Reversibility of chronic cyclosporine nephropathy in rats after withdrawal of cyclosporine

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Cyclosporin A (CsA) is one of the most potent immunosuppressants used for the management of multiple-organ transplantation. However, the clinical utility of CsA as an immunosuppressive agent has been significantly limited by the frequent occurrence of chronic CsA nephropathy, characterized by progressive renal insufficiency, arteriolopathy, interstitial inflammation, CsA nephropathy, and this is closely associated with recovery from renal injury.

Cyclosporin withdrawal; osteopontin; macrophage; tubulointerstitial fibrosis; renin-angiotensin system

Osteopontin (OPN) is a highly acidic phosphoprotein containing an arginine-glycine-aspartic acid (RGD) motif. It is involved in cell adhesion and migration and is expressed by several cell types in a constitutive or inducible fashion. These include osteoclasts, some epithelial cells, macrophages, T cells, smooth muscle cells, and some tumor cells.

The effects of CsA dose reduction, or complete withdrawal of CsA, have been previously examined in clinical trials and experimental studies. However, the results obtained are conflicting. The majority of these divergent studies are focused on morphological changes and lack evidence of a molecular basis. Moreover, most of the clinical trials are based on protocols of CsA dose reduction or complete withdrawal.
and addition of other nonnephrotoxic immunosuppressants (e.g., mycophenolate mofetil). Thus it is not clear in the clinical setting whether improved chronic allograft nephropathy (or chronic CsA nephropathy) is due to CsA dose reduction or elimination alone or the beneficial effects of other drugs. Therefore, we designed this study to investigate the progressive nature of chronic CsA nephropathy after long-term drug discontinuation and to determine the possible molecular mechanism.

MATERIALS AND METHODS

Animals and drugs. Male Sprague-Dawley rats (Charles River, Wilmington, MA), initially weighing 200–220 g, were housed in cages (Nalge, Rochester, NY) in a temperature- and light-controlled environment and allowed free access to standard laboratory chow and tap water. Rats were placed on a salt-deficient diet (0.05% sodium, Teklad Premier, Madison, WI) throughout the treatment. Cyclosporin (Novartis Pharma, Basel, Switzerland) was diluted in olive oil to a final concentration of 15 mg/ml.

Experimental design. The experimental protocol was approved by the Animal Care Committee of the Catholic University of Korea. Rats were randomized to six groups as depicted in Fig. 1. Animals received a daily subcutaneous injection of CsA (15 mg/kg) for 5 wk or CsA for 5 wk followed by 5 (CsAW5) or 10 wk (CsAW10) of CsA withdrawal. Control vehicle-treated (VH) groups received a daily subcutaneous injection of olive oil (1 ml/kg) for 5 (VH5), 10, and 15 wk (n = 5 rats/group). At each time point, animals were euthanized under ketamine anesthesia and the kidneys were rapidly removed for morphological and molecular studies.

Functional parameters. After the treatment was started, rats were pair-fed and daily body weight was monitored. Systolic blood pressure (SBP) was recorded in conscious rats by the tail-cuff method, with plethysmography using a tail manometer-tachometer system (BP-2000, Visitech System, Apex, NC); at least three readings for each rat were averaged. Before death, the animals were individually housed in metabolic cages for 24-h urine collection, and blood samples were obtained to evaluate serum creatinine (SCr). The creatinine clearance rate (C_{Cr}) was calculated using a standard formula. Whole blood CsA levels were measured by monoclonal radioimmunoassay (Incstar, Stillwater, MN). Plasma renin activity (PRA) was measured by radioimmunoassay (angiotensin I-Biotecx radioimmunoassay; Biotecx, Friendswood, TX).

Histopathology. Harvested rat kidney tissues were fixed in periodate-lysine-paraformaldehyde (PLP) solution and embedded in wax. After dewaxing, 4-μm sections were processed and stained with periodic acid-Schiff (PAS) or Masson’s trichrome and hematoxylin. Arteriolopathy of the afferent arterioles was manifested by expansion of the cell cytoplasm of terminal arteriolar smooth muscle cells by eosinophilic, granular material and semiquantitatively evaluated by counting the percentage of juxtaglomerular afferent arterioles with arteriolopathy per total number of juxtaglomerular afferent arterioles available for examination with a ×20 objective; at least 60 glomeruli/specimen were assessed. A finding of tubulointerstitial fibrosis (TIF) was defined as a matrix-rich expansion of the interstitium with tubular dilatation, tubular atrophy, tubular cast formation, sloughing of tubular epithelial cells, or thickening of the tubular basement membrane. A minimum of 20 fields/section was assessed and graded using a color image analyzer (Mustek Paragon 800 SP, Macintosh PowerPC 7100, NIH Image, version 1.5). The extent of TIF was estimated by counting the percentage of areas injured per field of cortex using a scoring scale of 0–3+: 0 = normal interstitium; 0.5 = <5% injured area; 1 = 5–15% injured area; 1.5 = 15–25% injured area; 2 = 25–35% injured area; 2.5 = 35–45% injured area; and 3 = >45% injured area, as previously described (18). Histopathological analyses were performed in randomly selected cortical fields of sections by a pathologist blinded to the identity of the treatment groups.

Northern blot analysis. A 1-kb cRNA probe was generated from a 2B7 cDNA clone of rat smooth muscle OPN (7). Sense and antisense cRNA probes were labeled with digoxigenin (DIG)-UTP using a T7 RNA polymerase kit (Boehringer Mannheim, Mannheim, Germany). Probes were precipitated, and incorporation of DIG was determined by dot blotting. Northern blotting was performed as previously reported by others (49). Briefly, kidney cortex was homogenized. Total RNA was extracted using the RNAzol reagent (TEL-TEST), and 20-μg samples were denatured with glyoxal and dimeth-
ylosulfide, size fractionated on 1.2% agarose gels, and capillary blotted onto positively charged nylon membranes (Boehringer Mannheim). Membranes were hybridized overnight at 68 or 42°C with DIG-labeled cRNA (or 32P-labeled cDNA probes for GAPDH) in a DIG wash and Block Buffer Set solution (Boehringer Mannheim). After hybridization, membranes were washed finally in 0.1×/100 SSC/0.1% SDS at 68°C or 0.2×/100 SSC/0.1% SDS at 42°C. Bound probes were detected using sheet anti-DIG antibody (Fab) conjugated with alkaline phosphatase (Boehringer Mannheim) and development with CSPD-star-enhanced chemiluminescence (Boehringer Mannheim). Densitometry analysis was performed using NIH Image software. Three determinations for each band were averaged and referenced to GAPDH.

**In situ hybridization.** In situ hybridization was performed on wax-embedded sections using a microwave-based protocol as previously described by others (49). After dewaxing, sections were treated with a microwave oven twice for 5 min, incubated with 0.2 mol/l HCl for 15 min, followed by 1% Triton X-100, washed, and then digested for 20 min with 10 μg/ml proteinase K at 37°C (Boehringer Mannheim). Sections were washed in 2×/100 SSC, prehybridized, and then hybridized with 0.3 ng/μl DIG-labeled sense or antisense OPN cRNA probe overnight at 37°C in a hybridization buffer containing 50% deionized formamide, 4×/100 SSC, 2×/100 Denhardt’s solution, 1 mg/ml salmon sperm DNA, and 1 mg/ml yeast tRNA. Sections were finally washed in 0.1×/100 SSC at 37°C, and the hybridized probe was detected using sheep anti-DIG antibody (Fab) conjugated with alkaline phosphatase and color development with nitro blue tetrazolium/X-phosphate (Boehringer Mannheim). No signal was seen with the sense riboprobe labeled to the same specificity.

**Immunohistochemistry.** After dewaxing, sections were incubated with 0.5% Triton X-100-PBS solution for 30 min and washed three times with PBS. Nonspecific binding sites were blocked with normal horse serum diluted 1:10 in 0.3% BSA.
for 30–60 min and then incubated for 2 h at 4°C in mouse antiserum against OPN (MPIIB10; obtained from the Developmental Studies Hybridoma Bank, University of Iowa, Iowa City, IA) diluted 1:1,000 in a humid environment. After a rinsing in Tris-buffered saline (TBS), sections were incubated in peroxidase-conjugated rabbit anti-mouse IgG (Amersham Pharmacia Biotech, Piscataway, NJ) for 30 min. For coloration, sections were incubated with a mixture of 0.05% 3,3′-diaminobenzidine containing 0.01% H2O2 at room temperature until a brown color was visible, washed with TBS, counterstained with hematoxylin, and examined under light microscopy. The procedure of immunostaining for ED-1 (Serotec) and renin was similar to that for OPN. The antibody against renin was kindly provided by Dr. Kirsten Madsen (Dept. of Medicine, University of Florida, Gainesville, FL). This antibody is known to recognize rat renin and prorenin (23). The number of ED-1-positive cells was counted in at least 20 fields of cortex/section under ×200 magnification, and renin-positive glomeruli were evaluated by counting a minimum of 50 glomeruli/specimen (43).

Statistical analysis. Data are expressed as means ± SE. All parameters were compared with the VH5 group (n = 5), because there were no significant differences in the control vehicle-treated rats at any time point. Multiple comparisons among groups were performed by one-way ANOVA with the post hoc Bonferroni test (SPSS software, version 9.0, Microsoft). The Pearson single-correlation coefficient was used to compare osteopontin mRNA expression with renal injury (ED-1-positive cell and the TIF score) and plasma renin activity. Statistical significance was assumed as P < 0.05.

Fig. 3. Degree of renal tubulointerstitial fibrosis in the experimental groups and semi-quantitative scoring. Representative photomicrographs showing that striped tubulointerstitial fibrosis, inflammatory cell infiltration, and extracellular matrix deposition were produced in the kidneys after CsA treatment for 5 wk, whereas lesions were significantly reduced by 5 wk of CsA withdrawal and further improved during 10 wk. Trichrome staining, original magnification, ×40. #P < 0.001 vs. VH. ##P < 0.05 vs. CsA. *P < 0.05 vs. CsAW5. 
RESULTS

Effects of cyclosporine withdrawal on functional parameters in rats with established chronic CsA nephrotoxicity. Table 1 summarizes the functional parameters in each group. In the present study, SBP and renal function in the VH rat kidneys on a low-salt diet were slightly different from that in rats on a normal-salt diet (SBP: $138 \pm 11$ vs. $117 \pm 6 \text{ mmHg}$; $\text{Scr}: 0.55 \pm 0.02$ vs. $0.65 \pm 0.02 \text{ mg/dl}$; $\text{Ccr}: 0.55 \pm 0.02$ vs. $0.47 \pm 0.02 \text{ ml/min} \cdot 100 \text{ g}^{-1}$, respectively), as previously reported by our laboratory (44). This may be associated with the stress condition, considering a low-salt diet for a long-term period. SBP measured by tail-cuff pressure was not significantly different between the treatment groups throughout the study. Whole blood CsA concentrations were dramatically decreased in the CsA-treated rats during the period of CsA withdrawal. The mean body weight of CsA-treated rats was significantly lower than that of the VH rats ($234 \pm 5$ vs. $285 \pm 4 \text{ g}$, $P < 0.001$). With CsA discontinuation, body weight was significantly increased compared with CsA-treated rats ($288 \pm 8 \text{ g}$; CsAW10, $305 \pm 6 \text{ g}$; $P < 0.001$ vs. CsA, respectively). Daily treatment of rats with CsA for 5 wk caused higher levels of $\text{Scr}$ ($1.14 \pm 0.11$ vs. $0.65 \pm 0.02 \text{ mg/dl}$, $P = 0.001$) and lower levels of $\text{Ccr}$ ($0.14 \pm 0.01$ vs. $0.47 \pm 0.02 \text{ ml/min} \cdot 100 \text{ g}^{-1}$, $P < 0.001$) than that in VH rats, whereas 5 and 10 wk of CsA withdrawal normalized these parameters.

Effects of cyclosporine withdrawal on histopathology in rats with established chronic CsA nephrotoxicity. CsA-treated rats showed the typical histopathological features of chronic CsA nephrotoxicity (afferent arteriolopathy, striped interstitial fibrosis, and tubular atrophy with focal inflammatory cell accumulation). Afferent arteriolopathy was manifested as the replacement of smooth muscle cells of the afferent glomerular arteriole by a PAS-positive material, resulting in a typical circumferential appearance of the lesion (Fig. 2). On our semiquantitative scoring system, the arteriolopathy was significantly higher in the CsA group than the VH group ($26 \pm 2$ vs. $11 \pm 1$, $P < 0.001$), whereas this was markedly decreased after 5 or 10 wk of CsA washout compared with the CsA group (CsAW5, 13 ± 1; CsAW10, 12 ± 1; $P < 0.01$ vs. CsA, respectively). A significant increase in TIF score (Fig. 3) was also observed in the CsA group compared with the VH group (1.8 ± 0.20 vs. 0.22 ± 0.04, $P < 0.001$). However, 5 wk of CsA withdrawal significantly decreased the TIF score compared with the CsA group (1.0 ± 0.07, $P < 0.001$), and a further decrease was found after 10 wk of withdrawal compared with the CsAW5 group (0.5 ± 0.07, $P = 0.034$).

Effects of cyclosporine withdrawal on the RAS in rats with established chronic CsA nephrotoxicity. We used immunohistochemistry for renin and PRA to evaluate the status of the RAS. Figure 4 shows the status of RAS.

![Image A](http://ajprenal.physiology.org/)

**Fig. 4.** A: immunohistochemistry of intrarenal renin. B: semiquantitative analysis of renin-positive glomeruli. C: plasma renin activity. Increased intrarenal immunoreactivity of renin, renin-positive glomeruli (arrows), and plasma renin activity seen in CsA-treated rat kidneys was markedly decreased when CsA was withdrawn. Immunohistochemical staining, original magnification, ×200. #P < 0.001 vs. VH. ##P < 0.05 vs. CsA.
in different experimental groups. Intrarenal expression of renin was minimal in the VH group (Fig. 4, A and B, 10 ± 1), but its immunoreactivity and the number of renin-positive glomeruli significantly increased in the CsA group compared with the VH group (26 ± 4, P < 0.001). With CsA withdrawal for 5 or 10 wk, immunoreactivity and the number of renin-positive glomeruli were significantly reduced and were similar to the levels in the VH group (CsAW5, 13 ± 2; CsAW10, 12 ± 2; both P < 0.05 vs. CsA). Similarly, the increased PRA in CsA-treated rats (35.2 ± 2 ng·ml⁻¹·h⁻¹, P < 0.05 vs. VH) was significantly decreased after CsA withdrawal (Fig. 4C, CsAW5, 24.9 ± 2 ng·ml⁻¹·h⁻¹, CsAW10, 23.0 ± 3 ng·ml⁻¹·h⁻¹; both P < 0.05 vs. CsA).

Effects of cyclosporine withdrawal on macrophage infiltration in rats with established chronic CsA nephrotoxicity. ED-1-positive cells were detected only infrequently in the kidneys with VH treatment (11 ± 1), but with CsA treatment for 5 wk their numbers increased markedly (53 ± 5, P < 0.001 vs. VH) in areas where TIF was observed (Fig. 5). After 5 wk of CsA withdrawal, ED-1-positive cells significantly decreased compared with the CsA group (31 ± 2, P < 0.001). Moreover, there was a further decrease in ED-1-positive cells when CsA was withdrawn for 10 wk (19 ± 1, P = 0.038 vs. CsAW5) accompanied by a reduction in TIF.

Effects of cyclosporine withdrawal on OPN expression in rats with established chronic CsA nephrotoxicity. Northern blot analysis of the kidney cortex revealed a dramatic increase in OPN mRNA in the CsA group vs. the VH group during the 5-wk period (Fig. 6; 8.7-fold, P < 0.001). Upregulation of OPN expression was significantly decreased after 5 wk of CsA discontinuation (4.8-fold relative to the VH group, P < 0.05) and was further decreased by 10 wk (2.6-fold relative to the VH group, P < 0.05). To localize OPN mRNA and protein, in situ hybridization and immunohistochemistry were carried out. In the VH-treated rat kidneys, much higher levels of OPN mRNA and protein were observed. These were confined to tubular epithelium, collecting ducts, and uroepithelial lining cells. Most cortical structures were negative for OPN. In contrast,

Fig. 5. Representative photomicrographs of immunohistochemistry for ED-1 in experimental groups (A) and semiquantitative analysis (B). CsA treatment induced a significant focal macrophage influx within the tubular interstitium, where fibrotic lesions had developed, but their numbers decreased gradually when CsA was withdrawn for 5 or 10 wk. Immunohistochemical staining, original magnification, ×100. #P < 0.001 vs. VH. ##P < 0.001 vs. CsA. *P = 0.038 vs. CsAW5.

Fig. 6. Northern blotting and quantitative analysis of osteopontin (OPN) mRNA. This Northern blot shows that the expression of OPN mRNA was significantly upregulated in the CsA-treated group, whereas their expression was markedly decreased after 5 wk of drug withdrawal and further decreased by 10 wk. Relative OPN mRNAs are referenced to GAPDH; data are expressed as relative-fold increases. #P < 0.001 vs. VH. ##P < 0.05 vs. CsA. *P < 0.05 vs. CsAW5.
the levels of OPN mRNA and protein were dramatically elevated in tubular epithelium and Bowman’s capsule cells in the CsA-treated rats. The most striking changes were seen in the renal cortex (Fig. 7), which normally express very little constitutive OPN. It is notable that the sites of strong OPN mRNA and protein expression were in areas of severe TIF. After 5 wk of CsA withdrawal, levels of upregulated OPN mRNA and protein were significantly decreased compared with the CsA group, and a further decrease was observed in the CsAW10 group.

**Correlations between OPN expression, renal injury, and plasma renin activity.** To study the relationships between OPN expression and renal injury and the RAS, correlation analysis was performed in the experimental groups (Fig. 8, n = 29). The decrease in OPN mRNA expression correlated well with the reduction in the number of ED-1-positive cells ($r = 0.651$, $P < 0.01$) and recovery from tubulointerstitial fibrosis ($r = 0.729$, $P < 0.01$). Furthermore, plasma renin activity was positively correlated with OPN mRNA expression ($r = 0.645$, $P < 0.01$) and the tubulointerstitial fibrosis score ($r = 0.762$, $P < 0.01$).

**DISCUSSION**

This study clearly demonstrated the evolution of chronic CsA nephropathy after CsA withdrawal. Both renal function and histopathology (arteriolopathy, interstitial inflammatory cell infiltration, and fibrosis) were significantly improved with CsA withdrawal. The upregulation of OPN expression in CsA-treated rat kidneys was dramatically decreased after discontinuation of CsA, and this decrease correlated well with reductions in macrophage infiltration and tubulointerstitial fibrosis. Thus one of the mechanisms by which long-term CsA withdrawal effectively reverses chronic CsA nephropathy may be via decreased expression of the proinflammatory cytokine OPN.

OPN has a number of functions in diseased kidneys, including inhibiting inducible NO synthase (32), protecting cells from apoptosis (24), promoting cell proliferation and regeneration in the recovery process after ischemic injury (41), and acting as a chemoattractant for monocyte/macrophages (4, 35). The diverse functions of OPN are thought to be mediated via distinct receptors (42). In the present study, we found that OPN mRNA and protein expression were markedly upregulated in cortical tubules after 5 wk of CsA treatment, along with macrophage infiltration into the tubulointerstitium, where severe fibrosis was observed. This finding is consistent with data on chronic CsA nephropathy showing an association between the degree of tubular OPN expression and the severity of interstitial macrophage accumulation and fibrosis (29, 45). Furthermore, mice lacking OPN (OPN $^-/-$) showed less chronic CsA nephrotoxicity than OPN wild-type (OPN $^{+/+}$) mice (21), indicating a pathological role for OPN in this model.

An interesting finding in this study is that CsA withdrawal decreased OPN mRNA and protein expression in a time-dependent manner. The decrease in OPN expression was accompanied by improved renal function and correlated well with the reduction in the number of macrophages ($r = 0.651$, $P < 0.01$) and recovery from tubulointerstitial fibrosis ($r = 0.729$, $P < 0.01$). Recent in vivo studies have demonstrated that upregulation of OPN expression was associated with loss of renal function, macrophage accumulation, and severe histological damage. Suppression of its expression reversed these abnormalities (47, 49). Thus we propose that chronic CsA nephropathy may be revers-
ible with long-term drug discontinuation and that this is related to decreased OPN expression.

It is generally accepted that renal function impairment induced by CsA improves after CsA withdrawal (6, 12, 14, 27, 40, 43; Wei C, Song H, Seta K, Kinjo M, Lau P, Fink JC, Drachenberg C, Papadimitriou J, Bartlett ST, and Weir MR, unpublished observations). However, the efficacy of CsA withdrawal on the progression of chronic CsA-induced fibrosis remains controversial. The reasons for this discrepancy are unknown. In previous studies, our laboratory has reported that CsA withdrawal for 8 wk did not reverse tubulointerstitial fibrosis (6). However, 5 wk of CsA withdrawal was effective in reversing the progression of tubulointerstitial fibrosis when chronic CsA nephrotoxicity was induced by administering a relatively low dose of CsA (7.5 mg·kg\(^{-1}\)·day\(^{-1}\)) (43). These findings raise the possibility that the effectiveness of CsA withdrawal on chronic CsA nephropathy is dependent on the CsA dose used and the timing of drug elimination.

How CsA withdrawal abolishes renal tubular OPN expression in this model is unclear, but it may be related to the decreased RAS activity seen in CsA-withdrawn rat kidneys. It is well known that the activation of RAS caused by CsA may stimulate OPN expression (29, 44), and blocking RAS with either an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor type I antagonist could reduce OPN expression (5, 31, 49). In the present study, we examined renin activity using plasma renin activity and immunohistochemistry, because both parameters have been shown to increase in chronic CsA nephropathy (3, 44, 46). The results of this study revealed that CsA discontinuation significantly decreased plasma renin activity, renin immunoreactivity, and the number of renin-positive glomeruli. Furthermore, plasma renin activity was positively correlated with OPN mRNA expression (\(r = 0.645, P < 0.01\)) and the tubulointerstitial fibrosis score (\(r = 0.762, P < 0.01\)). This finding was consistent with a previous report from our laboratory (43) and a human study (Wei C, Song H, Drachenberg CI, Papadimitriou JC, Bartlett ST, Fink J, and Weir MR, unpublished observations) describing the efficacy of CsA withdrawal on RAS activity.

It is also possible that CsA withdrawal decreases OPN expression by reducing CsA-induced hypoxia. Chronic CsA nephrotoxicity is associated with afferent arteriolopathy, which ultimately leads to a reduction in renal blood flow and thus may exert hypoxic injury (17, 38, 50). Recent in vitro studies in cultured mesangial and LLC-PK\(_1\) tubular epithelial cells exposed to a hypoxic environment showed increased proliferation and collagen synthesis, with stimulation of OPN release (36, 37). In the present study, CsA withdrawal markedly reversed CsA-induced arteriolopathy to a level similar to that in control animals. This finding is in agreement with recent reports (17, 37, 50) implicating a role for CsA-associated hypoxia in the induction of renal OPN expression. In addition, CsA is able to induce TGF-\(\beta\)1 production directly or indirectly (16, 30, 49).
34), which may stimulate OPN expression (20). Although we did not examine the levels of TGF-β1 in this study, a previous study from our laboratory showed that CsA withdrawal significantly reduced TGF-β1 mRNA expression (43). Similar results were also reported from a human study (Song H, Seta K, Kinjo M, Lau P, Fink JC, Drachenberg C, Papadimitriou J, Bartlett ST, Weir MR, and Wei C, unpublished observations). Therefore, it is likely that decreased TGF-β1 expression after CsA withdrawal may affect OPN expression in this model.

In summary, long-term CsA withdrawal is able to decrease interstitial inflammation induced by the proinflammatory cytokine OPN. This is closely associated with the reversal of chronic CsA nephrotoxicity. This study provides a rationale for how to reduce CsA-associated nephropathy in the clinical setting. Further clinical trials are required to determine the appropriate dose of CsA (or CsA withdrawal) that with the addition of nonnephrotoxic immunosuppressants (e.g., mycophenolate mofetil), will achieve optimal immunosuppression while avoiding the risk of acute rejection.

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