

Case Reports of Low Dose Cyclosporine A Therapy in Adult Minimal Change Nephrotic Syndrome

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Abstract

Introduction: Many centres still use steroids to induce remission in patients with minimal change nephrotic syndrome (MCNS) and failing that to give a course of cyclophosphamide, though some centres are already using cyclosporine A (CsA) as an alternative. We report the benefits of CsA therapy in 3 adults with difficult to treat MCNS in whom low dose CsA therapy proved to be efficacious. **Clinical Picture and Outcome:** The first patient had her 1st relapse after 8 years and thereafter had 2 more relapses, within 3 months of each other, in spite of therapy with cyclophosphamide. With CsA therapy, at a dose of 3.5 mg/kg body weight (BW)/day, she achieved lasting remission of 22 months as of September 1999 and is still in remission. The second patient had his relapses of nephrotic syndrome over a period of 10 years when treated with prednisolone and cyclophosphamide. On the 13th relapse, he achieved a remission lasting 21 months after a 3 month course of CsA at a dose of 4 mg/kg BW/day. With the 14th relapse, he took half the dose of CsA prescribed [only the morning dose of neoral CsA (2 mg/kg BW/day)] and still achieved a remission and has been in remission since. The third patient was a young woman, married for 2 years without children. She could not tolerate prednisolone because of erosive gastritis and she responded to a pulse dose of intravenous cyclophosphamide for her 1st episode of nephrotic syndrome with complete remission. However, when she relapsed 5 months later she did not respond to a similar dose of i.v. cyclophosphamide and was therefore treated with CsA (4 mg/kg BW/day) which induced a prompt remission 1 month after commencement of therapy and she is still in remission. The trough CsA levels for the 3 patients (range 41 to 107 ng/mL) and the calculated average CsA levels were lower than that used for post renal transplant immunosuppression. The trough CsA levels were, however, similar to that used in patients with MCNS from other series, though achieved at lower CsA doses. **Conclusion:** Our study shows that low dose CsA is a useful agent for induction of remission of MCNS and maintenance of lasting remission. A low dose CsA regimen will make CsA more affordable.

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Key words: Cyclosporine, Glomerulonephritis, Low dose, Treatment

Introduction

There have been many reports on the use of conventional doses of cyclosporine A (CsA)¹⁻³ in inducing remission among adults with minimal change nephrotic syndrome (MCNS), including those who fail steroids and cyclophosphamide therapy or who are steroid dependent and frequent relapsers. We report 3 cases which demonstrate the efficacy of low dose CsA in 3 adults with MCNS. In children, there are already several reports on the use of low dose CsA to maintain long-term remission.⁴⁻⁷

CsA offers great versatility in usage and can be tailored to the differing needs of various patients; the duration of therapy depending on the needs of the patients. Cost is not a great prohibitor especially if used in small doses. It should be an equally viable alternative to cyclophosphamide which

can cause serious side effects especially in terms of severe haemorrhagic cystitis in susceptible patients and more seriously, long-term gonadal toxicity among children and young adults.

Case Reports

Case 1

A 34-year-old female nurse was first seen in June 1989 with a 2-week history of generalised oedema associated with frothy urine with decreased urine output. She had no other symptoms and no past history of note. Physical examination revealed ankle oedema with blood pressure (BP) 150/100 mmHg. No other abnormality was detected.

Investigations revealed: haemoglobin (Hb), 15 gm/dL; total white cell count, $13.9 \times 10^9/L$; platelet count, 296,000

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$\times 10^9/L$; lupus markers were negative; and serum complement CH_{50} , 15 units/mL. Urine exam revealed: red blood cell (RBC), nil; white blood cell (WBC), 1-2 phpf; no casts; albumin, 3+; serum creatinine, 0.8 mg/dL; total serum protein, 58 gm/L; serum albumin, 27 gm/L; and total urinary protein, 5.8 gm/day. A renal biopsy showed MCNS.

She was given a course of prednisolone starting at 60 mg a day with reduction and tapering off over 3 months. There was complete remission and all her tests were normal. The total urinary protein was 0.1 gm/day at the end of 3 months. She remained well until February 1997 when she had a second relapse with ankle oedema and frothy urine. Physical examination revealed ankle oedema with a blood pressure of 160/100 mmHg. Investigations showed: urine RBC, nil; WBC, 1-2 phpf; no casts; albumin, 3+; serum creatinine, 92 $\mu\text{mol/L}$; total serum protein, 59 gm/L; serum albumin, 30 gm/L; and total urinary protein, 8.0 gm/day.

She was treated again with prednisolone and 3 months later, the total urinary protein was 0.48 gm/day but a week later she had a relapse with recurrence of oedema and proteinuria while on prednisolone at 10 mg a day. Prednisolone was increased to 20 mg a day and 100 mg oral cyclophosphamide was added. She was oedematous and proteinuria was 3.4 gm/day. After a month of oral cyclophosphamide and low dose steroid, the proteinuria was 0.91 gm/day and at the end of 3 months proteinuria was 0.1 gm/day. However, a month after cyclophosphamide was stopped, while still on prednisolone 10 mg a day, she had a relapse with proteinuria of 3.42 gm/day.

It was decided to commence therapy with neoral cyclosporine A (CsA). She was given a dose of 150 mg twice daily at 3.5 mg/kg BW/day. Her weight was 86 kg. Her oedema started to subside 3 weeks after commencement of CsA and after 1 month therapy, proteinuria was 0.95 gm/day. After 3 months of therapy, proteinuria was 0.8 gm/day. On the 4th month, CsA was reduced to 125 mg twice daily at 3.1 mg/kg BW/day. Her weight was 80 kg. On the 5th month, the dose of CsA was 100 mg twice daily and at 6 months 75 mg twice daily (2 mg/kg BW/day); urinary protein, 0.1 gm/day. On the 9th month, the dose of CsA was 50 mg twice daily. CsA was stopped after 12 months. She has since been in remission for 24 months now (Fig. 1). She required 6 months of CsA therapy to reduce the total urinary protein to 0.1 gm/day and about 9 months for complete disappearance of oedema even though serum albumin had normalised to 37 gm 3 months after commencement of CsA therapy. While on a CsA dose of 3.5 mg/kg BW/day at twice daily dosing, her CsA level measured in whole blood, by Abbott TDX monoclonal Fluorescent Polarization Immuno Assay, at 0 hours (C_0 , trough level) was 107 ng/mL and the CsA level at 2 hours post dose (C_2) was 714 ng/mL. An average CsA level was

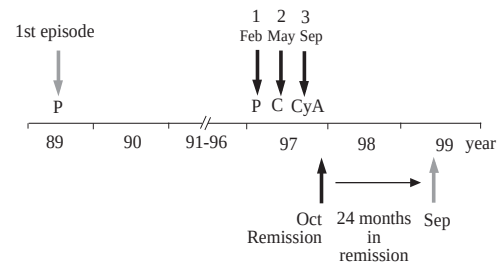


Fig. 1. Difficult case of MCNS responding to low dose cyclosporine A with long-term remission.

Footnote:

C : oral cyclophosphamide for 3 months

CsA : neoral CsA dose was as follows—3.5 mg/kg (150 mg/bd) in the 1st three months, 2.9 mg/kg (75 mg/bd) in the 4th month, 2.3 mg/kg (100 mg/bd) in the 5th month, 1.7 mg/kg (75 mg/bd) in the 6th to 9th month, and 1.2 mg/kg (50 mg/bd) from the 10th month for a period of 1 year before stopping

P : prednisolone for 3 months

1,2,3 refer to the number of relapses

calculated based on the sparse sampling strategy of Keown et al.⁸

Average CsA = $(1.84 \times C_0 + 4.39 \times C_2 + 312.66)/12$, where 12 represents the dosing interval of 12 hours.

At this dose, average CsA for Case 1 at the start of CsA therapy for MCNS was 304 ng/mL.

Case 2

A 24-year-old male mechanic was referred in March 1989 with complaints of facial and ankle oedema associated with decreased urine output over 2 weeks. There was no past illness of note. Physical examination revealed facial and ankle oedema; Muerchke's bands were present in his nails and BP was 110/60 mmHg. Investigations revealed: Hb, 15.9 gm/dL; total white cell count, $11,700 \times 10^9/L$; and platelet count $310,000 \times 10^9/L$. Urine RBC, 0-1 phpf; WBC 0-1 phpf; no casts; albumin, 3+; total serum protein, 3.9 gm/L; serum albumin, 1.3 gm/L; serum creatinine, 1.6 mg/dL; and total urinary protein, 3.84 gm/day.

A renal biopsy showed MCNS and he was treated with prednisolone 60 mg daily with gradual dose reduction and tapering off by the end of the third month. He responded to therapy by 3 months with urinary protein of 0.1 gm/day. However, towards the end of the third month (last week of the 3-month period), when prednisolone was at 10 mg, he had his first relapse with recurrence of oedema; serum creatinine, 1.1 mg/dL and total urinary protein, 9.2 gm/day. Oral cyclophosphamide was commenced at a dose of 75 mg daily together with an increased dose of prednisolone at 20 mg a day. After 3 months of cyclophosphamide, he had remission with disappearance of proteinuria to 0.1 gm/day but 3 months after stopping cyclophosphamide, he had his second relapse of nephrotic syndrome; total urinary protein, 5.4 gm/day. Prednisolone was started at 60 mg a day and after 3 months, the proteinuria was 0.1 gm/day. But

10 months later, he had his third relapse with proteinuria of 4.8 gm/day, total serum protein of 48 gm/L and serum albumin of 18 gm/L with reappearance of Muerchke's bands. Oral cyclophosphamide 75 mg was re-instituted together with prednisolone 20 mg daily. After 3 months of cyclophosphamide, his proteinuria was still 2.2 gm/day and it was decided then to continue with cyclophosphamide for another month. At the end of 4 months of cyclophosphamide, proteinuria was 0.1 gm/day.

He remained well for more than a year but in April 1992 had his fourth relapse with proteinuria of 4.08 gm/day with reappearance of Muerchke's bands on the nails. He remitted after another 3 months course of cyclophosphamide, but after another 2 months had his fifth relapse with proteinuria of 3.41 gm/day associated with reappearance of oedema and Muerchke's bands. This time he was given a course of prednisolone 60 mg/day and remitted after 3 months. Prednisolone was maintained at 10 mg a day for another 3 months.

He was in remission for about 2 years until September 1994 when he had his sixth relapse with proteinuria of 7.65 gm/day. He remitted with a course of prednisolone over 3 months with maintenance prednisolone 10 mg a day on the 4th and 5th month but at the end of the 5th month had a relapse with urine RBC, nil; WBC, 0-1 phpf; no casts; albumin, 4+; proteinuria, 13.6 gm/day; and serum creatinine, 85 µmol/L. BP was 130/80 mmHg.

Between September 1994 and September 1997, he had 7 more relapses (over 3 years) each time responding either to prednisolone or cyclophosphamide with total remission and though he was maintained with 10 mg of prednisolone these relapses continued. On the 12th relapse, he was treated with CsA (4 mg/kg BW/day). He achieved remission which lasted 21 months (September 1997 to June 1999) after a 3-month course of CsA. In the 22nd month, he had his 13th relapse and though he was prescribed 4 mg/kg BW/day of CsA in 2 divided doses he took only the morning dose to cut cost (2 mg/kg BW/day). This low dose fortunately induced a remission and he has been in remission since (Fig. 2). His C0 and C2 CsA levels were 41 ng/mL and 1059 ng/mL respectively at a CsA dose of 4 mg/kg BW/day while the calculated average CsA level was 419 ng/mL.

Case 3

A 28-year-old sales representative, married for 2 years with no children, presented in November 1998 with swelling of the face and legs associated with a bloated abdomen and decreased urine output. She was admitted to Changi Hospital, and diagnosed as having the nephrotic syndrome. She was prescribed prednisolone 15 mg thrice daily. One week later, she developed haemetemesis and epigastric pain and prednisolone was stopped. She was transferred to

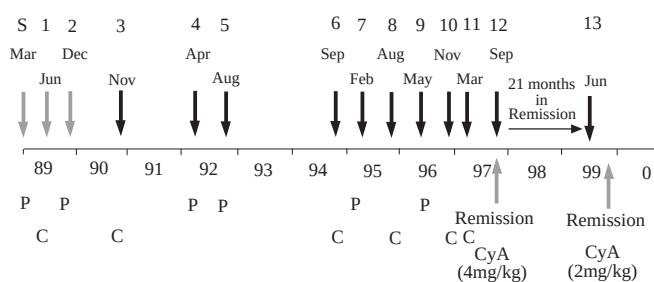


Fig. 2. Long-term remission of frequently relapsing nephrotic syndrome with low dose cyclosporine therapy.

Footnote:

C : oral cyclophosphamide for 3 months

CsA : cyclosporine (neoral) treatment duration for 3 months

P : prednisolone for 3 months

S : refers to the first episode and the numbers following are the relapses

Mount Elizabeth Hospital and a gastroscopy showed erosive gastritis with duodenitis. She was put under the care of a nephrologist who prescribed a single pulse of intravenous cyclophosphamide 400 mg. Her total urinary protein which was 4.3 gm/day initially decreased to 0.1 gm/day 2 weeks later in December 1998.

She remained well until April 1999 when she developed swelling of her legs associated with decreased urine output and frothy urine. She was diagnosed as having a relapse of the nephrotic syndrome and administered another single pulse of intravenous cyclophosphamide 400 mg again. This time though she did not respond to the therapy and 2 months later in June 1999, her urine still showed albumin, 3+; blood urea, 24 mg/dL; and serum albumin, 2.1 gm/L.

She sought treatment at the Singapore General Hospital on 23 June 1999, complaining of ankle swelling associated with bloated abdomen, decreased urine output and frothy urine. There was no history of joint pain, rash or alopecia. Physical examination revealed bilateral ankle oedema, without any facial oedema. She had ascites but no rash on her body. Her BP was 100/60 mmHg and there were no other abnormalities detected.

Investigations revealed: Hb, 13.1 gm/dL; WBC, 4,600 x 10⁹/L; and platelet count, 382,000 x 10⁹/L. Urine microscopy: RBC, nil; WBC 0-1 phpf; no casts; albumin, 3+; serum creatinine, 64 µmol/L; total serum protein, 43 gm/day; serum albumin, 18 gm/L; total urinary protein, 8.82 gm/day; and total serum cholesterol, 19.08 mM/L. Serum complement: C₃, 1.42 units; C₄, 0.34 units. Anti-nuclear factor, anti-DNA, HbsAg and HCV were all negative. A renal biopsy on 23 June 1999 showed MCNS.

In view of the history of erosive gastritis due to steroids, and since she had been married for 2 years without any children yet, and had had 2 pulse doses of intravenous cyclophosphamide, it was decided that she be offered therapy with neoral CsA 100 mg twice daily. Her weight was 48.3 kg (4 mg/kg BW/day).

She was reviewed at 2 weekly intervals and at the end of 4 weeks, her swelling subsided and there was no oedema. Investigations revealed: urine RBC, 0-1; WBC, 1-2 phpf; no casts; albumin, nil; serum creatinine, 69 $\mu\text{mol/L}$; and total urinary protein, 0.1 gm/day (Fig. 3).

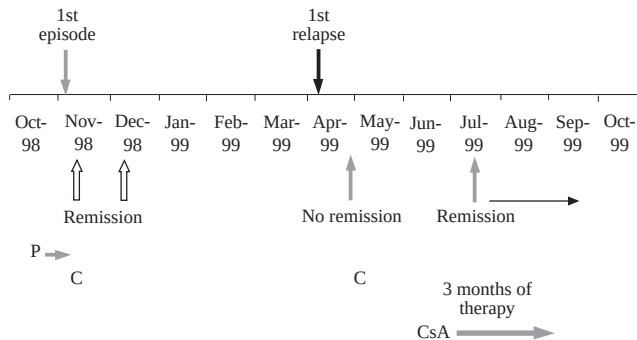


Fig. 3. Response to therapy with cyclosporine where prednisolone is contraindicated.

Footnote:

C : pulse intravenous cyclosporine 400 mg

CsA : neoral CsA dose was 4 mg/kg (100 mg/bd) for 3 months

P : prednisolone for 1 week was stopped because of erosive gastritis

Case 3: patient weighed 48.3 kg and had been married for two years without any children yet

* : erosive gastritis

Since then, she has been in remission. At a dose of 4 mg/kg BW/day CsA, her C0 and C2 levels were 70 ng/mL and 690 ng/mL, respectively, while the calculated average CsA level was 289 ng/mL.

Discussion

These 3 case reports demonstrate the efficacy of low dose CsA in 3 difficult cases of MCNS. In case 1, a patient with MCNS presented with difficulty in treatment with steroids and cyclophosphamide as she was having frequent relapses (3 in 8 months). It took 6 months for her to achieve complete remission (proteinuria, 0.1 gm/day) and after a year of low dose CsA therapy had sustained remission for 2 years and is still in remission. In case 2, the patient, who was steroid and cyclophosphamide sensitive but frequent relapser, achieved lasting remission after a 3-month course of low dose CsA. We would have preferred to treat him with CsA for 6 months because of his frequent relapses but he stopped his treatment on his own after 3 months and sustained a remission for 21 months. When he had a subsequent relapse, he again responded to CsA but at half the prescribed dose (2 mg/kg BW/day). Case 3 was a patient who could not be treated with steroids because of erosive gastritis and in whom oral cyclophosphamide was not advisable as she has been married for 2 years without any children yet. She responded dramatically to a short course of CsA at 4 mg/kg BW/day for 3 months.

Our previous Departmental policy for the use of CsA in patients with MCNS was for those who failed to respond to

prednisolone or cyclophosphamide. For patients who are steroid dependent or are frequent relapsers with prednisolone, we use cyclophosphamide to induce lasting remission. For frequent relapsers with cyclophosphamide, we resort to CsA which is more costly. CsA is prescribed in a dose of 5 mg/kg BW/day for 3 months. The subsequent CsA dosage and duration of therapy of up to 6 months is dependent on the circumstances of the case. Some patients with MCNS, who are steroid and cyclophosphamide responsive, non-steroid dependent and non-frequent relapsers, are given a 3-month course of CsA with no maintenance therapy and they have had lasting remissions.

There are serious side effects with the use of cyclophosphamide, especially with regards to gonadal toxicity. We are using CsA more frequently instead of cyclophosphamide. The above 3 cases illustrate the advantages of using CsA in difficult cases of MCNS.

Lately, we have also been using lower doses of CsA to induce remission, about 2 to 3 mg/kg BW/day as in these 3 cases where initial doses were 3.5 and 4 mg/kg BW/day. In case 2, a dose of 2 mg/kg BW/day was also shown to achieve remission. Low dose CsA (2 to 3 mg/kg BW/day) has been used to maintain remission in children with steroid-dependent nephrotic syndrome (SDNS).⁷ Tojo et al⁵ showed that the initial dose of CsA of 2.5 mg/kg BW/day was effective in children with frequent relapsing NS. Hino et al⁶ and Tanaka et al⁴ also reported the success of using initial low dose CsA for children with SDNS. Among adults with nephrotic syndrome, Hayashi et al⁷ reported 3 patients, 2 with MCNS and 1 with focal and segmental glomerulosclerosis (FSGS), responding to initial doses of CsA at 3.8 to 5 mg/kg BW/day.

In Europe and America, the average dose of CsA employed is about 5 to 6 mg/kg BW/day. The initial starting dose employed by Niaudet et al⁹ was 6 mg/kg BW/day, 5.4 0.2 mg/kg BW/day in the Collaborative Study Group of Sandimmun,¹⁰ 6.3 0.4 mg/kg BW/day by Gregory et al,¹¹ 5.5 0.8 mg/kg BW/day by Meyrier et al² and 6 mg/kg BW/day by Habib and Niaudet.¹²

In our 3 cases, none of them had any renal impairment and none suffered any side effects of CsA treatment. Most studies have shown that the incidence of CsA nephrotoxicity was not related to duration of treatment.^{9,12,13} Webb et al¹⁴ reported no evidence of nephrotoxicity in renal biopsies in 5 patients after 12 months of therapy with CsA, but a further biopsy 3 years later showed interstitial fibrosis in 1 patient. In Kano's series,¹⁵ only 1 patient out of 14 with SDNS treated with CsA for 2 years showed striped interstitial fibrosis.

Despite the increased use of CsA in the treatment of MCNS, its optimal dose has not been established. Most studies report the use of CsA without any mention of CsA

levels achieved. In the study by Gregory et al,¹¹ CsA dose was adjusted to maintain whole blood trough levels of 70 to 120 ng/mL. However, as there are significant differences in individual handling of CsA, CsA levels should also be examined in evaluating efficacy of therapy.

Some of the best lessons on CsA dosing for immunosuppression have been derived from renal transplant recipients (RTx) on CsA therapy. Although the correlation between CsA trough levels (C0) and post-transplant adverse clinical events such as graft rejection or CsA nephrotoxicity has limitations, they are still widely used to guide CsA dosing. In RTx on CsA therapy, target C0 levels in the first 6 months have been between 200 and 250 ng/mL; in the long-term, target C0 levels vary from centre to centre but are usually maintained between 100 and 150 ng/mL.

An alternative strategy has proposed the use of CsA monitoring at 2 hours post dose (C2) as a better correlate of adverse events post RTx. Target C2 levels of 1700 ng/mL have been recently recommended for the first 6 months post RTx as adequately immunosuppressive.¹⁶

Finally, due to the intra and interindividual variability in pharmacokinetics of CsA, there has been an increased tendency to dose CsA in RTx using area under the time-concentration-curve (AUC). Furthermore, several sparse sampling strategies have been proposed in RTx to predict AUCs without the need for extensive blood sampling. Keown et al⁸ have proposed a two-point strategy that calculates the average CsA level over a 12-hour dosing interval using C0 and C2 levels as described above. Amante and Kahan¹⁷ have proposed target average CsA levels of 550 ng/mL in the 1st month post-RTx, dropping gradually to 350 ng/mL beyond 12 months post-RTx. In our own centre, CsA dose is based on a sparse sampling strategy and target average CsA levels in the first 3 months post-RTx are 500 to 550 ng/mL.

The C0 and C2 levels achieved in our 3 patients with MCNS were much lower than that recommended in RTx patients. In addition, the average CsA levels as calculated by abbreviated AUC were also lower (289 to 419 ng/mL) than that recommended for immunosuppression. The C0 levels (41 to 107 ng/mL) achieved in our 3 patients were similar to that achieved in Gregory et al's¹¹ series of children with MCNS, but were obtained with much lower doses of CsA (3.5 to 4 mg/kg BW/day vs. 6.3 mg/kg BW/day).

We conclude that more patients with MCNS can be treated with CsA effectively to induce remission, especially in those with difficult to treat MCNS with frequent relapses or who are steroid dependent. To induce long-lasting remission, patients who are steroid dependent or frequent relapsers may need to be put on a small maintenance dose of CsA at 2 mg/kg BW/day over the second 6 months.

Initial starting doses of 3 to 4 mg/kg BW/day could be employed to induce remission for the first 2 to 3 months and thereafter gradual reduction of 2 to 3 mg/kg BW/day until 6 months and thereafter 2 mg from the 7th month to the 12th month. This regimen could avoid nephrotoxicity in the few patients as recorded by Webb et al¹⁴ and Kano et al,¹⁵ where long-term therapy may induce nephrotoxicity. Further, by monitoring C0, C2 or average CsA levels, CsA nephrotoxicity may be averted, especially as multiple courses or long-term therapy may often be required.

A further advantage of using a low dose CsA regimen (3 to 4 mg/kg BW/day) is cost savings, compared to 5 to 6 mg/kg BW/day as in Meyrier et al's series² (5.5 mg/kg BW/day), Habib and Niaudet's series¹² (6 mg/kg BW/day) and Gregory et al's series¹¹ (6.3 mg/kg BW/day). This is especially relevant in the underdeveloped and developing countries where cost of CsA is a problem. However, since most of the low dose CsA regimen are reported from Asian countries, it could be related to racial differences⁷ but more work will be required to establish if this is true including controlled trials to determine whether low dose CsA is equally efficacious and will sustain equal duration of remission compared to using the conventional dose.

Finally, we should consider using the less toxic CsA in low doses to induce remission of nephrotic syndrome in preference to cyclophosphamide in cases of failure to respond to steroids or where steroids are contraindicated. This will avoid the problem of gonadal toxicity in many young children and adults treated with cyclophosphamide. Cost will be a smaller concern as these patients can be put on a low dose CsA regimen. Patients who are non-steroid dependent or frequent relapsers may probably only require a 3-month course of CsA as in case 3 in our report. Further studies will be required to confirm if this is so since reports by Hayashi et al⁷ and Ittel et al³ seem to suggest that long-term therapy with CsA is also required in this group to prevent relapses.

REFERENCES

1. Ponticelli C, Edefonti A, Ghio L, Rizzoni G, Rinaldi S, Gusmano R, et al. Cyclosporine versus cyclophosphamide for patients with steroid-dependent and frequently relapsing idiopathic nephrotic syndrome: A multicentre randomized controlled trial. *Nephrol Dial Transplant* 1993; 8:1326-32.
2. Meyrier A, Noel L-H, Aurche P, Callard P. Long-term renal tolerance of cyclosporine A treatment in adult idiopathic nephrotic syndrome. *Kidney Int* 1994; 45:1446-56.
3. Ittel T H, Clasen W, Fubs M, Kindler J, Mihatsch M J, Sieberth H-G. Long-term cyclosporine A treatment in adults with minimal change nephrotic syndrome or focal segmental glomerulosclerosis. *Clin Nephrol* 1998; 44:156-62.
4. Tanaka R, Yoshikawa N, Kitano Y, Ito H, Nakamura H. Long-term

- cyclosporine treatment in children with steroid-dependent nephrotic syndrome. *Pediatr Nephrol* 1993; 7:249-52.
5. Tojo S, Narita M, Koyama A, Miyahara T, Nagasawa T, Kitagawa T, et al. Clinical evaluation of cyclosporine in the treatment of nephrotic syndrome — A multi-center double blind study (in Japanese). *Jin To Tohseki* 1994; 37:565-608.
6. Hino S, Takemura T, Okada M, Murakami K, Yagi K, Fukushima K, et al. Follow-up study of children with nephrotic syndrome treated with a long-term moderate dose of cyclosporine. *Am J Kidney Dis* 1998; 31:932-9.
7. Hayashi T, Saito N, Shoji T, Togawa M, Okada N, Tsubakiham Y. Cyclosporine A mono-therapy in nephrotic syndrome with contraindication of steroid therapy. *Intern Med* 1999; 38:272-5.
8. Keown P, Kahan B D, Johnston A, Levy G, Dunn S P, Cittero F, et al. Optimization of cyclosporine therapy with new therapeutic drug monitoring strategies: report from the International Neoral TDM Advisory Consensus Meeting (Vancouver, November 1997). *Transplant Proc* 1998; 30:1645-9.
9. Niaudet P, Tete M-J, Broyer M, Habib R. Cyclosporine and childhood idiopathic nephrosis. *Transplant Proc* 1998; 20:S265-8.
10. Collaborative Study Group of Sandimmun in Nephrotic Syndrome: Safety and tolerability of cyclosporin A in idiopathic nephrotic syndrome. *Clin Nephrol* 1991; 35:S48-60.
11. Gregory M J, Smoyer W K, Sedman A, Kershaw D B, Valentini R P, Johnson K, et al. Long-term cyclosporine therapy for pediatric nephrotic syndrome: A clinical and histological analysis. *J Am Soc Nephrol* 1996; 7:543-9.
12. Habib R, Niaudet P. Comparison between pre- and post-treatment renal biopsies in children receiving cyclosporine for idiopathic nephrosis. *Clin Nephrol* 1994; 42:141-6.
13. Feutren G, Mihatsch M J. Risk factors for cyclosporine-induced nephropathy in patients with autoimmune diseases. *N Engl J Med* 1992; 326:1654-60.
14. Webb K L, Sargent P, Burke J R. Cyclosporine therapy in steroid-dependent nephrotic syndrome. *J Paediatr Child Health* 1993; 29: 188-91.
15. Kano K, Kyo K, Yamada Y, Ito S, Ando T, Arisaka O. Comparison between pre- and post treatment clinical and renal biopsies in children receiving low dose cyclosporine A for 2 years for steroid-dependent nephrotic syndrome. *Clin Nephrol* 1991; 52:19-24.
16. Mahalati K, Belitsky P, Sketris I, West K, Panek R. Neoral monitoring by simplified sparse sampling area under the concentration-time curve. *Transplantation* 1999; 68:55-62.
17. Amante A J, Kahan B D. Abbreviated area under the curve strategy for monitoring cyclosporine microemulsion therapy in the immediate post transplant period. *Clin Chem* 1996; 42:1294.