Pediatr Nephrol (1994) 8: 401–403


Pediatric Nephrology

*Original article*

# Long-term cyclosporin A treatment of minimal-change nephrotic syndrome of childhood

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Received October 12, 1993; received in revised form April 4, 1994; accepted April 7, 1994

**Abstract.** We evaluated the efficacy of long-term cyclosporin A (CyA) treatment in the maintenance of remission in 40 children with steroid-dependent minimal-change nephrotic syndrome (MCNS). CyA was given in an initial dose of 5 mg/kg per day, adjusted to maintain a trough whole blood level of 50–150 ng/ml. All the 40 children received CyA for 1 year. In 18 patients, CyA was continued for a further period of at least a year without interruption; 9 patients had a second course of CyA therapy after an interval of at least 1 month. Of the 40 children 29 (72%) had one or more relapses during treatment with CyA, with 16 (40%) relapsing during the 1st year. During the second period of CyA, 10 (56%) of the 18 children treated continuously relapsed, whereas all the 9 children who had an interrupted course of therapy relapsed. CyA was discontinued at one time in 27 patients, all of whom subsequently relapsed, with a median time to relapse of 26 days. Long-term prednisolone in addition to CyA was required to maintain remission in 16 (40%) of the whole group. The results suggest that the long-term use of CyA is able to maintain remission of MCNS, although 40% of the patients also required low-dose alternate-day steroids; patients appeared to fare worse if the CyA course was interrupted; no patient experienced a long-term remission after CyA was stopped.

**Key words:** Cyclosporin – Minimal-change nephrotic syndrome

## Introduction

Cyclosporin A (CyA) is now a well-recognised treatment for children with steroid-dependent minimal-change nephrotic syndrome (MCNS) [1–4]. Trials of the short-term use of CyA have shown it to be effective in maintaining remission in 77%–100% of cases of MCNS [5–9]. In this paper we report the clinical results of the long-term use of CyA in the management of children with steroid-dependent MCNS. The effects of long-term CyA on renal function are detailed in a separate report [10].

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## Patients and methods

Forty children (33 males, 7 females) aged 6–17 years with steroid-dependent MCNS were studied. All patients had previously received at least one course of cyclophosphamide because of relapses whilst taking prednisolone in a dose of at least 1 mg/kg on alternate days. All had relapsed subsequently and had had two or more relapses in the 6 months prior to entering the study, despite a prednisolone dosage of at least 0.5 mg/kg on alternate days. A renal biopsy was performed in all the children during the 3 months prior to starting CyA and confirmed minimal change histology. Patients with focal global or segmental glomerulosclerosis were not included in the study.

CyA was started at a dose of 5 mg/kg per day taken by mouth twice daily. The dose was adjusted to maintain the trough whole blood level between 50 and 150 ng/ml as measured by high-performance liquid chromatography. Prednisolone treatment was gradually withdrawn and stopped after the first 8 weeks of CyA treatment. Renal and hepatic function were monitored every 2 weeks. Plasma creatinine concentration was measured using a kinetic Jaffé method with a coefficient of variation of 2.0%. The parents tested a morning urine sample from the child each day for protein using Albustix and reported to the hospital if there was a reading of 2+ or more for 3 consecutive days. Relapses were confirmed by a urinary albumin to creatinine concentration ratio greater than 1.0 mg/mg (normal $<0.1$ mg/mg [11]). Oral prednisolone 2 mg/kg per day (maximum 80 mg daily) was then restarted, and a remission was obtained in all patients within 3 weeks. The prednisolone was subsequently withdrawn within a few weeks or, if further relapses occurred, continued as alternate-day maintenance therapy. CyA dose was not tapered and therapy was continued during a relapse.

CyA was initially prescribed in all patients ($n = 40$) for 1 year. It was then discontinued in 22 patients in order to assess the duration of remission. CyA was continued in the remaining 18 children (group I) without interruption for a further median period of 1.3 years (range 1.1–2.3 years). Of the 22 patients in whom CyA was discontinued, treatment was restarted because of continued relapses in 9 patients (group II). These 9 patients had a second course of CyA lasting for a median of 1.5 years (range 0.25–3.1 years). The median interval between the two courses was 0.4 years (range 0.1–0.8 years). Prednisolone, using the regimen detailed above, was given concur-

**Table 1.** Relapses in children with minimal-change nephrotic syndrome treated with cyclosporin A (CyA)

| CyA | Group | Number | Relapsed (%) |
|---|---|---|---|
| 1st Year | All | 40 | 16 (40%) |
| Whole period | All | 40 | 29 (72%) |
| Second period (continuous) | Group I | 18 | 10 (56%) |
| Second period (interrupted) | Group II | 9 | 9 (100%) |

**Table 2.** Plasma creatinine in patient groups treated with CyA (mean ± SD)

| Group | Duration CyA (months) | CyA dose (mg/kg per day) | CyA level (ng/ml) | Creatinine (μmol/l) |
|---|---|---|---|---|
| All | 6 | 5.6 | 65±13 | 62±12 |
| All | 12 | 5.8 | 68±12 | 60±10 |
| I | 18 | 6.1 | 74±13 | 60±6 |
| I | >24 | 6.5 | 65±14 | 55±12 |
| II | 18 | 6.1 | 75±7 | 55±12 |

rently with CyA in these patients to induce remission. At the end of the study period 13 children from group I were still receiving CyA.

## Results

Of the 40 children, 29 (72%) experienced at least one relapse at some time whilst receiving CyA treatment, with 16 (40%) relapsing during the 1st year of CyA treatment (Table 1). During the first course of uninterrupted CyA (i.e. excluding the second course in group II), the initial relapse occurred 0.2–1.6 years after starting CyA, with life-table analysis showing 40% free of relapse at 2 years (Fig. 1). During the 2nd and subsequent years of continuous CyA treatment in group I, 10 of 18 children (56%) experienced a relapse compared with all of the 9 children in group II who were receiving a second course of CyA after a break of at least a month ($P < 0.05$ chi-squared analysis).

Despite adequate whole blood CyA levels, 16 of all the patients (40%) had two or more relapses and required long-term prednisolone (0.05–0.5 mg/kg per alternate day) in addition to CyA to maintain remission. This was the situation in 5 (12%) of the 40 children during the 1st year of treatment; during the second period of treatment 7 (39%) of the 18 children in group I and 4 (44%) of the 9 children in group II required additional prednisolone. Of the 5 children who relapsed during the 1st year of treatment, 2 did so when the prednisolone was tapered. Relapses which occurred in spite of CyA and a high dose of prednisolone of 0.5 mg/kg per alternate day were documented and designated "severe". These occurred in 1 child during the 1st year of treatment, in 4 children in group I and in 3 children in group II.

The plasma creatinine, mean CyA dose and level in the patient groups are shown in Table 2. There was no difference in the plasma creatinine or the CyA levels between the

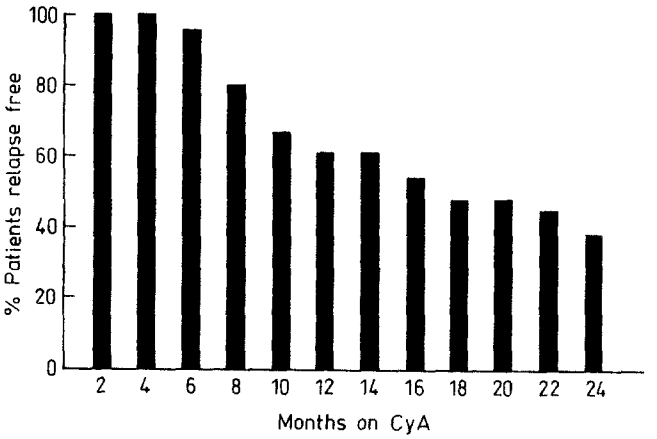


**Fig. 1.** Percentage of children with minimal-change nephrotic syndrome (MCNS) remaining free of relapse whilst receiving cyclosporin a (*CyA*) therapy

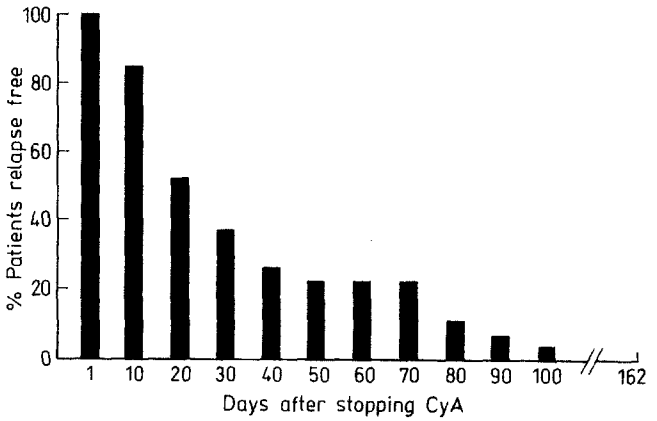


**Fig. 2.** Percentage of MCNS children remaining free of relapse after stopping CyA therapy

groups, and plasma creatinine did not change significantly during treatment. No patient exhibited raised transaminases; 13 (32%) of the children developed hirsutism; 8 (20%) gingival hyperplasia and 13 (32%) hypomagnesaemia. CyA was discontinued at one time in 27 children, all of whom subsequently relapsed, with a median time to relapse of 26 days (range 2–162 days) (Fig. 2).

## Discussion

The efficacy of CyA in the treatment of steroid-responsive MCNS has been widely reported and current recommendations suggest that CyA be used as a substitute for prednisolone in steroid-dependent cases, especially if there is evidence of corticosteroid toxicity [1, 4]. Early reports described sustained remissions of up to 14 months following a 6-month course of CyA [6]. Tejani et al. [12] reported a 40% sustained remission up to 20 months after discontinuation of CyA, with most of the relapses occurring within the first 6 months. Our data confirm that many difficult MCNS patients can be maintained in remission on CyA, but we did not observe any long-term benefit, with all

our patients relapsing within 6 months of discontinuing CyA and with a median time to relapse of 26 days. This implies persisting activity of the nephrotic syndrome and points to a lack of efficacy of CyA in establishing long-term remission, in contrast to the effect often achieved with alkylating agents.

Most reports on the use of CyA in children with steroid-dependent MCNS present results of short duration of drug treatment, usually 6 months [5–7, 9]; so far only a small number of patients have been reported on long-term CyA [4, 13, 14]. We report data in 40 patients who either had received CyA continuously for up to 39 months or who had discontinued CyA after 12 months and then resumed treatment. Our results using prolonged uninterrupted courses of CyA suggest on overall long-lasting remission rate lower than those previously published, and there is a tendency for the management to become more difficult with time, with more children requiring maintenance steroids in addition to CyA and experiencing "severe" relapses. The course of the nephrotic syndrome in the children reported in this study represents the group of patients who are difficult to treat, i.e. an older population, especially boys, who have already received cytotoxic agents and failed to respond.

Our data suggest that children who had discontinued CyA treatment and then resumed treatment later tended to have a greater frequency of relapse. The immunological mechanism of action of CyA in vivo is complex and has not been fully elucidated [15]. Although the pharmacological effects of CyA are quick in onset and often rapidly reversible when treatment is stopped, it is possible that interruption of CyA therapy permits escape of the immunopathogenic process in a manner which is subsequently less easily controlled by resumption of CyA.

Nonetheless, CyA is a valuable drug for the management of difficult cases of MCNS, particularly those in whom alkylating agents have failed and who are at high risk of corticosteroid toxicity, especially peripubertal boys. A parallel study shows that these effects can be achieved without significant nephrotoxicity [10].

*Acknowledgements.* S.-A. H. was supported by the Caring for Kids Trust; T. J. N. was supported by the Karl Reiser and Heinrich Paur Fund, Zurich, Switzerland.

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