (31).

Similar results have been obtained in prospective studies of serial GFR determinations with a variety
of reference substances (e.g., iothalamate, DTPA, and iohexol). In an analysis of 29 CsA-treated renal transplant recipients monitored for a mean of 32 months, Slomowitz et al. (32) found no deterioration in allograft function as measured by DTPA clearances. In a 1-yr analysis of 43 patients who had been transplanted 2 months to 9 yr before study entry, serial iohexol clearances revealed stable renal function, irrespective of initial function or time after transplantation (33). These results are consistent with those of retrospective studies indicating that attrition of renal allograft function associated with long-term CsA use reflects the chronic effects of immunologic injury rather than a primary toxic nephropathy. Appropriate CsA dosing may limit nephrotoxic side effects while providing necessary immunosuppression. Long-term CsA dosing strategies are reviewed by Helderman et al. (34) elsewhere in this symposium.

The stability of renal allograft function may also be enhanced by the use of contemporary antihypertensive agents. The vasodilatory and natriuretic properties of calcium channel blockers, for example, mitigate the pathophysiologic abnormalities seen in CsA-associated, salt-sensitive hypertension (35). In addition, nifedipine has been shown to inhibit CsA-induced platelet aggregation and release of thromboxane in renal transplant recipients (36). Moreover, calcium channel blockers may positively affect long-term renal function by interfering with five maladaptive processes involved in the progression of chronic renal insufficiency. These include hyperfiltration, renal hypertrophy, mesangial traffic of macromolecules, proximal tubular hypermetabolism, and renal calcinosis (35).

CARDIAC TRANSPLANTATION

Lewis et al. (37) described an initial decline in native renal function after cardiac transplantation and subsequent stabilization beyond the first 6 months (Figure 1). The cohort consisted of 100 patients with a minimum graft survival of 1 yr. Three- and 5-yr patient survival rates were 88 and 71%, respectively. Similar conclusions were reached by Lloveras et al. (38), who measured GFR and effective RPF in a cohort of 39 CsA-treated heart transplant recipients. After a sharp decline during the first 3 postoperative months, both parameters stabilized and no further decline during the first year after transplantation was noted. Gonwa et al. (39) found a significant fall in GFR in 78 cardiac transplant recipients but no significant change in serum creatinine at 6 wk compared with the preoperative value. No significant decrease in GFR occurred after the initial decline during the 4-yr follow-up period (Figure 2). Those authors also reported that the incidence of ESRD in CsA-treated cardiac recipients was between 1 and 2% at four major transplant centers evaluating a total of 1,014 patients (37,39,40).

LIVER TRANSPLANTATION

The major deleterious effect on native renal function associated with CsA use occurs early after liver transplantation. O'Grady et al. (41) discontinued CsA in 8 of 73 adult liver transplant recipients because of impaired renal function or hypertension. Four of these patients were taken off CsA during the early posttransplant period when renal dysfunction occurred in association with sepsis, hypotension, and/or other drug toxicity. In addition, the majority of the patients in this study received high-dose CsA monotherapy. The dosing regimen was thought to contribute to the nephrotoxic side effects seen. McDiarmid et al. (42) reported a slow progressive deterioration in renal function established by serial calculated GFR in 31 pediatric liver transplant recipients. Six of 31 patients had normal function, whereas the majority had a rapid fall in calculated GFR within the first 3 months with a subsequent slow progressive compromise. Function appeared to stabilize, however, at 2 to 3 yr. A subsequent study evaluating 48 patients found lower actual GFR as measured by DPTA glomerular clearances in individuals receiving CsA for more than 24 months versus those between 12 and 24 months posttransplantation (43). However, serial GFR determinations were not done. A strong correlation between lower CsA blood levels (high-performance liquid chromatography) and higher GFR was found. Wheatley et al. (44) demonstrated an initial 60% decrease in renal hemodynamic function, estimated by measurements of GFR and effective RPF, in 11
liver transplant recipients. During the subsequent 9 to 15 months, renal function stabilized and actually improved when CsA levels declined with reduced dosing. No further decline was witnessed during the second and third posttransplant years, suggesting reversible renal dysfunction due to CsA therapy. Gonwa et al. (45) reported similar findings in an analysis of 308 liver transplant recipients monitored for 3 yr (Figure 3). Several studies have emphasized the importance of pretransplant native renal function in predicting the severity of acute renal dysfunction after liver transplantation. Paul et al. (46) associated severe irreversible nephrotoxicity with pretransplant renal dysfunction in older recipients. In 31 patients with hepatorenal syndrome (HRS), Gonwa et al. (45) documented a posttransplant dialysis rate of 51.6 versus 9.1% in 263 patients without HRS. Of interest, renal function increased significantly after liver transplantation in the HRS cohort. However, ESRD developed in 10 versus 0.8% of patients with and without HRS, respectively (45).

**SUMMARY AND CONCLUSION**

Acute CsA nephrotoxicity manifests as a vasomotor abnormality. It is presumed to be mediated by multiple mechanisms, including sympathetic nerve stimulation, alteration in the prostacyclin-thromboxane prostaglandin ratio, hyperresponsiveness to vasoactive peptides, and generation of ET-1. The relationship between long-term CsA use and the occurrence of obliterator vasculopathic changes in renal allografts and native kidneys is uncertain. Chronic renal morphologic changes attributed to CsA are nonspecific. Both retrospective and prospective clinical studies suggest that attrition of renal allograft function in patients receiving long-term CsA reflect the effects of chronic immunologic injury rather than a universally occurring progressive toxic nephropathy. Similarly, the evolution of native renal function in CsA-treated extrarenal solid organ transplant recipients is characterized by an initial decline in GFR, reflecting the acute vasomotor effects of CsA as well as coexisting vectors of renal injury. This early decline in native renal function appears to stabilize and has not been shown to be associated with anordinate rate of progression to ESRD. To date, no indications have emerged for conversion from CsA to azathioprine after successful solid organ transplantation.

**REFERENCES**

1. European Multicenter Trial Group: Cyclosporine in cadaveric renal transplantation: One year