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Original Article

Long-term Treatment of Minimal-change Nephrotic Syndrome with Cyclosporin: A Control Biopsy Study

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Abstract. Seven patients with minimal-change nephrotic syndrome confirmed by renal biopsy were treated with cyclosporin (CsA). Four patients had frequent relapses and three others had primary steroid resistant nephrotic syndrome. Corticosteroids were discontinued as soon as CsA whole blood trough values of 200–500 ng/ml (RIA method) were reached. A full remission, defined as complete disappearance of proteinuria, was achieved in five patients under this treatment. In the two other patients proteinuria was reduced.

Two patients experienced an acute episode of dose-dependent nephrotoxicity; however, overall renal function, as determined by the creatinine clearance, was stable. Control biopsies in five patients after a mean treatment period of 10 months showed no significant vascular or interstitial toxicity.

Key words: Cyclosporin; Cyclosporin nephrotoxicity; Minimal-change nephrotic syndrome; Kidney biopsies; Steroid-dependent nephrotic syndrome; Steroid-resistant nephrotic syndrome

Introduction

Minimal-change nephrotic syndrome typically responds to corticosteroids and generally has a good prognosis. Spontaneous remissions are frequent. Three groups of patients, however, cause therapeutic problems, i.e., frequent relapsers, patients with steroid-dependent disease, and finally patients who are steroid and cytostatics resistant. Long-term corticosteroid therapy in these patients is followed by severe side-effects, e.g. cushingoid syndrome, peptic ulcers, osteopathy and, especially in young patients, reduced growth and delayed puberty.

Immunological studies in minimal-change nephrotic syndrome suggest a defect in cellular immunoregulation [1,2]. As CsA selectively inhibits the cellular immune response [3], and successful pilot studies of its use in minimal-change nephropathy were reported [4], a long-term study was performed in seven adult patients with a mean observation period of 18 months.

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Patient Data and Treatment Protocol

Seven adult nephrotic patients (five males and two females) with a mean age of 25 (17–43) years were studied (Table 1). Proteinuria exceeded 3.5 g/day on at least two consecutive measurements, plasma albumin was less than 25 g/l, and all patients had variable oedema. Minimal-change nephropathy was confirmed by biopsy in all patients during the nephrotic state. Control biopsies could be obtained from five patients after a mean CsA treatment of 10 months.

All patients had highly selective proteinuria, normal GFR and normal complement concentrations. Severe hypertension was present in one patient (patient no. 2),

Table 1. Patient data and pretreatment

Patient no.	Initials	Age/sex	Age at onset (years)	Status	Pretreatment	Side-effects of corticosteroids
1	PS	18/M	1	*Frequent relapser*	*Steroids; cyclophosphamide*	*Osteoporosis, gastric ulcers, growth retardation, pubertas tarda*
2	UF	31/F	5	Frequent relapser	Steroids	Peptic ulcers, cushingoid syndrome hypertension (?)
3	ML	17/M	3	Frequent relapser	Steroids	Osteoporosis, adrenal insufficiency, growth retardation, pubertas tarda
4	AP	43/F	42	Steroid–cyclophosphamide resistant	Steroids; cyclophosphamide	Cushingoid syndrome, steroid acne
5	HK	20/M	14	Infrequent relapser	Steroids	Gastritis, cushingoid syndrome, steroid acne
6	DH	18/M	15	Steroid–cyclophosphamide resistant	Steroids; cyclophosphamide; indometracin	Cushingoid syndrome, steroid acne
7	MF	27/M	25	Steroid–cyclophosphamide resistant	Steroids; cyclophosphamide	Cushingoid syndrome, steroid acne

M = male; F = female

two patients had mild hypertension (patients no. 3 and 5). Before the onset of this study three patients were on steroid monotherapy (patients no. 2, 3 and 5), four patients (patients no. 1, 4, 6 and 7) had pretreatment with a steroid-cyclophosphamide combination.

All patients had steroid-related side-effects of varying degree. CsA was given initially at a dose of 3–5 mg/kg bodyweight twice daily. Steroids were gradually discontinued when CsA whole blood trough values reached the target therapeutic window of 200–500 ng/ml (RIA method, Sandoz Ltd). No other immunosuppressive drugs were given at the same time. Renal function, total protein, proteinuria (Biuret method), type of proteinuria (gradient gel electrophoresis), liver function and CsA whole blood trough concentrations were checked twice a week during the first 3 weeks. Later, the above-mentioned laboratory controls were carried out every 3 weeks. CsA doses were adapted to reach 200–500 ng/ml whole blood trough levels.

Kidney biopsies were investigated by light microscopy, by immunohistochemistry using the PAP method for the demonstration of IgG, IgM, IgA, complement C_3 and fibrinogen, and also by electronmicroscopy according to standard techniques.

Results

Five of seven patients (patients no. 1–5) achieved full remission (proteinuria below 0.2 g/day) within 4 weeks onset of CsA (Fig. 1). Mean cyclosporin dose was 4.3 mg/g per day and the average blood concentration was 355 ng/ml during the treatment. Relapses of the nephrotic syndrome occurred in all five patients when CsA was stopped (patients no. 2, 4 and 5) or when blood CsA fell below the therapeutic range (patients no. 1 and 3).

After 4 months of full remission with CsA in patient 2, pre-existing arterial hypertension deteriorated and CsA was stopped. Subsequently, hypertension was more easily controlled, but 10 days later the nephrotic syndrome recurred followed by pulmonary embolism due to deep leg-vein and pelvic-vein thrombosis. After reintroduction of CsA monotreatment, full remission was achieved and hypertension could be controlled by converting-enzyme inhibitors. Recurrences of the nephrotic syndrome were found after 6 and 8 months of full remission in patients no. 1 and 3 when blood CsA fell below 100 and 200 ng/ml respectively. On increasing the CsA doses, proteinuria disappeared again with a return to normal serum protein.

In patient no. 3, gradient gel urine electrophoresis showed a change to unselective proteinuria, and a control biopsy showed a focal glomerular sclerosis. Patients no. 4 and 5 had relapses of their nephrotic syndrome when CsA was stopped after 12 and 18 months of full remission. The relapses occurred 2 weeks and 6 months respectively after discontinuation of CsA treatment. Reintroduction of CsA combined with prednisolone (1 mg/kg body weight for 14 days, with steroids being tapered over 4 weeks) caused a second complete remission in both patients.

The two non-responders (patients no. 6 and 7) had a slight decrease in proteinuria during CsA therapy, and oedema was more easily controlled. Immunosuppression with CsA was discontinued after 6 and 10 months.

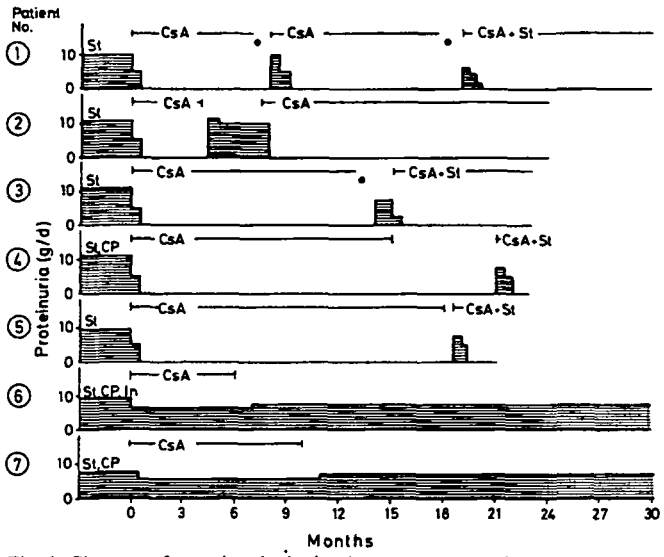

Fig. 1. Changes of proteinuria during immunosuppressive pretreatment and with cyclosporin. CsA, cyclosporin; CP, cyclophosphamide; St, corticosteroids; In, indomethacin; ● = CsA < 100 ng/ml.

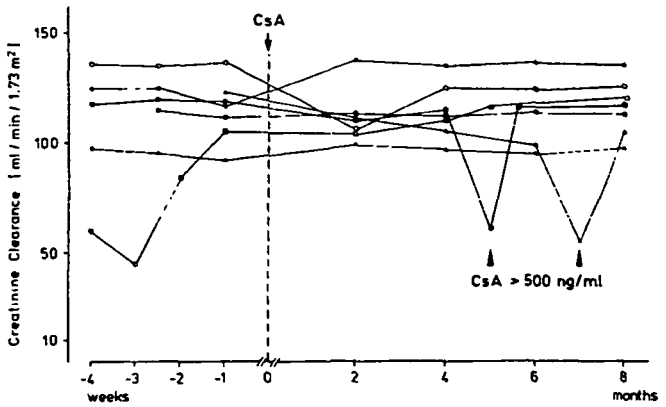

Fig. 2. Creatinine clearance before and during treatment with CsA.

Renal function did not change during the observation period (Fig. 2). Mean creatinine clearance in all patients remained stable (pretreatment: 115 ± 13 vs post-treatment 112 ± 11 ml/min) (Table 2). Two patients had transient nephrotoxicity when CsA whole blood concentrations exceeded 500 ng/ml. Creatinine clearances returned to normal after CsA dose reduction.

Control biopsies from five patients after a mean treatment of 10 months (Table 3) showed minimal or slight focal interstitial fibrosis and tubular atrophy. One patient had slight arteriolopathy. The morphologic lesions, however, were not typical and severe enough to be attributed to CsA toxicity. Significant tubular toxicity was not found. Other side-effects caused by CsA, e.g. hypertrichosis, gingival hyperplasia and tremor were slight and could easily be reduced by dose reduction. There were no signs of hepatotoxicity.

Discussion

The effect of CsA in minimal-change nephropathy has been examined in only a few patients. Tejani [5] treated five children with steroid-dependent, and four children with steroid-resistant, minimal-change nephropathy CsA dose 7 mg/kg bodyweight daily) for 2 months. In all patients, complete remission was achieved for at least 10 months. Meyrier and co-workers [6] induced complete remissions in three adults with 12–42 days of CsA therapy (5 mg/kg bodyweight; trough levels 125–750 ng/ml). Brodehl et al [7,8] reported five children with frequently relapsing disease, where CsA (trough levels 200–400 ng/ml) reduced the number of relapses and prednisolone requirement; two patients reached full remissions for 6 months under CsA treatment.

In the present study, CsA maintained long-lasting remissions in five of seven adult patients with minimal-change nephrotic syndrome. Of the responding patients, four were frequent relapsers and one had steroid and cyclophosphamide resistance. Especially in our young patients (patients no. 1 and 3) with long-term corticosteroid pretreatment, there was substantial benefit with this therapy: puberty commenced, bone growth restarted and the steroid-induced cushingoid syndrome resolved (Fig. 3).

However, all CsA responders became CsA dependent. Relapses of their nephrotic syndrome occurred between 10 days and 6 months after withdrawal of CsA, but second remissions could be achieved in all those patients with reintroduction of the drug. The exact mechanism of action of CsA remains elusive. The beneficial effect of this T-cell-specific agent, however, favours the hypothesis of a T-cell-mediated disorder in minimal-change nephropathy [2, 9–14].

CsA is increasingly used for the treatment of various autoimmune disorders. As compared with conventional immunosuppression, CsA carries no risk of osteoporosis, myelotoxicity, growth and sexual retardation or teratogenicity. However, CsA may cause severe side-effects including nephrotoxicity, hypertension and occasionally hepatotoxicity. Thus, in non-fatal autoimmune diseases the risk and benefit of CsA therapy have to be evaluated.

Dose-dependent nephrotoxicity is well known in all groups of patients treated with CsA including those with autoimmune diseases [15–17]. There was a slight increase of morphological scores in our control biopsies during treatment, but these findings were not so pronounced as to indicate CsA toxicity, and GFR remained unchanged during the observation period of 6–30 (mean 18) months.

The fact that no significant nephrotoxicity was found in our patients may be due to two reasons: (a) slow increase in CsA dose; (b) low dose and low trough CsA concentration.

Table 2. Clearance, proteinuria and clinical course under CsA

Patient no.	Creatinine clearance* (ml/min per 1.73 m^2)		Serum protein* (g/l)		Proteinuria* (g/day)		Duration of CsA treatment (months)	Mean CsA trough** level (ng/ml) full blood	Outcome
	B	U	B	U	B	U			
1	123±23	111±8.5	32.6±1.8	70.2±3.5	5.7±1.1	0	30	439±274	Remission, recidive when CsA blood level < 200 ng/ml. 2. remission with CsA; grew 10.5 cm
2	92±10	99±12	29.5±1.1	65±2.8	9.6±0.9	0	23	332±164	Remission, recidive after stopping CsA for severe hypertension. 2. remission with CsA
3	112±16	113±14	41.2±3.1	63.5±3.0	5.8±1.2	0	23	279±151	Remission, relapse when CsA blood level < 100 ng/ml. 2. remission with CsA; grew 10 cm
4	105±13	104±10	39±2.9	67.5±2.4	8.7±1.3	0	18	173±42	Remission, relapse 6 months after stop of CsA. 2. remission
5	119±17	110±15	37±3.0	68±3.1	9.2±1.0	0	17	274±66	Remission, relapse 1 month after stop of CsA. 2.: remission
6	137±22	106±11.5	46.2±4.1	49±3.2	6.1±1.2	4.2±1.1	10	326±126	Slight reduction of proteinuria; stop of CsA after 10 months
7	117±8	138±8.5	46.6±1.6	50±3.7	6.5±1.3	4.5±1.6	6	663±147	Slight reduction of proteinuria; stop of CsA after 10 months
Mean	115±13	112±11	38.9±5.9	61.9±8.1	7.4±1.6		18.1±8.1		

*Mean of 3 consecutive measurements; **mean of all trough level measurements during treatment; B, before treatment with CsA; U, after 2 months under CsA

Table 3. Results of renal control biopsies before and during CsA

Patient no.		No. of glomeruli	Obsolescent glomeruli (*n*)	Segmental focal glomerulosclerosis (*n*)	Arteriolopathy (score 0–4)	Interstitial fibrosis and tubular atrophy (score 0–4)	Interstitial infiltrates	Immuno-fluorescence
1	B	8	0	0	0	1	0	IgM
	D	10	0	0	1	2	2	IgM
2	B	5	0	0	1	0	0	neg.
	D	2	0	0	0	1	0	IgM
3	B	13	0	0	0	0	0	IgM
	D	10	0	1	0	2	1	neg.
4	B	6	0	0	0	1	0	IgM
	D	17	1	0	2	1	0	neg.
5	B	4	0	0	0	0	0	neg.
	D	3	0	0	0	1	0	IgM

B = before CsA; D = during CsA
Score: 0 = not present; 1 = minimal; 2 = slight; 3 = medium severe; 4 = severe

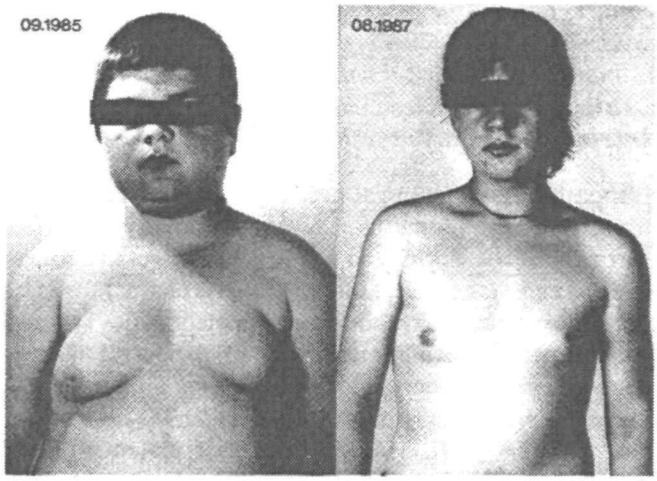

Fig. 3. Patient no. 3 before and during therapy with CsA.

CsA doses were considerably lower than in auto-immune patients in whom CsA toxicity has been reported [16,17].

Our data indicate that CsA may be effective and safe in minimal-change nephrotic syndrome. Strict control of blood CsA, and renal and hepatic function are necessary to prevent toxicity. The use of CsA in adult patients with minimal-change nephropathy is suggested in the following conditions: (a) inadequate response with conventional immunosuppression; and/or (b) severe side-effects due to conventional immunosuppression.

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