Kidney International, Vol. 43 (1993), pp. 1377–1384

A randomized trial of cyclosporine in steroid-resistant idiopathic nephrotic syndrome

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A randomized trial of cyclosporine in steroid-resistant idiopathic nephrotic syndrome. To compare the efficacy (induction of remission) and safety of cyclosporine (CsA) with those of supportive therapy in patients with steroid-resistant idiopathic nephrotic syndrome (INS), we organized an open, prospective, randomized, multicentric, controlled study for parallel groups, stratified for adults and children. Forty-five patients with steroid-resistant INS were randomly assigned to supportive therapy or CsA (5 mg/kg/day for adults, 6 mg/kg/day for children) for six months, then tapered off by 25% every two months until complete discontinuation. Four patients were lost to follow-up. During the first year 13/22 CsA-treated patients versus three of 19 controls attained remission of the nephrotic syndrome ($P < 0.001$). A symptom score was assessed at time 0 and at six months. The mean score significantly decreased in the CsA group ($P < 0.001$), but remained unchanged in the controls. At month 6 the mean urinary protein excretion, the mean serum proteins and plasma cholesterol had significantly improved in the CsA group but were not changed in the controls. There were no significant differences in serum creatinine and creatinine clearance between treatments (interaction time* treatments, $P = 0.089$ and $P = 0.935$, respectively) at month 6 versus basal. The CsA-related side-effects were mild; no significant difference in blood pressure between the two groups was seen at any time. This study shows that CsA can bring about remission in some 60% of patients with steroid-resistant INS. In patients with normal renal function and without severe hypertension, CsA at the therapeutic scheme adopted did not produce severe renal or extrarenal toxicity.

The term idiopathic nephrotic syndrome (INS) encompasses a spectrum of clinicopathological entities. Some investigators divide INS in different subgroups on the basis of the histological findings at renal biopsy, mainly minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS). Others, however, think that the response to corticosteroids is even more important than the initial histological picture in predicting the long-term renal outcome of patients with INS and recommend dividing patients with INS into steroid-sensitive and steroid-resistant [1, 2]. Patients who respond to steroids generally maintain normal renal function over time, while patients with steroid-resistant INS show FSGS sooner or later in renal biopsy and often progress to end-stage renal disease.

Recently, cyclosporine (CsA) has been used to treat INS. The drug was able to cause disappearance of proteinuria in most steroid-sensitive patients [3–7]. The results in patients with steroid-resistant INS have been more controversial. Some investigators found CsA not useful in this condition [8] and others reported worsening of renal lesions in a few patients given CsA [9]. Conversely, reviews of the literature show that CsA caused remission of the proteinuria in a good proportion of patients [10, 11] without significantly changing serum creatinine, at least in patients who started treatment with normal renal function [12]. Unfortunately, none of the published studies conducted with CsA in INS have been controlled. The criteria for selection, the doses of CsA, the duration of the treatment and the length of follow-up varied considerably in the different studies and this can well have biased the final conclusions.

To better assess the effects of CsA in patients with steroid-resistant INS, we started a prospective, controlled, multicenter trial in 1986. Patients who did not respond to a standard treatment with prednisone were randomly assigned to either symptomatic therapy or CsA, given at a "full" dose for six months and then gradually tapered off over the following six months.

Methods

Eligibility criteria

Patients with nephrotic syndrome (see *Definitions*) and creatinine clearance greater than 80 ml/min/1.73 m^2 for children or 60 ml/min/1.73 m^2 for adults and with renal biopsies showing either MCD or FSGS were considered for the study. Patients younger than 2 or older than 65 years, those with nephropathy secondary to a well identified cause, patients with neoplasia, hereditary angioedema, gastrointestinal malabsorption, concomitant infection or liver dysfunction, pregnant women, non-compliant patients, drug or alcohol abusers, patients requiring antiepileptic drugs and those with diastolic blood pressure

Received for publication January 23, 1992
and in revised form January 28, 1993
Accepted for publication January 28, 1993

higher than 95 mm Hg, if untreated, or higher than 90 mm Hg if on antihypertensive treatment, were not admitted to the study. Patients who were given immunosuppressive agents or cyclosporine in the previous 12 months were also excluded from the study.

Adult patients who met the eligibility criteria were given 1 mg/kg/day prednisone for six weeks and children 60 mg/m^2/day for five weeks. Only patients who did not have either complete or partial remission of the nephrotic syndrome were admitted to the study.

Definitions

Patients younger than 16 years were considered children, those older than 16 adults. The nephrotic syndrome was defined by a proteinuria greater than 40 mg/m^2/hr for children or greater than 3.5 g/day for adults, with variable edema. Corticosteroid resistance was defined as the persistence of the nephrotic syndrome after six weeks on prednisone (1 mg/kg/day) for adults or five weeks of prednisone (60 mg/m^2/day) for children. A partial remission was defined as proteinuria less than 40 mg/m^2/hr (children) or 3.5 g/day (adults) during three non-consecutive days. A complete remission was defined as proteinuria less than 4 mg/m^2/hr (children) or 0.2 g/day (adults), on three different non-consecutive days. The time for response was the number of days from the start of treatment to the first day of complete remission (or of partial remission, if complete remission was not obtained). A relapse of nonnephrotic proteinuria was defined in those patients who had attained a complete remission of proteinuria as the reappearance of proteinuria greater than 4 mg/m^2/hr (children) or 0.2 g/day (adults) for at least two weeks. A relapse of the nephrotic syndrome was defined in those patients who had attained complete or partial remission as the reappearance of proteinuria greater than 40 mg/m^2/hr (children) or 3.5 g/day (adults) for at least two weeks. Arterial hypertension was defined as a diastolic blood pressure higher than 95 mm Hg in adults and equal to or greater than the 95th percentile for age in children, as assessed in at least two consecutive occasions by the attending physician [13, 14]. The histological diagnosis of the renal disease was based on the criteria of the WHO [15]. The presence of even one glomerulus with segmentary hyalinosis was sufficient for a diagnosis of FSGS. Vascular lesions and interstitial fibrosis with tubular atrophy were classified as present or absent. Small areas of tubular atrophy or interstitial fibrosis, that constituted less than 10% of the biopsy specimen, were considered to be negative.

Randomization

The research protocol was approved by our institutional review board. This study was an open, randomized trial. A by-center stratified randomization was not deemed suitable due to the little sample size. After eligibility criteria were met and the patients' (or parents') informed consent was obtained, each patient was randomly assigned to either cyclosporine or supportive therapy within each stratum (adults or children).

For all patients, the indication for the therapy was contained in sealed, completely opaque envelopes numbered in sequence according to a table of random numbers. The enrollment of new patients ended in 1989, when the planned number of 20 patients in each treatment group was reached. This was considered sufficient to have a power of 0.80 for demonstrating a 0.05 increase in the cumulative proportion of clinical response in the control group versus a 0.40 increase in the CsA group at month 6, using a two-tailed statistical test performed at 0.05 significance level. Therefore we performed the final analysis.

Treatment

Experimental group. Cyclosporine was administered orally, at the initial dose of 5 mg/kg/day to adults and 6 mg/kg/day to children, divided in two doses (before breakfast and before supper). The doses were then adjusted to maintain the trough blood levels of CsA between 250 and 600 ng/ml, as measured by the non-specific polyclonal RIA method [16] in blood samples taken 10 to 14 hours after the last administration. Trough blood levels were measured every week in the first month, every two weeks in the second and the third month, monthly until the sixth month and then every two months until the end of the year. Further measurements were made if there was a relapse of the nephrotic syndrome or serum creatinine increased more than 30% over the baseline values. The "adjusted" dose was reduced by 25 to 50% if there was: an increase in serum creatinine to 30% or more over the basal values; an increase in serum potassium level to 6 mEq/liter or more; a doubling of the levels of serum transaminases, alkaline phosphatase, bilirubin and/or gammaglutamyltranspeptidase; an arterial hypertension refractory to treatment; or other severe side effects. According to the protocol if the reduction of the dose did not normalize the abnormal parameters within two weeks, CsA had to be further reduced by 25 to 50%, and if abnormalities still persisted after two weeks, CsA had to be definitively stopped.

After the sixth month, CsA was stopped in patients who had not obtained either complete or partial remission. For patients who responded, the dose was reduced by 25% every two months, independently of the blood levels of CsA, so that CsA was stopped by the end of the year.

Control group. Patients were given only supportive treatment for one year. A "rescue treatment" with corticosteroids, at doses and for the periods established by the attending nephrologist, was allowed for those patients who showed rapidly progressive renal failure or a devastating nephrotic syndrome. This choice was made on the assumption that some few patients who have not responded to the initial course of prednisone might take advantage by a more prolonged administration of corticosteroids [17]. These patients were still considered in the statistical analysis as controls.

Supportive therapy. With the exception of "rescue treatments," corticosteroid and immunosuppressive agents were forbidden. The clinicians were asked not to use erythromycin, cotrimoxazole, aminoglycosides, converting enzyme inhibitors, non-steroidal antiinflammatory drugs and/or anti-epileptic drugs which could affect either CsA metabolism or urinary protein excretion. Other treatments could be given. Patients were asked to reduce their salt intake. Protein intake was free. Efforts were made to give similar supportive therapies to each of the two groups.

Clinical and laboratory investigations. The frequency of follow-up and of laboratory tests and procedures was the same for both groups (every week for the first month, every 2 weeks in the second and the third months, every month until the sixth month and then every 2 months until the end of the follow-up). The patients were examined whenever they came for laboratory

analyses or reported any symptoms. At each visit, blood pressure was measured twice with a standard mercury sphygmomanometer.

The following signs or symptoms were arbitrarily scored from 0 to +++ and summed to construct a symptom score: edema, weakness, anorexia, nausea, diarrhea, depression. The following biochemical parameters were measured at all controls: leukocyte, erythrocyte and platelet counts; serum creatinine; creatinine clearance assessed by 24 hour urine collection; urinary excretion of protein (mg/m^2/hr); azotemia; serum albumin; plasma cholesterol; glucose; serum uric acid; transaminases; total bilirubin; alkaline phosphatase; gammaglutamyltraspeptidase; sodium, potassium, and magnesium.

Statistical analysis

The distribution of categorical variables such as sex, stratum (adult-child), the diagnosis after renal biopsy (MCN, FSGS), the outcome (prevalence of partial and complete remission—no remission), the presence of hypertension or not, was compared by the chi square test. For the continuous variables (laboratory parameters), changes from baseline within and between treatment groups were evaluated by means of the *t*-tests for paired and unpaired data. To analyze the overall proteinuria data without dividing the sample into two subgroups, we transformed the proteinuria of the adult patients, in g/day, into the unit of measurement for the children's proteinuria, mg/m^2/hr.

To obtain normal distribution, proteinuria, serum creatinine, creatinine clearance were transformed into log values. A mixed factorial ANOVA was performed on these transformed data, without considering the "center" as a factor. Since the little number of patients per center, the "among centers" factor has not been taken into account in the analysis, and the related variability is therefore confounded with the "among patients" one. Patients who did not complete the treatment were included in the analysis according to the intention-to-treat principle. The effect of treatment on the time of partial or complete remission as first event was analyzed by a univariate approach, using "survival" curves calculated according to the Kaplan-Meier product limit estimate [18]; differences in survival distributions were assessed by the log-rank test.

The analysis was performed with SAS software under PC-DOS.

Results

Of 45 patients admitted to the study, four were dropped within the first 45 days after assignment. One woman, aged 20 years, assigned to CsA, had a creatinine clearance of less than 60 ml/min/1.73 m^2 and uncontrolled hypertension at the moment of random assignment. Treatment was therefore stopped after a few days because the patient did not meet the criteria for inclusion. Three children (two girls, aged 7 and 10 years, one boy aged 9) assigned to the control group were dropped because they did not come for the required visits.

Of the remaining 41 patients, 22 were on CsA and 19 on symptomatic treatment. At the time of randomization, the two groups were similar in age, sex, duration of disease before admission, mean creatinine clearance, mean urinary protein excretion, presence or absence of hypertension and histological features (Table 1). The median duration of follow-up was 18 months (3 to 24) for the CsA group and 24 months (12 to 24) for the control group. One boy, aged 2, stopped CsA on day 60 because of a intercurrent symptomatic urinary tract infection. After recovery from the infection, his doctor decided not to restart CsA. This patient was lost to follow-up. A woman, aged 46, stopped CsA after six months because of lack of effect, in accord with the study protocol. She did not come for the following visits. The data for both these patients up to their last visits were considered in the analyses according to the intention-to-treat principle. Three controls were given corticosteroids as rescue treatment, without any effect on proteinuria or renal function.

The mean trough blood levels of CsA were within the expected therapeutic window in the first six months for adults and remained lower than scheduled for children, in spite of increasing doses (Fig. 1).

Changes in proteinuria

During the first year of observation, 13 of 22 patients assigned to CsA entered either complete or partial remission. One-third of CsA-treated patients (3 adults and 4 children) attained complete remission while four other adults and two children had partial remissions [mean (± SEM) proteinuria from 172.8 ± 18.8 to a minimum of 78.0 ± 26.0 mg/m^2/hr at month 6]. In most cases, the remission occurred within the first month. Only three adult controls attained partial remissions and none had a complete remission (Table 2). Thus, the cumulative probability of obtaining a remission of the nephrotic syndrome within one year was 0.65 for the CsA group and 0.16 for the control group, the difference between the two curves being highly significant (Fig. 2).

Considering only those patients who obtained remission, two controls had relapses of the nephrotic syndrome within three months after remission. Of the 13 CsA-treated patients who obtained remissions, three had relapses of the nephrotic syndrome in the third month and six other patients relapsed between the tenth and the twelfth month, while CsA was being gradually tapered off. At one year, when CsA was stopped 38% of patients who had had remissions on CsA were still without nephrotic syndrome. Of the seven CsA-treated patients who obtained complete remissions, four (2 adults and 2 children) remained without proteinuria until the twelfth month, two had relapses of the nephrotic syndrome in the eleventh and the twelfth month and one adult had a relapse of nonnephrotic proteinuria in the seventh month (Table 2).

Eleven patients per group were followed up for two years after assignment. During the second year of observation, four patients previously treated with CsA who were in partial or complete remission at the end of the first year were followed for a further 9 to 12 months. At the last control visit, one child still did not have proteinuria, two (one child and one adult) were in partial remission and one adult had had a relapse of NS. The control patient (adult) who was in partial remission at the end of the first year remained in partial remission up to the twenty-fourth month.

The mean proteinuria, expressed in mg/m^2/hr for both adults and children, had decreased significantly at month 6 for the CsA group and was unchanged for the control group. However, when CsA was reduced gradually, proteinuria tended to return to the baseline values (Fig. 3). It should be noted that for

Table 1. Characteristics of patients according to renal biopsy at the time of admission

Characteristics	CsA group		Control group	
	FSGS	MCD	FSGS	MCD
N of patients	14	8	14	5
Adults	10	2	9	3
Children	4	6	5	2
Age *years*				
Adults	33.3 ± 13.2	19.0 ± 1.4	43.0 ± 14.7	40.0 ± 11.5
Children	6.5 ± 4.7	6.8 ± 3.5	6.6 ± 1.8	7.5 ± 7.8
Sex *male/female*	6/8	7/1	8/6	5/0
Duration of disease *median, years*				
Adults/children	4.5/0.5	0.5/2.0	1.0/2.0	1.0/1.0
Interstitial lesions				
Present-adults/children	6/2	2/0	7/3	1/1
Absent-adults/children	4/2	0/6	2/2	2/1
Vascular lesions				
Present-adults/children	2/1	2/0	5/0	3/0
Absent-adults/children	8/3	0/6	4/5	0/2
Obsolescent glomeruli >50% all glomeruli				
Present-adults/children	2/1	0/1	1/2	0/0
Absent-adults/children	8/3	2/5	8/3	3/2
Creatinine clearance *ml/min/1.73 m²*				
Adults	99.89 ± 35.99	147.80 ± 44.79	99.42 ± 29.36	144.63 ± 79.40
Children	147.95 ± 100.24	164.13 ± 30.09	121.90 ± 30.52	149.60 ± 52.89
Proteinuria *mg/m²/hr*				
Adults	167.15 ± 55.84	115.61 ± 34.06	196.16 ± 159.66	160.57 ± 77.91
Children	220.15 ± 140.33	169.85 ± 109.26	230.46 ± 200.88	113.70 ± 37.00
Hypertension				
Present-adults/children	6/0	0/2	5/1	0/0
Absent-adults/children	4/4	2/4	4/4	3/2

Data are means ± SEM. All other values are numbers of patients unless otherwise indicated. Data for one treated and three control patients who dropped out of the study during follow-up are not included in this table.

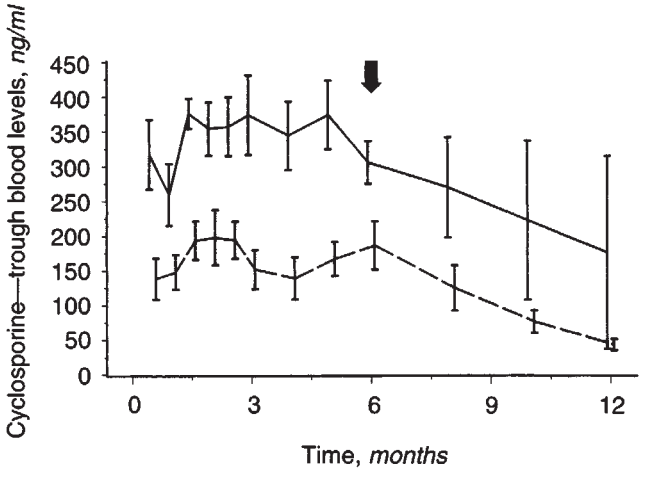

Fig. 1. *Trough blood levels of CsA (means ± SEM).* The means were within the expected therapeutic window in the first 6 months for adults (solid line) and remained lower than scheduled for children (dashed line). Start of reduction of CsA doses (arrow).

patients on CsA who obtained remission, proteinuria dropped after two weeks (from 167.8 ± 79.6 to 78.7 ± 56.9 mg/m²/hr).

The mixed factorial ANOVA performed on the log-transformed data of proteinuria showed significant differences in the interaction time * treatments ($P < 0.05$), the variability between strata (adults and children) being considered noninfluential.

Univariate analysis showed that no variable among those investigated (age, sex, duration of the disease, initial creatinine clearance, initial proteinuria, initial plasma albumin, initial plasma cholesterol, or histological features of the renal biopsy) influenced the occurrence of remission.

Changes in renal function

The mixed factorial ANOVA, applied to the log-transformed data for the renal function parameters (log serum creatinine, log creatinine clearance), showed no statistically significant differences at month 6 versus baseline for serum creatinine and creatinine clearance for the interaction time * treatments, while the stratum (adults or children) was the influential factor ($P < 0.01$). In the experimental group, the serum creatinine of one patient doubled in spite of the early decrease and discontinuation of cyclosporine. With the exclusion of this patient from the analysis, the mean values of serum creatinine were 67.2 μmol/liter at baseline and 73.4 μmol/liter after 12 months of treatment.

Twenty-two patients, 11 per group, were followed for two years. Of these, one CsA-treated patient and three controls had greater than 50% decreases in creatinine clearance, which occurred between the 18th and 24th months. An additional patient of the control group had to be placed on regular dialysis 18 months after the start of the study.

Table 2. Outcome of nephrotic syndrome in 22 CsA-treated patients

Patient No.	Age *years*	Sex	Renal biopsy	Basal proteinuria *mg/m²/hr*	Response to therapy	Time at response *mg/m²/hr*	Proteinuria at response *mg/m²/hr*	Outcome	
								Discontinuation month 12	After CsA month 24
1	48	M	FSGS	173.4	NS	—	—	NS	NS
4	20	F	FSGS	240.8	NS	—	—	NS	—
5	34	M	FSGS	108.4	PR/CR	25/162	12.0/0.0	NS	NS
7	22	F	FSGS	120.4	NS	—	—	NS	—
9	18	M	FSGS	151.7	PR	7	14.4	NS	NS
15	35	F	FSGS	180.6	PR	20	77.1	NS	PR
17	46	F	FSGS	250.5	PR	15	67.4	—	—
20	18	M	MCD	92.0	NS	—	—	NS	PR
21	27	F	FSGS	224.0	PR	60	84.3	NS	PR
23	57	M	FSGS	108.4	NS	—	—	NS	—
26	20	M	MCD	139.7	PR/CR	15/300	28.0/4.8	CR	CR
28	26	M	FSGS	113.2	PR/CR	30/360	72.3/0.0	CR	—
42	2	M	MCD	186.6	NS	—	—	NS	—
48	11	F	FSGS	41.0	NS	—	—	NS	NS
49	12	F	MCD	125.0	PR	30	35.0	PR	PR
52	3	F	FSGS	364.6	CR	52	0.0	NS	—
54	9	M	MCD	368.0	NS	—	—	NS	—
56	10	F	FSGS	185.0	PR	234	26.3	PR	NS
57	4	M	MCD	96.4	CR	15	0.0	NS	CR
60	2	M	FSGS	290.0	NS	—	—	—	—
61	7	M	MCD	185.1	CR	22	0.4	CR	—
63	7	M	MCD	58.0	CR	15	3.0	CR	—

Abbreviations are: M, male; F, female; FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; NS, nephrotic syndrome; PR, partial remission; CR, complete remission.

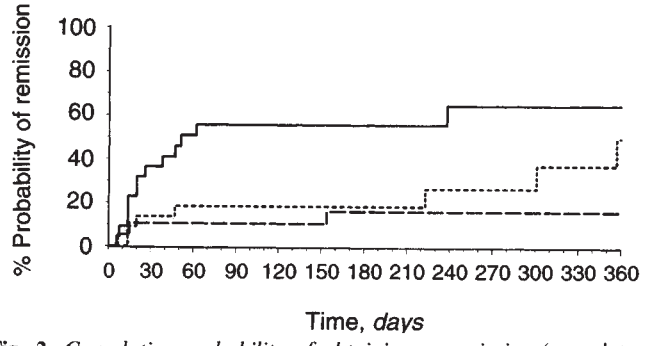

Fig. 2. *Cumulative probability of obtaining a remission (complete + partial) of the nephrotic syndrome within one year.* The difference between curves A (complete + partial remission in CsA-treated group, ——) and C (only partial remission in the control group, – – –) is significant ($P < 0.001$). Curve B (- - -) represents the cumulative probability of achieving complete remission within one year in CsA treated patients. No complete remission was obtained in the control group.

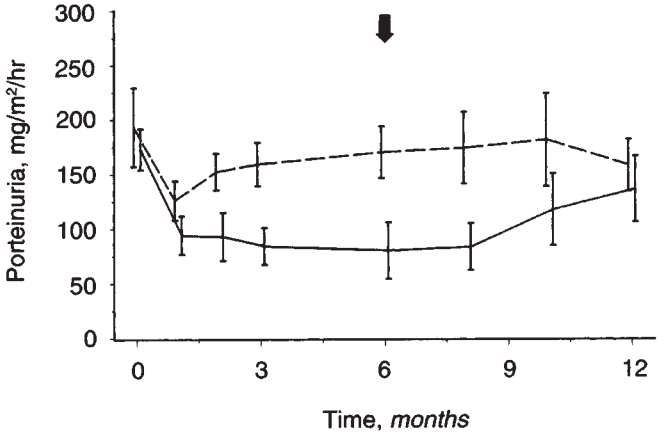

Fig. 3. *Proteinuria (means ± SEM) in mg/m²/hr for both adults and children was significantly decreased at month 6 ($P < 0.05$) in the CsA group, and not modified in the control group.* When CsA was reduced gradually (arrow), proteinuria tended to return to the baseline values.

Changes in other laboratory parameters

In the CsA group there was a significant increase in plasma albumin and total proteins at six months and a significant decrease in plasma cholesterol ($P < 0.05$, paired *t*-test vs. basal). These changes tended to be maintained up to the twelfth month, in spite of CsA tapering off until complete discontinuation. On the other hand, in the CsA group there was also a significant increase in serum alkaline phosphatase and azotemia. In both groups, circulating leukocytes decreased, probably as a consequence of the interruption of prednisone (Table 3).

Side effects

All adverse events that developed in both groups within the first year were recorded. Five infections (3 children) occurred in the CsA group and six (3 children) in the control group. Seven CsA-treated patients complained of gum hyperplasia, three developed hypertrichosis and four had transient gastric discomfort. A mild increase in conjugated bilirubinemia (one case per group); headache (one case per group); bronchospasm (one case per group); paresthesia, flushing, epicondylitis, tendinitis (one case per each symptom in CsA group); extrasystoles and anemia (one case per each symptom in the control group)

Table 3. Outcome of some laboratory parameters until month 12 in 22 CsA treated patients and 19 controls

	Cyclosporine (N = 22)			Cyclophosphamide (N = 19)		
	Basal	Month 6	Month 12	Basal	Month 6	Month 12
Proteinuria	172.8 ± 18.8	78.0 ± 26.0	136.1 ± 30.1	193.1 ± 36.2	170.0 ± 23.7	157.8 ± 23.6
(mg/m²/hr)-(Lg)	(2.184 ± 0.050)	(1.415 ± 0.174)[a]	—	(2.179 ± 0.071)	(2.154 ± 0.064)	—
Serum creatinine	73.3 ± 7.1	82.1 ± 12.4	107.9 ± 35.4	68.8 ± 6.2	98.7 ± 12.4	95.5 ± 12.4
(μmol/liter)-(Lg)	(1.801 ± 0.044)	(1.822 ± 0.062)	—	(1.808 ± 0.038)	(1.927 ± 0.056)	—
Creatinine clearance	130.5 ± 12.0	109.3 ± 11.3	117.8 ± 12.3	117.8 ± 9.9	105.1 ± 13.6	100.6 ± 11.1
(ml/min/173 m²)-(Lg)	(2.080 ± 0.038)	(1.996 ± 0.042)	—	(2.047 ± 0.033)	(1.957 ± 0.056)	—
Serum urea *(mmol/liter)*	11.8 ± 1.6	15.7 ± 3.1[b]	12.5 ± 2.2	12.9 ± 1.8	15.0 ± 2.1	13.2 ± 2.5
Serum proteins *g/liter*	50.4 ± 1.9	60.9 ± 2.2[b]	57.1 ± 2.6[b]	52.7 ± 1.6	51.2 ± 2.5	51.6 ± 1.7
Serum albumin *g/liter*	25.4 ± 1.5	34.5 ± 1.8[b]	31.2 ± 2.3[b]	27.6 ± 1.7	26.4 ± 1.7	27.5 ± 1.8
Plasma cholesterol *mmol/liter*	0.103 ± 0.008	0.062 ± 0.007[b]	0.076 ± 0.008[b]	0.089 ± 0.007	0.094 ± 0.009	0.094 ± 0.010
Serum alkaline phosphatase *U/liter*	153.2 ± 21.7	290.5 ± 52.8[b]	254.7 ± 32.8[b]	128.9 ± 27.3	169.1 ± 40.6	224.2 ± 45.2
Leukocytes *10⁹/liter*	9.2 ± 0.65	6.7 ± 0.40[b]	7.0 ± 0.93	10.5 ± 0.91	7.7 ± 0.59[a]	7.1 ± 0.63[a]

Data are mean ± SEM.

[a] $P < 0.05$, mixed factorial ANOVA (month 6 vs. basal), time × treatment interactions, performed on log-transformed values of proteinuria, S_{Cr}, C_{Cr}. The analysis was performed until month 6, when CsA full doses were administered.

[b] $P < 0.05$, paired t-test vs. basal

occurred sporadically. All these symptoms had disappeared after the first year of observation. In no case did CsA have to be stopped or even to be reduced by 50% or more.

Blood pressure was checked regularly in both groups. There were no differences between the two groups at any time, nor were there any differences between children and adults (data not shown).

Symptom score

The basal mean symptom scores were 1.5 ± 0.4 for the CsA group and 1.4 ± 0.2 for the control group. At six months the score had significantly decreased for the CsA group (0.4 ± 0.2; $P = 0.0017$) and was unchanged for the control group (1.2 ± 0.3; NS).

Discussion

There is not yet a widely accepted treatment for patients with steroid-resistant INS. Some investigators have reported good rates of remission for patients with FSGS treated by prolonged administration of prednisone [17], but others think that continuing to give corticosteroids to steroid-resistant patients is useless and dangerous [19]. Immunosuppressive agents have been found to be beneficial by some investigators [20] but a controlled trial did not show any advantage of cyclophosphamide over corticosteroids in children with FSGS [21]. It has been claimed that aggressive treatment with methylprednisolone pulses and cytotoxic agents improves the outcome for patients with steroid-resistant FSGS [22]. Unfortunately, however, no controlled trial to support the effectiveness of this approach has been published. In view of the uncertain results of the available treatments, many clinicians prefer not to persist with steroid therapy in steroid-resistant patients.

Previous non-controlled trials have shown that about half of patients with steroid-resistant INS may obtain complete or partial remission of the nephrotic syndrome on CsA [3–7, 23–28]. However, since CsA can cause vascular and tubulointerstitial lesions [29] and lead to progressive renal dysfunction [30], there is concern that long-term administration of this drug might accelerate the evolution to renal failure in patients with FSGS. There is little information, however, comparing the outcome of renal function in patients with steroid-resistant INS given CsA with that in untreated patients.

The aim of this study was to assess the effectiveness and the safety of CsA in steroid-resistant INS. A main problem has been definition of steroid resistance. According to the International Study of Kidney Diseases in Children [31], some 90% of the steroid sensitive children enter remission within four weeks on prednisone. The response may be later in adults, but most of patients who respond do so within six weeks [32]. Therefore we chose to consider as steroid-resistant those children who did not respond within five weeks and adults who did not respond within six weeks. We are, however, aware that some few patients might have responded to more prolonged prednisone treatment. We gave higher doses of CsA to children than to adults because pediatric patients have a higher clearance of CsA [33]. In spite of this, the mean blood concentration remained lower in children and this might have influenced the response to treatment. In fact, contrary to what we expected, the response was similar to or even a bit lower in children than in adults. Some 60% of patients assigned to CsA obtained remission of the nephrotic syndrome, which in most cases persisted while therapeutic doses of CsA were being given. It was of interest that the proteinuria of the responders decreased significantly within a few days, and most patients who obtained remission did so within the first month. On the contrary, only three control patients had partial remissions of the nephrotic syndrome and two of them had early relapses. Most studies have reported that the nephrotic syndrome returned a few days after CsA was abruptly stopped [3–7, 23–27]. In our trial, however, in which the drug was tapered off, some 38% of the responders remained in remission until the twelfth month, and three of the four followed for 18 to 24 months were still in remission at the last visit. It is possible that the gradual reduction of CsA adopted in this protocol instead of abrupt stopping may have prevented an early relapse into proteinuria in some patients. No clinical or histological parameter at

presentation was useful for predicting which patient would maintain remission.

After this trial was completed, three patients who had complete remission under CsA with relapse of nephrolic syndrome after stopping the drug asked to again resume CsA. Two patients again entered complete remission, while the third patient who had had a renal function deterioration in the meantime did not show any response in proteinuria or in serum creatinine.

These data show, therefore, that CsA can improve proteinuria in a consistent proportion of patients with steroid-resistant INS. However, patients assigned to CsA had significant increases in plasma albumin and in total proteins and significant decreases in plasma cholesterol. These changes were particularly evident after six months of therapy, when CsA was being given at the "full" dose, but persisted even at 12 months, after gradual tapering off of CsA. Signs and symptoms, as assessed by the symptom score, had also improved significantly in CsA patients after six months of therapy.

Patients assigned to CsA showed a slight decline in creatinine clearance after six months, which was partially reversible when the CsA dose was reduced. After one year, the mean decrease in creatinine clearance for the treated group was about 10%, but this mean includes that patient with rapid renal function decline because of very severe underlying renal disease. These data confirm previous retrospective observations showing that, when given at appropriate doses, CsA can reduce proteinuria in steroid-resistant patients without causing significant changes in serum creatinine [12]. After 12 months the control group had a greater decline in creatinine clearance than the CsA-treated patients, and this worse renal function in control patients was confirmed in patients followed for two years, although the difference between the two groups was not significant.

The use of creatinine clearance to assess the glomerular filtration rate might be criticized, however. Theoretically, CsA may interfere with the tubular handling of creatinine and this would lead to an overestimation of the glomerular filtration rate. However, a strong correlation between changes in serum creatinine and changes in glomerular filtration rates, as assessed by inulin clearance or radioisotopic measurements, has been found in careful studies of patients with autoimmune diseases [34]. Thus, repeated measurements of serum creatinine and/or creatinine clearance can be considered a reliable index for assessing changes in renal function in CsA-treated patients.

We did not perform repeated renal biopsies to evaluate the possible renal toxicity of CsA and this might be considered a weak point of the study. This was a deliberate choice, however. There was agreement among the participating clinicians that in steroid-resistant patients, who generally have FSGS, it would have been extremely difficult to recognize whether the development or the worsening of tubulointerstitial and microvascular lesions should be attributed to the natural evolution of the disease or to CsA toxicity. Moreover, most of us felt it was not justified ethically to submit them or control patients, for whom the results of biopsy would not modify the therapeutic policy, to renal biopsy, which carries a small but substantial risk of complications [35].

The CsA-related side effects were mild. The incidence of infections during the follow-up was similar in the two groups. No significant change in blood pressure was seen and mean blood pressure values between the two groups did not differ at any time. Gingival hypertrophy and hypertrichosis occurred frequently in CsA-treated patients but both disappeared after the drug was stopped. Therefore, at the doses and for the duration adopted in this trial, CsA did not produce severe renal or extra-renal toxicity. It must be pointed out, however, that our patients were selected on the basis of still having relatively normal renal function, without severe hypertension.

In conclusion, this controlled study shows that CsA can bring about remission of the nephrotic syndrome in some 60% of patients with steroid-resistant INS. In many cases CsA was effective only while it was being given and relapses into NS occurred when the drug was discontinued. On the other hand, since the tolerance of CsA was good in this study, we feel that for steroid-resistant nephrotic patients with normal renal function and normal blood pressure, a trial with CsA may be justified to identify the responders.

Since a response is observed within a few weeks, in most cases the treatment may be considered ineffective and, therefore, interrupted if proteinuria does not improve after three months of therapy.

For those patients who respond and tolerate well CsA, the drug might be continued for about one year and then tapered off along six months or so. If a relapse of nephrolic syndrome occurs, CsA might be reassumed for another year and then discontinued again. Before considering further administration, a careful evaluation of glomerular filtration rate and possibly a control renal biopsy should be performed.

Acknowledgments

This study was supported in part (drug, organization, Investigators' meeting) by Sandoz P.F., Milano, Italy. The authors thank: Dr. Maria Di Gregorio, Dept. of Statistics, Sandoz P.F., Milano, Italy, for assistance with the statistical analysis and Dr. Bruno M. Cesana, Epidemiologic Laboratory, Scientific Direction, Ospedale Maggiore, Milano, Italy, for revising the methodology of the statistical analysis.

Other participants in the Italian multicenter study group were: Giuliano Mecca, M.D. (Bergamo); Graziella Zacchello, M.D. (Padova); Giulio A. Cinotti, M.D. (Roma); Enrico Imbasciati, M.D. (Sondrio); Rosario Maiorca, M.D. (Brescia); and Giuliana Lama, M.D. (Napoli).

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