Long-Term Renal Effects of Low-Dose Cyclosporine in Uveitis-Treated Patients: Follow-Up Study

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Abstract. Cyclosporine (CsA), a widely used immunosuppressive drug, is an effective treatment of sight-threatening posterior idiopathic uveitis. CsA’s main side effect is nephrotoxicity. The aim of this single-center prospective cohort study (conducted in a tertiary care teaching hospital in Paris, France) was to assess the long-term renal tolerance of a low-dose CsA treatment in patients with previously healthy kidneys on clinical, biologic, and pathologic criteria. Forty-one patients treated with 4.3 ± 1.6 mg/kg body wt per day CsA for 44.9 ± 3.6 mo were included. Mean follow-up was 55.4 ± 0.2 mo. BP, CsA trough level, and renal function were prospectively monitored together with blood urea, creatinine clearance, GFR, and effective renal plasma flow. Eleven patients underwent serial kidney biopsies before and after 2 yr of a 4 ± 0.9 mg/kg daily CsA treatment. Sustained low-dose CsA treatment induced a significant increase in plasma creatinine (P < 0.0001), a significant decrease in creatinine clearance (P < 0.0001), and isotopic GFR (P < 0.0001) over time. The highest dose induced more severe alterations in any of the renal parameters than the lowest dose. Prevalence of hypertension was particularly high. Histopathologic data showed significant interstitial fibrosis (P < 0.003) and tubular atrophy (P < 0.003) after 2 yr. Low-dose long-term CsA treatment induces significant renal impairment and a high incidence of hypertension. Our study suggests that lowering daily dosage may prevent CsA-induced nephrotoxicity if a daily dose of ≤3 mg/kg is used. Whether once established it is reversible is still prospective, although the occurrence of interstitial fibrosis in the kidney would argue against reversibility.

Although new potent immunosuppressive agents have been recently released, cyclosporine (CsA) is still widely used in transplant (1) and autoimmune disease patients (2–5). CsA remains the cornerstone therapy in noninfectious posterior uveitis (6), nephrotoxicity being the major drawback for its use. The main unsolved issues are related to whether CsA-induced renal dysfunction is dose-dependent and reversible. None of them has been clarified despite extensive use of this drug. In a previous study, we have drawn attention on the high incidence of CsA-induced nephrotoxicity and hypertension in autoimmune uveitis patients treated with CsA with a mean initial daily dosage of 5 mg/kg per d (7). We now report on the long-term effects of CsA on renal function and BP after low-dose treatment in sight-threatening uveitis patients. Because of the absence of any disease-related renal abnormalities and no concomitant nephrotoxic drug, any alteration in renal function or any pathologic damage evidenced in these settings can be largely attributed to CsA treatment.

Materials and Methods

Patient Selection and Study Design

After obtaining approval from the institutional review boards of our institution and informed consent from patients, we enrolled 41 patients between April 1986 and December 1997 in a nonrandomized, open-label, prospective study. Inclusion criteria were age >18 yr and idiopathic autoimmune intermediate or posterior uveitis resistant to steroid treatment. Significant alteration of renal function was an exclusion criteria if creatinine clearance was below 75 ml/min per 1.73 m². CsA was administered orally at a mean initial dosage of 4.3 ± 1.6 mg/kg body wt per day (in two divided doses) and gradually tapered after each outpatient visit at the ophthalmology clinic provided that ocular inflammatory activity grade decreased and best-corrected visual acuity was stable or improved. Patients enrolled after December 1990 received a lower initial daily dose (3.16 mg/kg per d) than patients enrolled earlier. Patients were seen at regular intervals as designated by the protocol or sooner if the patient felt any change in his or her status. Data were collected at baseline, after 3, 6, 12, and 18 mo, and on a yearly basis thereafter. Clinical (body weight, systolic and diastolic BP, and pulse rate) and biologic parameters (CsA trough levels, serum creatinine level and creatinine clearance, serum uric acid level, serum urea nitrogen level, plasma electrolyte levels, plasma cholesterol and triglyceride, urinary creatinine, and proteinuria) were recorded at baseline and at each subsequent visit. End of the study was defined by CsA treatment withdrawal or end of the follow-up. GFR
and effective renal plasma flow (ERPF) were assessed before treatment and yearly thereafter.

**Laboratory Evaluation**

The serum creatinine level was measured by an autoanalyzer using the Jaffe colorimetric assay. GFR and ERPF were estimated by single injection plasma methods previously described respectively by Russel (8) for 99mTc-diethyletriaminepentaacetic acid (99mTc-DTPA) and by Tauxe et al. (9) for 131I-ortho iodo hippurate. CsA trough levels were measured 12 h after the last dose and were initially determined using a commercial radioimmunoassay (RIA; Novartis, Basel, Switzerland). During the follow-up, the pharmacology department decided to use the polyclonal fluorescence polarization immunoassay (FPIA), Abbott TDx (Abbott Laboratories, Rungis, France). It has been demonstrated that CsA concentrations measured with FPIA TDx are usually 15 to 20% above the RIA measurements (10). For the purpose of this study, the measurements obtained with the TDx test were decreased by 20% before being pooled together with the initial dosages (obtained by RIA) to allow statistical comparison.

**Histologic Examination**

A subgroup of 11 patients agreed to undergo a percutaneous kidney biopsy before initiation of treatment and after 2 yr. These patients were not selected on the basis of level of renal function or other medical criteria. No specific signed informed consent or ethical committee was demanded by the investigational review board of our institute at that time, but clear and appropriate information was given and oral consent retrieved from all patients before procedure. All samples were analyzed in a blinded fashion. Each renal specimen was processed for light microscopy after fixation in Dubosq-Brazil fluid. Pathologic examination was done on several serial 3-μm-thick sections stained principally by Masson trichrome with light green and periodic acid-Schiff (PAS) and silver methenamine. A second semiquantitative evaluation of interstitial fibrosis was performed with red Sirius. Lesions associated with CsA therapy were evaluated following the data of the advisory board of nephropathologists (11). Some criteria were evaluated semiquantitatively either by counting the number of lesions by tissue section or by assigning a grade of severity. The morphologic findings assessed on the renal biopsies were as follows.

**Glomeruli.** Total number in section with most glomeruli present; number of ischemic collapsed glomeruli; number of obsolescent glomeruli with global sclerosis; number of glomeruli with thickening of Bowman capsule basement membrane.

**Arterioles in Cortical Area.** Total number of arterioles; number of arterioles with vacuolization of endothelial and/or smooth muscle cells; number of arterioles with subendothelial hyalinosis as seen in hypertension or diabetes; number of arterioles with characteristic CsA arteriolopathy (individual hyaline deposits on outer surface of vascular wall or ring of nodular hyaline deposits).

**Tubulointerstitial Space.** Tubular atrophy and interstitial fibrosis were scored from 0 to 4+; 0 was given in the absence of any lesion (normal); 1 was given to biopsies showing minimal changes; 2 was given to biopsies showing light lesions that were present in all sections; 3 indicated moderate changes; 4 indicated severe changes.

**Statistical Analyses**

Values are expressed as mean ± SD or % (n). Repeated measures across time were compared using linear mixed model (ANOVA with random effect), with a random effect for patient and a fixed effect for time (12). Tukey-Kramer adjustment for multiple comparisons was used. We hypothesized that renal function started from a value at baseline (a) and decreased to long-term value (b). i is the time elapsed since initiation of the treatment and (c) expressed in days = 1, a parameter accounting for evolution rate. Parameters (a) and (b) may vary across individuals, accounting for interindividual variability, (c) being kept constant. The mean difference (a − b) expresses the effect of CsA treatment on renal function and is tested to 0 using the likelihood ratio test. Analyses are based on linear mixed models (Mixed Procedure on SAS) (13) with (c) maximizing log-likelihood. A refined but similar model was used to compare the effect of CsA on renal function between groups of patients (low- or high-dose). Renal histology was compared before and after a 2-yr period of CsA treatment using a Wilcoxon paired signed rank test. P values less than 0.05 were considered statistically significant. Statistical analyses were performed using the SAS 8.1 statistical package (SAS Institute, Cary, NC).

**Results**

Forty-one patients (23 female and 18 male) were included in the study within 140 mo. Mean age was 49 ± 10 yr, and baseline body weight was 70 ± 14 kg. None of the patients had received any other nephrotoxic drugs (including nonsteroidal antiinflammatory drugs). Baseline biochemical parameters were normal (Table 1).

Mean treatment duration was 44.9 ± 3.6 mo. Mean CsA daily dosage was gradually tapered from 4.3 ± 1.6 mg/kg to 1.8 ± 0.9 mg/kg (5 yr). Before treatment all patients but six were normotensive, but a significant number of patients became hypertensive (diastolic BP >95 mmHg or systolic BP >160 mmHg or both) during CsA therapy. Hypertensive patients were treated with either a β-adrenergic receptor blocking agent, an ACE inhibitor, a calcium channel blocker, or a diuretic. In all but two patients, BP was treated with one drug.

Nineteen patients were already taking steroids before starting CsA. Among patients who became hypertensive during follow-up, steroid therapy was present in 50%, 50%, 59%, 61%, 78%, 69%, and 77% after 3 and 6 mo and 1, 2, 3, 4, and 5 yr, respectively. Among the six patients who did not experience hypertension (HTA) during the study, all of them were concomitantly treated with steroids.

None of our patient had gout while being treated with CsA. Uric acid, serum cholesterol, triglyceride, potassium, and total bilirubin levels increased significantly over time (Table 1). Fasting glucose levels and serum calcium remained unchanged during the follow-up. Renal function before treatment was normal in all patients (Table 1). No patient had proteinuria or urine sediment abnormalities before CsA therapy was initiated. Mean observed serum creatinine value was 0.93 ± 0.15 mg/dl (82 ± 13 μmol/L) at entry and increased significantly over time (P < 0.0001; c = 100 −1) (Table 1 and Figure 1, panel A). Observed creatinine clearance was 102 ± 24 ml/min per 1.73 m² at baseline and decreased significantly over time (P < 0.0001; c = 100 −1) (Table 1 and Figure 1, panel B). Observed effective renal plasma flow was 435 ± 159 ml/min before treatment and tended to decrease over time (P = NS). Observed GFR was 106 ± 26 ml/min before treatment and decreased significantly over time (P < 0.0001) (Table 1 and Figure 1, panel C). Mean observed blood urea value increased significantly over time (P < 0.0001).
Table 1. Demographic and biological data at baseline and during treatment with low-dose CsA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>3 mo</th>
<th>6 mo</th>
<th>2 yr</th>
<th>4 yr</th>
<th>5 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>CsA daily dosage (mg/kg)</td>
<td>4.3 ± 1.6 (n=41)</td>
<td>4.4 ± 1.3 (n=41)</td>
<td>4.5 ± 1.2 (n=22)</td>
<td>4.5 ± 1.3 (n=22)</td>
<td>4.1 ± 1.2 (n=22)</td>
<td>3.9 ± 1.0 (n=22)</td>
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<tr>
<td>Hypertensive patients on steroids (%)</td>
<td>67</td>
<td>50</td>
<td>50</td>
<td>59</td>
<td>61</td>
<td>78</td>
</tr>
<tr>
<td>Plasma creatinine (mol/L)</td>
<td>82</td>
<td>116</td>
<td>20</td>
<td>174</td>
<td>107</td>
<td>103</td>
</tr>
<tr>
<td>Isotopic ERPF (ml/min)</td>
<td>435</td>
<td>159</td>
<td>405</td>
<td>117</td>
<td>357</td>
<td>96</td>
</tr>
<tr>
<td>Observed creatinine clearance (ml/min per 1.73 m²)</td>
<td>102</td>
<td>106</td>
<td>106</td>
<td>106</td>
<td>106</td>
<td>106</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
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<td>6.0</td>
<td>6.0</td>
<td>6.0</td>
<td>6.0</td>
<td>6.0</td>
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<tr>
<td>Triglycerides (mmol/L)</td>
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<td>1.4</td>
<td>1.4</td>
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<td>1.4</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.1</td>
<td>4.1</td>
<td>4.1</td>
<td>4.1</td>
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<tr>
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<td>20</td>
<td>174</td>
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<td>405</td>
<td>117</td>
<td>357</td>
<td>96</td>
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<td>106</td>
<td>106</td>
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<td>106</td>
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<tr>
<td>Cholesterol (mmol/L)</td>
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<td>6.0</td>
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<td>6.0</td>
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<tr>
<td>Triglycerides (mmol/L)</td>
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<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
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<td>4.1</td>
<td>4.1</td>
<td>4.1</td>
<td>4.1</td>
<td>4.1</td>
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</table>

To determine whether initial CsA dosage is critical to renal tolerance over time, we compared renal parameters in two subgroups of patients based on initial daily dosage with a cut-off value of 3.16 mg/kg per d. Twenty-eight patients were initially included with a daily CsA dose of at least 3.16 mg/kg per d with a mean treatment period of 54.6 ± 4.1 mo. Thirteen patients received less than 3.16 mg/kg per d initially with a mean treatment period of 24.0 ± 4.1 mo. The increase in observed serum creatinine value was significantly higher in patients treated with the highest dose (0.32 mg/dL [28 mmol/L]) compared with the lowest dose (0.09 mg/dL [8 mmol/L]; P < 0.003) as was the decrease in creatinine clearance and also in GFR. Indeed, a 38 ml/min per 1.73 m² difference in creatinine clearance level (P < 0.0001) and a 23 ml/min difference in the GFR level (P < 0.0009) were observed over time between the two subgroups, strengthening the significant better renal tolerance of patients receiving the lowest initial dose (Figure 2, panels A, B, and C). Taking into account cumulative dosage of CsA showed the same results (cumulative dosage increases with time). The higher the trough level of CsA, the poorer the renal function was. Same effect was evidenced for urea blood levels with an increase over time of 7.8 mg/dL (2.8 mmol/L) versus 2.8 mg/dL (1.0 mmol/L) in high-dose and low-dose patients, respectively (P < 0.02). Initial CsA daily dosage showed no specific effect on ERPF. Similarly, incidence of HTA was not enhanced by higher initial CsA dosage. No change in urinalysis occurred during follow-up.

Renal Histology

Renal histology results are shown in Table 2. In 11 patients (7 men and 4 women; mean age, 53 ± 8 yr), a kidney biopsy was performed before initiation (RB1) and after 2 yr of treatment (RB2). Mean CsA daily dosage was 4.4 ± 0.9 mg/kg per d initially and 3.4 ± 1.0 mg/kg per d after 2 yr. Mean creatinine clearance was 105 ± 24 initially and 86 ± 17 ml/min per 1.73 m² after 2 yr (P > 0.12). Mean GFR was 104 ± 24 and 81 ± 20 ml/min per 1.73 m² after 2 yr (P < 0.04). Immunofluorescence microscopy study showed no deposits on RB1 and was therefore not performed on RB2. No interstitial infiltrate was observed in either biopsy, ruling out the possibility of interstitial nephritis in our uveitis patients. We observed a significant increase in glomerular sclerosis (P < 0.05) and a significant thickening of the Bowman capsule (P < 0.003) as well as significant tubular atrophy (P < 0.003) and interstitial fibrosis (P < 0.003) after 2 yr compared with initial pathologic pattern. Same results were shown with Sirius red staining with a significant increase in the score for interstitial fibrosis (P < 0.003). A nonsignificant increase in the number of vascular sections exhibiting lesions of interest (arteriolar hyalinosis) was observed. Neither glomerular nor arteriolar thrombotic microangiopathy was present. The higher the initial daily dose of CsA, the higher the number of obsolescent glomeruli (r = 0.61; P > 0.05). There was no other significant correlation evidenced between dose or daily dosage and histologic parameters.
Discussion

Our study demonstrates that long-term low-dose CsA treatment significantly impairs renal function in patients with healthy native kidneys. A decrease in GFR together with irreversible renal damage assessed by kidney biopsy is evidenced despite continuous drug dosage tapering. Moreover, incidence of hypertension is dramatically increased concomitantly with CsA treatment. Initial daily dosage seems critical to renal tolerance, because patients receiving less than 3.16 mg/kg per d seem to experience less renal damage than those taking a higher dosage. If the establishment of significant interstitial fibrosis and glomerular sclerosis is an indicator of irreversible renal damage, then even low-dose CsA treatment seriously impairs renal function. We have previously reported (7) a significant decrease of GFR and ERPF after a 5 mg/kg per d CsA treatment for 24 mo. It is well known that CsA treatment induces intrarenal vasoconstriction (14–17) and enhances vascular reactivity to various contractile agonists (18) that is thought to become permanent and irreversible after 3 mo (19,20). CsA-induced alteration of GFR has been studied primarily in liver (21), renal (22,23), and cardiac transplant recipients (24,25). In those patients, CsA-induced nephrotoxicity may lead to end-stage renal failure and dialysis (26–29). The situation is most severe in cardiac transplant patients, with a 12% incidence of severe renal failure 10 yr after transplantation (30). However transplantation is a condition often associated with multifactorial decline in renal function (31,32). Most studies were descriptive and retrospective, evaluated renal function on the basis of plasma creatinine, which is a notoriously inaccurate marker of renal function, did not include any value (either by measurement or calculation) of the GFR, and did not report pathologic data corroborating with biologic evidence of renal failure (33,34). For the same reasons, and because of the underlying renal lesions, CsA renal effects in glomerulonephritis or nephrotic syndrome cannot be interpreted easily.

Nephrotoxicity is so far the main problem of CsA treatment in autoimmune diseases. Most reports of histopathologic data obtained after exposure to CsA included patients with heterogeneous autoimmune diseases, such as relapsing polychondritis, Behcet disease, Sjogren syndrome, and systemic lupus erythematosus (35). In many studies, serial biopsies were not performed but pathologic data were compared to autopsy material or age-matched transplant donors (36,37). In rheumatoid arthritis patients, analysis of CsA renal effect is hampered by the fact that the disease itself, as well as associated nonsteroidal antiinflammatory drugs, may adversely affect the kidney (38,39). In patients with psoriasis, Young et al. (37) compared kidney biopsy specimens from 19 CsA-treated psoriasis patients (3.9 mg/kg per d for 1 yr) with 38 age-matched transplant donors showing increased interstitial fibrosis and tubular atrophy secondary to CsA therapy. Additional interstitial fibrosis and tubular atrophy and the onset of CsA-associated arteriopathy were observed on serial kidney biopsies performed in 11 patients after an additional 2 yr of CsA treatment. Powels et al. (40) reported on renal function in two cohorts of patients with chronic plaque psoriasis who had been treated with low-dose CsA (2.8 mg/kg per d). In seven patients treated for 10 yr, persistent increase in serum creatinine over 30% of the baseline value was present over follow-up. GFR was >30% below the baseline value in three patients. Two of them had repeated renal biopsies because of deterioration of renal function showing evidence of CsA nephrotoxicity. In a second group of patients (n = 20) treated for 6 yr, serum creatinine was persistently 30% above baseline in nine patients and 50% above baseline in five patients. BP was also reported to increase.

**Table 2. Quantitative assessment of pathological lesions induced by CsA**

<table>
<thead>
<tr>
<th>Pathological Lesion</th>
<th>Renal Biopsy (day 0)</th>
<th>Renal Biopsy (2 yr)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glomerular lesions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>number of glomeruli</td>
<td>21 ± 9</td>
<td>28 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>obsolete glomeruli</td>
<td>0.7 ± 1.2</td>
<td>3.5 ± 5.8</td>
<td>0.05</td>
</tr>
<tr>
<td>ischemic glomeruli</td>
<td>0</td>
<td>0.7 ± 2.1</td>
<td>NS</td>
</tr>
<tr>
<td>thickening of the bowman capsule</td>
<td>0.6 ± 1.2</td>
<td>3.3 ± 3.3</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Tubulointerstitial lesions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tubular atrophy</td>
<td>0.6 ± 0.7</td>
<td>2.0 ± 0.9</td>
<td>0.003</td>
</tr>
<tr>
<td>interstitial fibrosis</td>
<td>0.6 ± 0.17</td>
<td>2.0 ± 0.9</td>
<td>0.003</td>
</tr>
<tr>
<td>interstitial fibrosis (Red sirius)</td>
<td>0.41 ± 0.45</td>
<td>2.0 ± 0.74</td>
<td>0.003</td>
</tr>
<tr>
<td>interstitial infiltration</td>
<td>0.18 ± 0.4</td>
<td>0.82 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Arteriolar lesions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>number of vessel sections</td>
<td>28 ± 17</td>
<td>31 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>arteriolar hyalinosis</td>
<td>7.6 ± 5.1</td>
<td>12.6 ± 6.6</td>
<td>0.05</td>
</tr>
<tr>
<td>vacuolization of smooth muscle cells</td>
<td>2 ± 1.9</td>
<td>3.4 ± 3.9</td>
<td>NS</td>
</tr>
<tr>
<td>CsA arteriolopathy</td>
<td>0</td>
<td>0.7 ± 1</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*Figures express the number of lesions observed on renal biopsy (fibrous glomeruli, glomeruli with thickening of Bowman capsule, ischemic glomeruli, arterial hyalinosis, vacuolization of smooth muscle cells, CsA arteriolopathy) or the grade of severity (tubular atrophy, interstitial infiltrate, and interstitial fibrosis). P < 0.05 considered as significant.*
significantly during treatment (41) together with chronic renal failure (42). Zachariae et al. (43) performed pretreatment and posttreatment biopsy specimen in 12 psoriasis patients treated for 6 to 18 mo with 1.8 to 6 mg/kg per d CsA. They showed a slight but significant increase in interstitial fibrous tissue, which negatively correlated with creatinine clearance.

Birdshot uveitis is not associated with renal involvement,
and no other potentially nephrotoxic drug is usually added to steroid treatment. CsA nephrotoxicity has been described in uveitis treated patients as early as 1985 by Palestine et al. (44), who showed that a chronicity index (defined to assess atrophic and sclerosing glomerular and tubulointerstitial lesions) was significantly higher in 17 patients who had been treated for an average of 2 yr with 10 mg/kg per d CsA than in renal biopsy specimens from control patients with idiopathic hematuria. In the past 10 yr, the minimal dosage considered as effective in uveitis patients has decreased drastically. Our study is the first report analyzing long-term renal tolerance with both clinical and pathologic criteria in uveitis patients treated with a low dose of CsA.

Apart from renal tolerance, our study also draws attention to the known metabolic consequences of CsA treatment, some of them being recognized vascular risk factors.

Since its first use in the field of transplantation, CsA is still widely helpful in a broad spectrum of diseases, therefore it seems critical to evaluate carefully the renal tolerance of this therapy. An increase in serum creatinine is a late marker of renal alteration and is not necessarily correlated to the severity of the renal side effects. We suggest that to provide the expected benefit to uveitis patients treated with CsA, the lowest dosage should be proposed and a careful monitoring of renal parameters, including renal biopsy if necessary, should be offered.

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