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A prospective study of renal structure and function in psoriasis patients treated with cyclosporin

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A prospective study of renal structure and function in psoriasis patients treated with cyclosporin. The impact of long-term cyclosporin therapy on kidney structure and function was evaluated in psoriasis patients with normal baseline renal function. Patients received cyclosporin at an average dose 3.9 mg/kg/day for up to three years and underwent serial kidney biopsies and measurements of iothalamate clearance and serum creatinine concentration. Kidney biopsy specimens (assessed on a scale of 0 to 4 where 0 = normal and 4 = severe) from 19 cyclosporin-treated patients as compared to 38 age-matched transplant donors showed increased interstitial fibrosis (1.9 ± 0.2 vs. 0.3 ± 0.1, $P < 0.0001$) and tubular atrophy (1.6 ± 0.2 vs. 0.3 ± 0.1, $P < 0.0001$) at one year. Eleven patients had a second biopsy after an additional two years of cyclosporin treatment demonstrating additional interstitial fibrosis (1.8 ± 0.2 to 2.4 ± 0.3, $P = 0.002$) and tubular atrophy (1.4 ± 0.2 to 1.9 ± 0.2, $P = 0.053$), and the onset of cyclosporin-associated arteriolopathy (0 to 0.5 ± 0.2, $P = 0.02$). Quantitative digital morphometric analysis of trichrome-stained specimens also showed increased interstitial fibrosis (22.5 ± 1.5 to 32.0 ± 2.0% of interstitial area, $P = 0.0008$). Iothalamate clearance declined at an average rate of −3.1 ml/min/1.73 m^2 per year (95% CI −5.8, −0.3) during the period of cyclosporin treatment. The slope of reciprocal serum creatinine declined by −0.06 dl/mg per year (95% CI −0.08, −0.04). Chronic cyclosporin treatment of otherwise healthy psoriasis patients is associated with progressive renal structural injury and reduced glomerular filtration rate.

Cyclosporin is the mainstay of immunosuppressive therapy in organ transplantation and is being used increasingly for the treatment of various inflammatory and autoimmune diseases, including psoriasis [1]. However, the benefits of cyclosporin for non-transplant indications must be balanced against the long-term risks, particularly nephrotoxicity. Renal toxicity, which is well described in transplant patients, may not occur to the same degree in other patient groups because of differences in baseline renal function, concomitant diseases and medications, cyclosporin dose, and the confounding effect of rejection. To make judgments about the risk of cyclosporin therapy in non-transplant patients, it is important to understand the long-term renal side effects of cyclosporin when given alone in low doses over an extended period of time to patients with normal baseline renal function and few other confounding factors.

To address this issue, we performed serial assessments of renal structure and function in a selected group of psoriasis patients treated with cyclosporin for up to three years. Because psoriasis is not associated with kidney abnormalities, we were able to assess the direct renal effect of cyclosporin in the absence of substantive interference by concurrent diseases or therapy.

Methods

Study design and subjects

This report describes a group of patients who received oral cyclosporin (Sandimmune®, Sandoz Pharmaceuticals Corp.) for up to three years in whom renal structure and function were systematically assessed. The study group was drawn from a larger group of patients with severe or disabling chronic psoriasis who were previously enrolled in a prospective study of the efficacy and safety of oral cyclosporin for the treatment of psoriasis [2]. At entry to the original study, patients had a normal serum creatinine, blood pressure ≤150/90 mm Hg, and no history of kidney disease. Patients were initially treated with cyclosporin at doses of 3.5 to 7.5 mg/kg per day for two months. Patients who had complete or near-complete clearing of their psoriasis were then treated with doses of 1.5 to 5 mg/kg per day (as necessary to maintain remission) for another 10 months. At the end of approximately one year of therapy, cyclosporin was stopped.

At this one-year point, twenty-five patients agreed to participate in the current study of the long-term renal effects of cyclosporin. Twenty patients successfully underwent a kidney biopsy; five patients did not have a biopsy due to technical or logistical problems. The kidney biopsy from one patient showed dense focal inflammatory infiltrates in scarred areas suggesting chronic interstitial nephritis or chronic pyelonephritis unrelated to cyclosporin use; this patient was withdrawn from the study and excluded from analysis.

All remaining patients had recurrence of psoriasis after a one to two month medication-free period and resumed cyclosporin at dosages of up to 5 mg/kg per day. The dose was decreased to the lowest effective level or in response to a decline in renal function, indicated by changes in the serum creatinine concentration or

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iothalamate clearance rate. Subsequently, one patient had a cerebrovascular accident and was withdrawn. Three patients died (accident, suicide, and colon cancer). Five patients withdrew because they or their physician were concerned about possible cyclosporin nephrotoxicity. In all, 16 patients were treated with cyclosporin for an additional two years (3 years total) including 11 patients who had an initial biopsy and the five patients who did not. Fourteen patients underwent a kidney biopsy after approximately three years of therapy including all 11 patients who had an initial biopsy and were still enrolled in the study.

Throughout the study, patients were instructed to avoid aspirin or other non-steroidal anti-inflammatory drugs, potentially nephrotoxic drugs and drugs known to alter cyclosporin metabolism (for example, ketoconazole, erythromycin, phenytoin, barbiturates, carbamazepine, isoniazid, or rifampin). All patients were informed of the details, procedures, and potential risks of the study and gave written consent for all treatments and procedures. The protocol was approved by the Institutional Review Board of the University of Michigan Medical Center and an application for the use of an investigational new drug was filed by the manufacturer with the Food and Drug Administration.

Kidney biopsies

Percutaneous kidney biopsies were performed with ultrasound localization using standard techniques. Tissue was fixed in formalin and stained with hematoxylin and eosin, PAS, and trichrome and evaluated by light microscopy. The biopsy specimens were read and scored by two pathologists (KJJ, MJM) who were blinded to the clinical data and the temporal sequence of the biopsies. The pathologists jointly scored the specimens using an ordinal scale designed for evaluation of cyclosporin nephrotoxicity [3, 4]. The degree of interstitial fibrosis, tubular atrophy, arteriolar hyalinosis, and cyclosporin-associated arteriolopathy was each scored on a scale of 0 to 4 (0 = absence of abnormality, 1 = minimal changes in a few sections, 2 = slight changes present in all sections, 3 = medium severe changes, and 4 = severe changes). Arteriolar hyalinosis is not considered to be specific for cyclosporin. Cyclosporin-associated arteriolopathy is characterized by transmural nodular deposits in the arteriolar wall and mucoid intimal thickening [3, 4]. The percent of glomeruli displaying obsolescence and juxtaglomerular hypertrophy was measured.

Specimens from the patients who underwent two kidney biopsies were also evaluated with the semiquantitative lupus chronicity index [5] and by a quantitative digital morphometric technique. The lupus chronicity index is the sum of individual scores for interstitial fibrosis, tubular atrophy, glomerular sclerosis, and fibrous crescents, each rated on a scale of 0 to 3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe) [5]. For the quantitative morphometric analysis, the interstitial areas of trichrome-stained biopsy slides were scanned with a video imaging system (Olympus BH-2 microscope connected to a Sony CCD/RGB color video camera) at 40× magnification using IP Lab Spectrum software (Signal Analytic Corp., Vienna, Virginia, USA) and a Macintosh IIfx computer. Scanning windows were set for each specimen to quantify blue staining representing interstitial fibrosis. All available fields were scanned for each biopsy, providing an average of 19 fields (range 4 to 39) per biopsy. Results were expressed as the percentage of interstitial area which stained for fibrosis.

The one-year biopsy specimens from our psoriasis patients were compared to specimens obtained from kidney transplant donors who had normal renal function at the time of donation. Each patient was age and sex matched with two donor controls. As an additional control, we used kidney biopsy specimens from 16 unmatched patients with severe psoriasis who had not received cyclosporin and who were in the same age range as our patients (graded by MJM and reported previously [6]). For patients with paired biopsies, the results from the one-year and three-year specimens were compared.

Table 1. Characteristics of study population

Characteristic	Value
Number	25
Mean age [range]	43 [19–66]
Sex (M/F)	22/3
Mean baseline creatinine *mg/dl* [range]	1.0 [0.7–1.4]
Cyclosporin	
Mean dose *mg/kg/day*	3.9 ± 0.2
Median blood level *ng/ml*	94 ± 8
No. of hypertensive patients	
Baseline	5 (20%)
During cyclosporin therapy	11 (44%)

Values following ± indicate standard error.

Renal function tests

Glomerular filtration rate (GFR), as estimated by iothalamate clearance, was measured in most subjects at baseline and after approximately 2, 6, 12, 18, 24, 30, and 36 months of cyclosporin treatment. The renal clearance of subcutaneously injected ^{125}I-iothalamate (IsoTex Diagnostics, Friendswood, Texas, USA) was measured using standard techniques [2, 7]. The serum creatinine concentration was measured at frequent intervals during treatment using an autoanalyzer method.

Statistical analysis

The paired *t*-test was used to compare the paired scores from the one-year biopsy with the matched donor controls and to compare the paired scores from the one-year and three-year kidney biopsies [8]. The two-sample *t*-test was used to compare the one-year biopsy with the unpaired psoriatic control specimens [8]. For individual patients, the rates of change of iothalamate clearance and reciprocal serum creatinine ($1/S_{Cr}$) over time were determined by least-squares linear regression using all measurements performed while the patient was taking cyclosporin. Slopes with 95% confidence intervals were used to describe the mean rates of change of iothalamate clearance and reciprocal serum creatinine. Potential predictors of cyclosporin toxicity were evaluated by linear regression. Results are given as mean ± SEM unless otherwise noted. All *P* values are two-tailed.

Results

Patient characteristics

Baseline characteristics of the 25 patients who entered the long-term study of the renal effects of cyclosporin are given in Table 1. In this subset of the original study population, the maximum cyclosporin dose (administered for less than two months) was 7.5 mg/kg per day in six patients, 5 mg/kg per day in 16 patients, and ≤4 mg/kg per day in the remainder. The average dose throughout the study was 3.9 mg/kg per day.

Table 2. Histology scores for first kidney biopsy specimen and control specimens[a]

	A	B	C	*P* value	
	Matched kidney donor controls[b] (*N* = 19 pairs)	Untreated psoriatic controls[c] (*N* = 16)	Cyclosporin-treated psoriasis patients (*N* = 19)	C vs. A[d]	C vs. B[e]
Age	45 ± 3	43 ± 3	44 ± 3	0.8	0.8
Interstitial fibrosis score[f]	0.3 ± 0.1	0.3 ± 0.2	1.9 ± 0.2	<0.0001	<0.0001
Tubular atrophy score[f]	0.3 ± 0.1	0.4 ± 0.2	1.6 ± 0.2	<0.0001	<0.0001
Arteriolar hyalinosis score[f]	0.5 ± 0.1	0.6 ± 0.2	0.6 ± 0.2	0.4	0.8
Arteriolopathy score[f]	ND	ND	0	NA	NA
Obsolescent glomeruli %	2.4 ± 0.9	4.1 ± 1.5	5.5 ± 1.3	0.08	0.5
Juxtaglomerular apparatus hypertrophy %	0.8 ± 0.4	ND	1.9 ± 0.7	0.2	NA

[a] Results are mean ± SEM; Abbreviations are: ND, not done; NA, not applicable.
[b] Kidney specimens were obtained from two different kidney donors with normal renal function who were age- and sex-matched for each cyclosporin-treated patient.
[c] Kidney specimens obtained from psoriasis patients who had not been treated with cyclosporin [6].
[d] By paired *t*-test.
[e] By unpaired *t*-test.
[f] Assessed by an ordinal scale [3, 4] where 0 indicates the absence of the characteristic and 4 indicates a severe degree of the characteristic.

Renal structural changes

An interpretable initial kidney biopsy specimen was obtained from 19 patients who had received cyclosporin for an average of 1.1 ± 0.1 years. The scores for interstitial fibrosis and tubular atrophy were significantly higher in specimens from the cyclosporin-treated patients than from the untreated transplant donors and the untreated psoriasis patients (Table 2, Fig. 1). Non-specific arteriolar hyalinosis was found in control and patient specimens. Characteristic cyclosporin-related arteriolopathy was absent in patient specimens. The percentage of glomeruli showing obsolescence and juxtaglomerular hypertrophy did not differ in patient and control specimens.

After approximately three years of cyclosporin therapy, additional renal structural injury was evident in the biopsy specimens (Fig. 1 summarizes the data from 19 patients who had a biopsy at 1 year and 14 patients who had a biopsy at 3 years). Eleven patients (10 men and one woman) had two biopsies taken 2.1 ± 0.1 years apart. There was an increase in the interstitial fibrosis, tubular atrophy, and chronicity index scores in the three-year biopsy compared to the one-year biopsy (Table 3, Fig. 2). Similarly, an increase in the quantitative digital morphometric measure of interstitial fibrosis was observed in all patients (Table 3, Fig. 3). Transmural deposits of the arteriolar wall were absent in all 11 initial biopsies but were present in the second biopsy specimens from five patients, yielding a higher arteriolopathy score (Table 3).

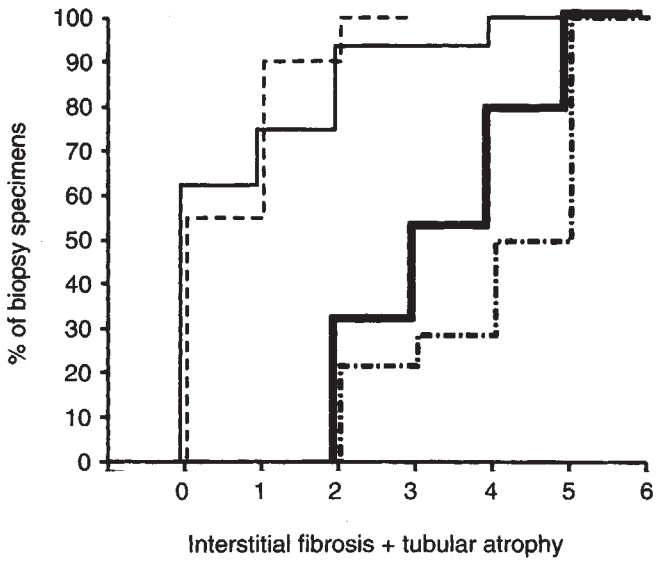

Fig. 1. *Cumulative frequency distribution of the sum of interstitial fibrosis and tubular atrophy scores for donor control specimens (N = 38, broken line), psoriatic control specimens (N = 16, solid line), and for the first (N = 19, thick line) and second (N = 14, thick dashed line) kidney biopsies taken from cyclosporin-treated psoriasis patients.*

Table 3. Summary scores for the 11 patients who had two kidney biopsies[a]

	1-year biopsy	3-year biopsy	*P* value[b]
Duration of cyclosporin treatment *years*	1.1 ± 0.1	3.4 ± 0.1	NA
Interstitial fibrosis score[c]	1.8 ± 0.2	2.5 ± 0.2	0.002
Tubular atrophy score[c]	1.5 ± 0.2	1.9 ± 0.2	0.053
Arteriolar hyalinosis score[c]	0.7 ± 0.2	1.3 ± 0.3	0.14
Arteriolopathy score[c]	0	0.5 ± 0.2	0.02
Obsolescent glomeruli %	5.3 ± 1.7	8.4 ± 3.1	0.4
Juxtaglomerular apparatus hypertrophy %	1.3 ± 0.6	3.0 ± 1.4	0.3
Chronicity index[d]	2.8 ± 0.2	3.9 ± 0.4	0.014
Quantitative morphometric interstitial fibrosis%[e]	22.5 ± 1.5	32.0 ± 2.0	0.0008

[a] Results are mean ± SEM; Abbreviation is: NA, not applicable.
[b] By paired *t*-test.
[c] Assessed by an ordinal scale [3, 4] where 0 indicates absence of the characteristic and 4 indicates a severe degree of the characteristic.
[d] Sum of individual lupus chronicity scores for interstitial fibrosis, tubular atrophy, glomerular sclerosis, and fibrous crescents, each rated on a scale of 0 to 3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe) [5].
[e] Assessed by quantitative digital analysis of all interstitial areas of trichrome stained slides.

Renal function

Serial measurements of iothalamate clearance and serum creatinine for the 16 subjects who completed three years of cyclosporin treatment are shown in Figure 4. Mean iothalamate clearance declined immediately after cyclosporin was started and it increased when the drug was stopped. For the patients who had both measurements, iothalamate clearance returned to 94 ± 3% ($P = 0.08$) of the baseline value when cyclosporin was discontinued after one year. With the resumption of cyclosporin, iothalamate

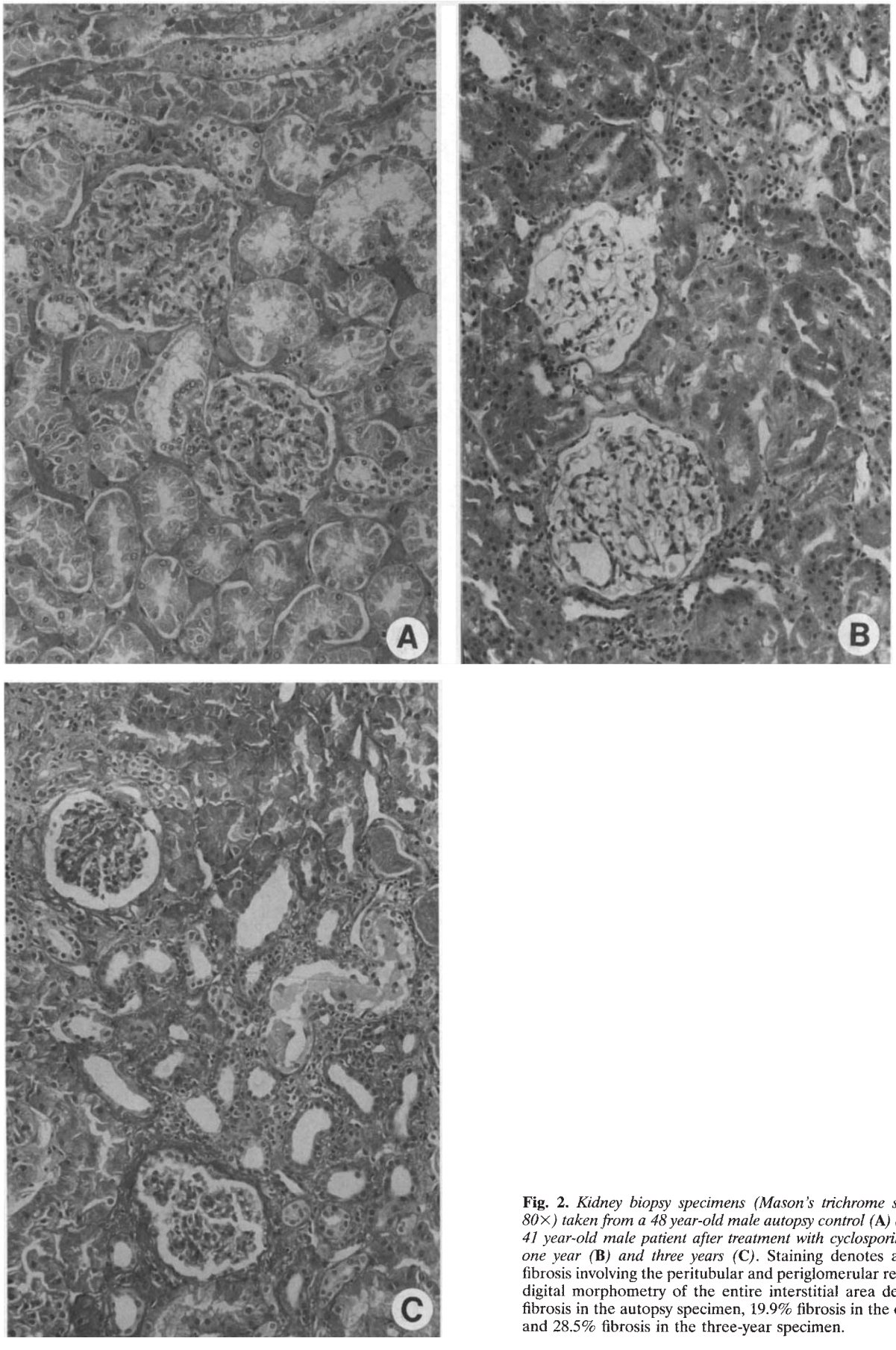

Fig. 2. *Kidney biopsy specimens (Mason's trichrome stain, magnification 80×) taken from a 48 year-old male autopsy control (***A***) and a representative 41 year-old male patient after treatment with cyclosporin for approximately one year (***B***) and three years (***C***).* Staining denotes areas of interstitial fibrosis involving the peritubular and periglomerular regions. Quantitative digital morphometry of the entire interstitial area demonstrated 10.6% fibrosis in the autopsy specimen, 19.9% fibrosis in the one-year specimen, and 28.5% fibrosis in the three-year specimen.

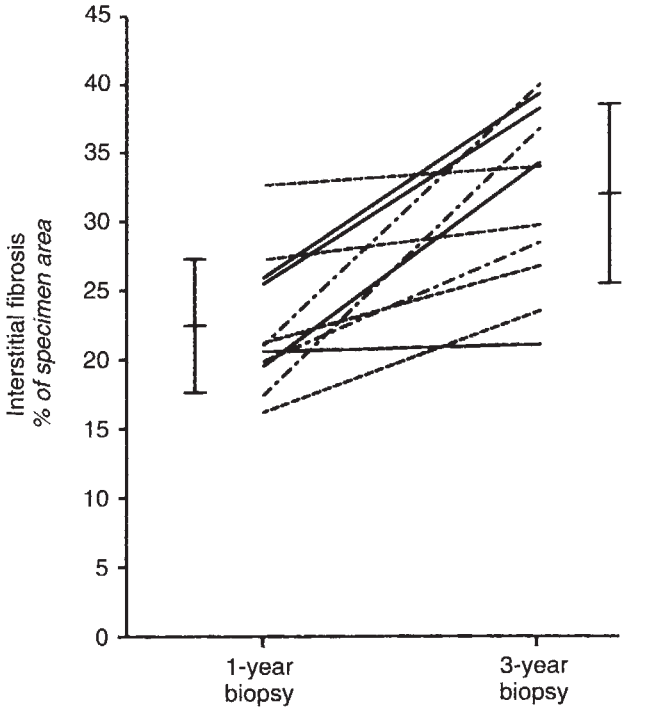

Fig. 3. *Quantitative digital morphometric measurements of interstitial fibrosis of biopsy specimens from patients who received cyclosporin for approximately two years between biopsies.* Paired readings are connected by a line. Vertical bars indicate mean ± SD. The difference between the two measurements is significant ($P = 0.0008$).

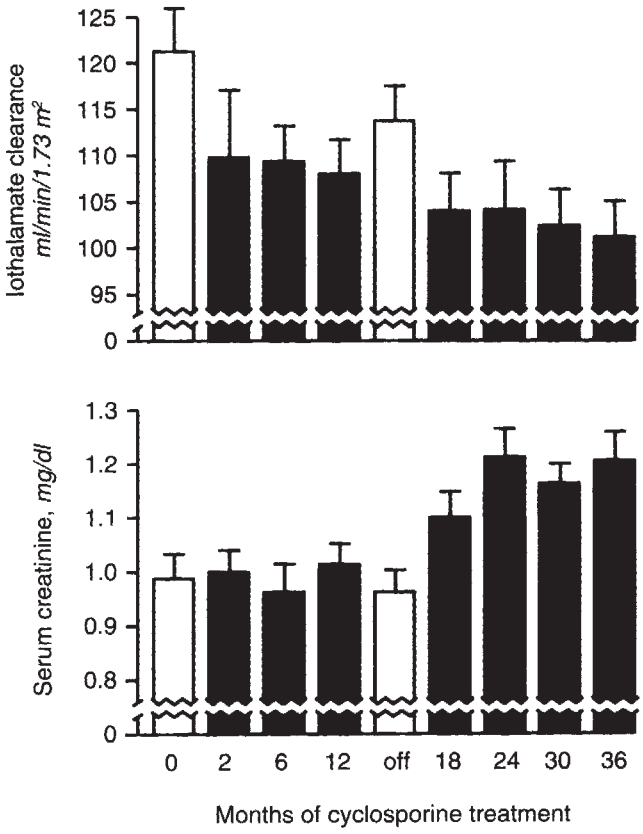

Fig. 4. *Serial measurements (mean ± SEM) of iothalamate clearance (A) and serum creatinine (B) for 16 patients who received cyclosporin for three years.* Time 0 denotes baseline measurement before cyclosporin was started. Value marked by "off" indicates measurement taken during a 1 to 2 month cyclosporine hiatus, approximately 12 months after initiation of therapy. Not all patients had an iothalamate clearance measurement at each time point; each time point represents the nearest temporal measure from the start of the study.

clearance again declined (Fig. 4). The changes in serum creatinine generally mirrored the changes in iothalamate clearance (Fig. 4).

Trends in renal function were further analyzed by regression analyses of iothalamate clearance versus time and reciprocal of serum creatinine versus time for each patient in order to estimate the average rate of change (slope) of filtration rate. The slope analysis was based on measurements performed while patients were taking cyclosporin; measurements done at baseline and during the drug withdrawal period were excluded. On average, each patient had seven measurements of iothalamate clearance and 46 measurements of serum creatinine. While patients were taking cyclosporin, iothalamate clearance changed by -3.1 ± 1.3 ml/min/1.73 m^2 per year (95% CI -5.8, -0.3). For individual patients, the iothalamate clearance declined over time in nine (significantly different from 0 slope in 3) and increased over time in seven (none significant). Without adjustment for body surface area, iothalamate clearance changed by -3.0 ± 1.5 ml/min per year (95% CI -6.3, 0.2). The reciprocal of serum creatinine changed by -0.06 ± 0.01 dl/mg per year (95% CI -0.08, -0.04). The slope declined in all 16 patients and was significantly different from zero in 13. During the course of therapy, the highest serum creatinine measurement exceeded the baseline value by an average of 56 ± 7%; most patients (75%) had at least one creatinine measurement during treatment that was more than 30% above the baseline measurement. Six patients from the total group developed new hypertension while taking cyclosporin (Table 1).

Structure-function relationships and prediction of nephrotoxicity

In general, measures of renal structure were not strongly or consistently correlated with measures of function. Interstitial fibrosis was not significantly correlated with iothalamate clearance at baseline or at the times of biopsy. The chronicity index was correlated with patient age ($r = 0.74$, $P < 0.001$ using the lower chronicity index for patients with 2 biopsies). Also, the percentage recovery of iothalamate clearance when cyclosporin was stopped at one year was inversely correlated with patient age ($r = -0.54$, $P < 0.0001$). However, the quantitative morphometric measure of interstitial fibrosis was not related to patient age. The increase in interstitial fibrosis from year 1 to year 3 did not differ when patients were grouped according to whether the peak serum creatinine concentration exceeded the baseline value by less than 30% (43 ± 33%, $N = 2$) or by greater than 30% (47 ± 12%, $N = 9$). Patients who were hypertensive during cyclosporin treatment had less complete recovery of iothalamate clearance when cyclosporin was discontinued at one year (86 ± 11% of baseline clearance) than did normotensive patients (101 ± 12%, $P = 0.023$). Hypertensive patients also had a greater increase in interstitial fibrosis between the one-year and the three-year kidney biopsies than did normotensive patients (76 ± 12 vs. 22 ± 8%, $P = 0.003$). Markers of nephrotoxicity were not correlated with cyclosporin dose or blood levels (as measured by high pressure liquid chromatography [9]).

Discussion

Nephrotoxicity is a clinically important problem when cyclosporin is used for transplant immunosuppression; however, the risk and expression of cyclosporin toxicity in the setting of renal transplantation are modified by multiple other conditions including allograft ischemia, rejection, denervation, other nephrotoxic medications, recurrent disease, and concomitant illnesses. Cyclosporin-related nephrotoxicity in non-renal transplant patients [10–14] may also be confounded by other factors that could contribute to renal injury such as other drugs and concomitant illnesses. Psoriasis patients provide an excellent opportunity to learn the direct renal effects of low-dose cyclosporin because these individuals are free of intrinsic renal disease [6, 15] as well as most other factors that confound the expression of cyclosporin toxicity in transplant patients.

This study addressed changes in both renal structure and function in otherwise normal psoriasis patients treated for up to three years with relatively low doses of cyclosporin (that is, ≤5 mg/kg per day for most of the treatment period). Interstitial fibrosis and tubular atrophy were present in all biopsies performed after approximately one year of exposure to cyclosporin whereas these features were uncommon in control specimens from kidney donors and psoriasis patients not taking cyclosporin (Table 2, Fig. 1). After an additional two years of cyclosporin treatment, specimens from all patients with paired biopsies demonstrated progression of interstitial, tubular, or vascular pathology characteristic of cyclosporin nephrotoxicity [3, 4] (Table 3, Fig. 1 through 3). The processes of patient selection and drop-out from the study tended to exclude subjects who developed overt renal problems related to cyclosporin. Therefore, the histologic progression we found may be regarded as a conservative estimate for the general population of cyclosporin-treated psoriasis patients.

GFR, estimated as iothalamate clearance, showed a slow but significant decline while patients were taking cyclosporin (Fig. 4). The rapid return of GFR toward the baseline value when cyclosporin was temporarily discontinued indicates a reversible component of renal dysfunction, presumably due to cyclosporin-induced vasoconstriction. However, the overall downward trend in filtration function persisted throughout the period of cyclosporin treatment. In our selected sample of patients, iothalamate clearance declined at an overall rate of −3.0 ml/min per year (95% CI −6.2, 0.2), whereas the reported age-related fall in creatinine clearance is −0.75 ± 0.12 ml/min per year (mean ± SE) for normal individuals and −0.92 ± 0.32 ml/min per year for subjects with treated hypertension [16]. In our patients the slope of reciprocal serum creatinine fell by −0.06 dl/mg per year (95% CI −0.08, −0.04) as compared to a reported rate of −0.009 ± 0.001 dl/mg per year (mean ± SE) for white men with mild to moderate, treated hypertension [17]. While our patients appeared to lose GFR faster than expected, it is uncertain if the rapid decline is attributable to structural injury or reversible vasoconstriction. Follow-up studies of cyclosporin are planned to assess the long-term functional significance of the renal injury.

In agreement with our findings, Zachariae et al reported an increase in interstitial connective tissue and fibrosis in each of 12 psoriasis patients treated with low-dose cyclosporin for six to 18 months [15]. Powles et al found tubular atrophy and vascular changes in biopsy specimens from a selected group of six psoriasis patients treated with cyclosporin for five years; interstitial fibrosis was found in specimens from four of the patients [18]. The International Kidney Biopsy Registry of Cyclosporin in Autoimmune Diseases reported a 29% incidence of biopsy-proven nephrotoxicity among adults; however, renal injury was absent in all 11 psoriasis patients included in the registry [19]. The same pathologist (MJM) contributed to both the registry study [19] and the current study. In the registry study, nephrotoxicity was unusual if the serum creatinine concentration during treatment increased by less than 30%. It may be noteworthy that most of our patients had at least one creatinine measurement that was ≥30% above the baseline value. However, in our small sample we did not find that the increment in serum creatinine predicted progressive fibrosis. Our results are in agreement with others who have found that cyclosporin treatment is associated with a fall in estimated GFR in non-transplant patients [2, 13, 15, 18, 20–23]. The long-term effect of cyclosporin on GFR in non-transplant patients is unknown except for the suggestion from our study that the age-related fall in GFR is more rapid than expected while patients are taking the drug.

The poor correlation between renal structural and functional measurements could be due to the relatively small sample size or to a variable mixture of vasoconstrictive and fibrotic components to the functional changes. Marked dissociation between GFR and histology was also found in an experimental model of cyclosporin nephrotoxicity [24]. The presence of hypertension during cyclosporin therapy predicted a greater degree of progressive renal interstitial fibrosis on serial biopsies. Our data suggest that older patients may be more vulnerable to cyclosporin-induced renal injury. No clinical measurement predicted the magnitude of renal histologic changes in individual patients.

Although published reports differ regarding the frequency and extent of nephrotoxicity, our longitudinal study clearly shows that cyclosporin is associated with renal structural changes and a small decline in GFR. The clinical predictors of cyclosporin nephrotoxicity are imprecise when applied prospectively to individual patients. While the long-term renal consequences of cyclosporin treatment in non-transplant patients are uncertain, it is known that interstitial fibrosis is associated with diminished renal function [25]. At this time it would be reasonable to exercise caution in the long-term use of cyclosporin for patients with psoriasis.

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