

# Cyclosporin A in steroid-sensitive nephrotic syndrome with frequent relapses

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**Summary:** Eight patients with steroid-sensitive nephrotic syndrome which frequently relapsed despite cyclophosphamide treatment were given cyclosporin A (7.5 mg/kg/day to 10 mg/kg/day) for 8 to 12 weeks. Six had minimal change glomerulonephritis and two had focal segmental glomerulonephritis. Cyclosporin A was given to 5 patients when their nephrotic syndrome was in relapse and to 3 patients when the nephrotic syndrome was in remission. Cyclosporin A induced a transient remission in only one patient.

## Introduction

Minimal change glomerulonephritis produces a nephrotic syndrome which is responsive to treatment with corticosteroids. Relapses often occur when steroid is discontinued or reduced in dose. Cyclophosphamide has been used to prevent such relapses. Both prolonged steroid and cyclophosphamide treatment is associated with considerable morbidity. Cyclosporin A (CyA), a novel anti-T-lymphocyte immunosuppressive agent that has been used with great success in organ transplantation, has been tried in experimental glomerulonephritis.<sup>1</sup> We report our experience of using CyA in the treatment of the nephrotic syndrome which has frequently relapsed despite repeated steroid and cyclophosphamide therapy.

## Patients and methods

Eight patients with a relapsing nephrotic syndrome were treated with CyA. Six had biopsy proven minimal change glomerulonephritis and 2 had focal segmental glomerulosclerosis (FSGS) (one diagnosed on initial biopsy and the other on repeat biopsy). Their age ranged from 23 to 40 years with a mean of 28 years. All patients with minimal change glomerulonephritis were males as was one patient with FSGS. The age at which the patients initially presented with the nephrotic syndrome varied from 13 to 34 years and the number of relapses varied from 2 to 17 episodes with a mean of 9.5 episodes in 81 months. All patients with minimal change showed good response to steroids initially. All except one patient had been treated with cyclophosphamide. CyA was given to all patients in a dose

varying from 7.5 mg/kg to 10 mg/kg daily in two divided doses for 8 to 12 weeks. The response to treatment was assessed in the conventional manner by clinical examination, determination of 24 h urinary protein excretion and renal function profiling which included serum albumin and cholesterol concentrations.

## Results

In 5 patients (patients 1 to 5, Table I) CyA was given when the patients were nephrotic. In one patient the response was good. The nephrotic syndrome remitted in 4 weeks but relapsed 4 weeks after discontinuation of CyA. One patient, who had already suffered aseptic necrosis of the hips because of prolonged and repeated steroid therapy, showed a partial response. Proteinuria decreased but a full nephrotic syndrome recurred 14 weeks after CyA had been discontinued. One patient, who was given CyA in a dose of 7.5 mg/kg for 8 weeks, showed no signs of response to the treatment. His nephrotic syndrome remitted promptly when steroid was introduced again. The last patient in this group had FSGS on the first renal biopsy. She showed a partial response to a combination of cyclophosphamide and steroids. When the nephrotic syndrome recurred, she was given 7.5 mg/kg of CyA for 8 weeks. Her nephrotic syndrome did not improve; 250 mg CyA was then given by intravenous infusion daily for 5 days. She developed acute deterioration in renal function which improved when CyA treatment was withdrawn. There was no response in proteinuria.

Three patients (Patients 6-8, Table I) were given CyA when the nephrotic syndrome was in remission. In all, the nephrotic syndrome relapsed when CyA and

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**Table I** Use of cyclosporin A in steroid-sensitive nephrotic syndrome with frequent relapses

Patient	Age*	No. of relapses†	Cyclophosphamide‡	CyA (mg/kg/day)	Response	Side effect
1 (m)	31 (21)	10 (120 m)	no	7.5 (8 wks)	no	↑ creatinine
2 (m)	40 (34)	13 (66 m)	yes × 3	10 (8 wks)	yes	gum hypertrophy
3 (f)	33 (31)	2 (18 m)	yes × 2	7.5 (8 wks)	no	↑ creatinine
4 (m)	25 (23)	5 (20 m)	yes × 1	10 (8 wks)	partial	nil
5 (m)	25 (18)	17 (84 m)	yes × 1	10 (8 wks)	no	hypertrichosis
6 (m)	23 (14)	9 (102 m)	yes × 2	10 (12 wks)	no	nil
7 (m)	23 (14)	10 (108 m)	yes × 3	10 (8 wks)	no	nil
8 (m)	24 (13)	10 (132 m)	yes × 2	10 (12 wks)	no	nil

\*Number in parenthesis indicates age at first presentation; †Number in parenthesis indicates time in months during which the relapses occur; ‡Cyclophosphamide treatment consisted of 100 mg/day for 8 to 12 weeks.

steroid treatment was completely withdrawn and remitted when steroid was reintroduced. Three patients showed noticeable gingival hyperplasia and one had hypertrichosis. Serum creatinine concentrations increased in two patients but returned to pre-treatment level after CyA had been discontinued.

## Discussion

All our patients had a rather protracted relapsing nephrotic syndrome. Untoward side effects of steroid, for example, aseptic necrosis of the hips, and of cyclophosphamide, for example, reduced fertility, renders it desirable to search for a substitute for steroid and cyclophosphamide treatment. The pathogenesis of minimal change glomerulonephritis remains unsettled and many investigators regard FSGS as a variant of minimal change glomerulonephritis.<sup>2</sup> Although cyclophosphamide has been reported to reduce relapses of nephrotic syndrome, all our patients had frequent relapses despite cyclophosphamide therapy. This, together with the suggestion that minimal change glomerulonephritis results from a T-cell defect,<sup>3,4</sup> prompted us to use CyA in our patients in spite of the cost of the drug. CyA acts on T helper cells and reduces the production of lymphokines<sup>5</sup> and therefore appears ideal for a condition thought to be mediated by lymphokines.<sup>3</sup> CyA has been shown to reduce IgE synthesis<sup>6</sup> and patients with the nephrotic

syndrome often have high IgE levels.<sup>7,8</sup> Our preliminary experience is rather disappointing. Certainly when given alone to patients who were nephrotic, CyA induced a remission in only one out of 4 patients. The prompt response of the nephrotic syndrome to the reintroduction of steroids reflects the fact that CyA and steroids have distinctly different immunosuppressive properties. Although the follow-up after discontinuation of CyA was too short to make a firm conclusion that the 'frequency' of relapses cannot be reduced by CyA, the fact that the nephrotic syndrome promptly recurred when CyA was withdrawn is rather discouraging. There was good compliance in our patients. The mean trough plasma CyA levels measured in 4 patients by radioimmunoassay was 200 ng/l. To circumvent the possibility that CyA absorption might be impaired in the nephrotic state, we infused CyA intravenously in one patient without therapeutic effect despite nephrotoxicity. The dose of CyA we used (7.5 mg/kg to 10 mg/kg) was comparable to that used in organ transplantation, and the duration of treatment (8 to 12 weeks) should be long enough for a therapeutic effect to be observed. Nevertheless, used the way we did in steroid-sensitive nephrotic syndrome which relapses frequently despite cyclophosphamide treatment, CyA is disappointing at least in the short term, although others have reported more favourable results.<sup>9-12</sup> It may be relevant that the nephrotic syndrome has recurred after renal transplantation despite continuous CyA treatment.<sup>13</sup>

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