

CYCLOSPORINE EXPERIENCE IN NEPHROTIC SYNDROME

K. Phadke, S. Ballal and V. Maiya

From the Division of Pediatric Nephrology, Department of Pediatrics, Manipal Hospital, Bangalore

Reprint requests: Dr. K.D. Phadke, Division of Pediatric Nephrology, Department of Pediatrics, Manipal Hospital, 98, Rustombagh, Airport Road, Bangalore 560 017

*Manuscript received: January 2, 1997; Initial review: completed February 7, 1997;
Revision accepted: September 18, 1997.*

Objective: To analyze the use of Cyclosporine (CyA) in nephrotic syndrome **Methods:** Thirty five children of mean age of 5.9 years with steroid dependent (n=26) or steroid resistant (n=9) primary nephrotic syndrome with normal renal functions and who received CyA were studied CyA was used at a dosage of 6-7 mg/kg/day orally in two divided doses The mean duration of therapy was 9.6 weeks All received a minimum of 8 weeks of CyA therapy In a few who received longer therapy, the dose was reduced to 4 mg/kg/day All patients were monitored serially for hepatotoxicity and nephrotoxicity The nephrotic state was evaluated serially with biochemical tests and followed up for a mean period of 2.55 years **Results:** Thirty one patients completed the study The response to therapy was categorized into 5 groups-no response (4 patients), good response (4 patients), partial response (4 patients), cyclosporine dependence (16 patients), and infrequent relapsers (3 patients) Good response was defined as complete remission lasting for at least one year after cessation of therapy. Patients who showed partial response had reduction in quantitative proteinuria and needed less diuretics Sixteen patients went into complete remission while on therapy but relapsed within 3 months of discontinuation (CyA dependence). The response to CyA correlated more with steroid-responsiveness than with the underlying histopathology The drug was well tolerated. **Conclusion:** In steroid-dependent or steroid-resistant nephrotic children with normal renal functions, CyA therapy may be considered as one of the possible therapeutic options Our results suggest that a longer duration of CyA therapy may possibly be indicated in these cases

Key words: Cyclosporine, Focal segmental glomerulosclerosis, Minimal Change glomerulonephritis, Nephrotic syndrome.

ALTHOUGH most children with idiopathic nephrotic syndrome respond to corticosteroid therapy, 40-90% of respondents have subsequent relapses(1-3). One of the major problems in the management of children who have frequent relapses is the serious side effects resulting from continuous steroid therapy. In these children as well as in children who are steroid resistant, there is a need to explore other modalities of immunosuppression. Alkylat-

ing agents such as cyclophosphamide and chlorambucil have been used as adjuncts to steroid therapy for inducing longer remissions in patients with frequently relapsing nephrotic syndrome. Although the effect of these drugs is well established in patients without steroid dependence, it is very unsatisfactory in steroid-dependent patients(4,5).

Nephrotic syndrome (NS) is considered as an immunological disorder, a disorder

of T cell function(6). In 1985, several investigators(7-9) reasoned that the postulated role of lymphokines in proteinuria of nephrotic syndrome might justify treatment with cyclosporine. Subsequently, several prospective studies have treated a heterogeneous group of both steroid responsive and resistant cases with varying histopathology using different cyclosporine regimens. This communication presents our experience with cyclosporine in nephrotic syndrome.

Subjects and Methods

Thirty five children with nephrotic syndrome who received Cyclosporine therapy were studied. Twenty six patients were steroid dependent, 9 were steroid resistant. All these patients had normal renal functions and blood pressure. The criteria for diagnosis of nephrotic syndrome, remission, relapse, steroid dependence, steroid resistance were as per the definitions used by the International Study of Kidney Disease in Children(10,11). Twenty three were males, twelve were females. The mean age of patients at the time of use of CyA was 5.9 years (range 3-17 years). The mean duration after onset of nephrotic syndrome at the time of use of CyA was 2.68 years (range 1-11 years). Twenty four patients had received a course of cyclophosphamide (2-3 mg/kg/day for 8 weeks), 6 patients received a course of chlorambucil (0.2-0.3 mg/kg/day for 8 weeks) prior to institution of CyA therapy. Those who did not receive these cytotoxic drugs had focal segmental glomerulosclerosis on kidney biopsy. In two patients, cytotoxic drugs had to be discontinued because of neutropenia. Informed consent was obtained from all patients before CyA treatment. Histopathological diagnosis prior to CyA therapy was minimal change nephrotic syndrome (MCNS-16 patients), mesangial proliferative glomerulonephritis (MesPGN

4 patients), membranoproliferative glomerulonephritis (MPGN 2 patients), focal segmental glomerulosclerosis (FSGS 10 patients), and membranous (Memb 1 patient). In one patient, the biopsy specimen was inadequate. One patient did not give consent for kidney biopsy.

CyA was used at a dosage of 6-7mg/kg/day, either in oral solution form or capsules, in two divided doses after the patients had attained remission with steroid therapy (in those who were steroid responders). The mean duration of treatment was 9.6 weeks (the range being 8-32 weeks). In a few who opted to continue CyA longer, the dose was reduced to 4 mg/kg/day and therapy continued for a longer period. Concurrent steroids were not used in this study in order to minimize risk of infection due to added immunosuppression, as infection is a major factor contributing to the morbidity of NS in developing countries.

All patients were monitored for nephrotoxicity and hepatotoxicity by serial assessment of renal and hepatic functions every two weeks. Evaluation of nephrotic state was made serially by assessment of serum albumin, cholesterol and urine protein/creatinine ratios. A close watch was kept on blood pressure. CyA levels were measured by Cyclosporine monoclonal whole blood assay using fluorescent polarization immuno-assay (FPIA) technology (12), the target levels being 100-200 ng/ml. CyA levels were estimated whenever there was 'no response' or 'partial response' as defined in the article.

Results

In four patients, Cyclosporine had to be discontinued before 8 weeks of treatment. In two cases, CyA was discontinued in view of altered liver function tests which returned to normal two weeks after

discontinuation of treatment. In one patient, CyA was discontinued due to rise in serum creatinine which returned to normal baseline subsequently. In one patient, CyA was discontinued on suspicion of empyema and sepsis.

In the remainder thirty one patients, the mean follow up period was 2.55 years (range 6 months-8 years) after starting CyA therapy.

The response to CyA therapy was categorized as follows:

1. **No response:** Unchanged nephrotic range proteinuria in spite of treatment persisted in 4 patients. All of these patients had FSGS on kidney biopsy, and developed end stage renal disease within 2-3 years.
2. **Good response:** This was defined as complete remission lasting for at least one year after cessation of CyA treatment. Four patients belonged to this category. They are in remission 2-6 years after completion of CyA treatment.
3. **Partial response:** Four cases did not go into complete remission. However, they had reduction in quantitative proteinuria (still in nephrotic range)

and needed less diuretics than before for control of edema.

4. **Cyclosporine dependence:** These went into complete remission while on CyA treatment. However, they relapsed within three months of discontinuation of CyA. Sixteen patients belonged to this category.
5. **Infrequent relapsers:** These patients responded to CyA treatment. However, they continued to have infrequent relapses (< 2 per 6 months or < 3 per year). The relapses occurred at least 3 months after cessation of CyA treatment. Three patients belonged to this category.

The outcome of CyA therapy in relation to histopathology and steroid responsiveness is depicted in *Tables I & II*, respective-

Cyclosporine treatment was well tolerated. No untoward gastrointestinal effects, gum hyperplasia, tremors, convulsions, hyperkalemia, hypomagnesemia, hypertension were noted in any of the patients. Mild hypertrichosis was noted in almost all cases which resolved after cessation of treatment. One patient who was requiring repeated paracentesis for pleural effusion

TABLE I—Outcome of CyA Therapy: Relationship to Histopathology

Outcome	Histopathology				
	Memb	MCNS	FSGS	MESPGN	MPGN
	1	16	10	4	2
CyA discontinued	—	1	—	—	1
No response	—	—	4	—	—
Good response	—	2	2	—	—
Partial response	—	—	3	—	1
CyA dependence	1	10	1	4	—
Infrequent relapser	—	3	—	—	—

TABLE II— *Outcome of CyA Therapy Relationship to Steroid Responsiveness*

Outcome	Steroid dependent (n=26)	Steroid resistant (n=9)
CyA discontinued	2	2
No response	0	4
Good response	3	1
Partial response	2	2
CyA dependence	16	0
Infrequent relapsers	3	0

developed empyema necessitating cessation of CyA treatment One patient developed pneumococcal meningitis which responded well to appropriate antibiotics.

Discussion

Although nephrotic syndrome in children is usually a benign disease, there are difficult situations when a child is either steroid resistant or is likely to develop steroid toxicity with continuous usage of steroids, if steroid dependent Although cyclophosphamide and chlorambucil are useful drugs in frequent relapsers without steroid dependence, their effect is poor in steroid-dependent cases Further, potential side-effects of those drugs, which seem to be dose dependent as for male gonadal toxicity, bone marrow suppression and possible oncogenicity, restrict their use(4,5) In the above mentioned situations, cyclosporine is being widely used in developed countries.

It is possible that CyA decreases proteinuria in nephrotic syndrome through three distinct mechanisms(13) The first is immunological, Cyclosporine prevents the release of interleukin-2 and interferon and possibly other lymphokines from activated T cells(14) The second mechanism could be a direct action on the permselectivity of the

glomerular basement membrane, and especially on the electromechanical barrier which repulses the anionic albumin molecules The third mechanism could be renal vasoconstriction produced by cyclosporine But this should lead to hypertension and decreased glomerular filtration rate which does not happen in all clinical situations.

Although centers in developed countries advocate long duration of Cyclosporine therapy, we decided to begin this pilot study using CyA for a relatively shorter period (mean 9.6 weeks) No data about use of CyA therapy in Indian children is available Also cost of the drug for prolonged therapy may be a significant constraint for our country The cost of cyclosporine course for eight weeks for a 15 kg child is approximately around Rs 5000-6000/- Analysis of this pilot study may give some directions for its future use It is interesting to note that occasional resistant patients who were resistant to steroids and cytotoxic drugs did show some response even to this short term treatment.

Our study clearly indicates a high incidence of Cyclosporine dependence in steroid dependent patients CyA induced remission is not long lasting and most patients relapse within few months after cessation of treatment(15) Therefore CyA may have to be administered for long periods of time Following this study, we have currently extended duration of CyA treatment to at least one year in situations where cost is not a restraining factor This will obviously require more vigorous monitoring including serial kidney biopsies to detect CyA nephrotoxicity(16) Some workers do continue CyA treatment for 24 months in such patients(17) Long term CyA treatment will have steroid sparing effect and help to achieve better growth in children Patients with steroid resistance in

comparison with steroid dependent patients do not seem to respond well to CyA. According to the literature, the rate of remissions is higher when CyA is administered in combination with prednisolone(18). But we did not use steroids simultaneously for the reasons mentioned earlier.

In the pediatric population, response to cyclosporine appears to correlate more with steroid-responsiveness than with the underlying histopathology (19-21), as is our observation. It is difficult to manage steroid dependent and steroid resistant nephrotic children who have inadequately responded to cytotoxic drugs. The therapeutic options are few. Though Levamisole which is an immunostimulant, may have a place in managing frequently relapsing nephrotic syndrome, it may not be useful in the above mentioned category of patients. Intravenous pulse methyl prednisolone therapy(22) needs experience in our country, especially in relation to its infectious complications. Cyclosporine therapy may be considered as one of the options of treatment, steroid dependent patients may do better than steroid resistant patients. It is worthwhile considering CyA therapy because it is possible that long term CyA therapy in steroid-resistant cases may reduce progression of FSGS to end-stage renal disease(23). It is necessary to keep in mind that long term therapy involves higher cost and the need to closely monitor the desired effects and side-effects of prolonged CyA treatment.

REFERENCES

- 1 Siegel NJ, Goldberg B, Krassen LS, Hayslett JP. Long term follow up of children with steroid responsive nephrotic syndrome. *J Pediatr* 1972; 81: 251-258.
- 2 Makker SP, Haymann W. The Idiopathic nephrotic syndrome of childhood. A clinical re-evaluation of 148 cases. *Am J Dis Child* 1974; 127: 830-837.
- 3 Schwartz MW, Schwartz GJ, Cornfield D. A 16 year follow up study of 163 children with nephrotic syndrome. *J Pediatr* 1972; 54: 547-552.
- 4 Garin EH, Pryor ND, Fennel RS, Richard GA. Pattern of response to prednisolone in Idiopathic minimal lesion nephrotic syndrome as a criterion in selecting patients for cyclophosphamide therapy. *J Pediatr* 1978; 92: 304-308.
- 5 Arbeitsgemeinschaft für Pädiatrische Nephrologie. Effect of cytotoxic drugs in frequently relapsing nephrotic syndrome with or without steroid dependency. *N Engl J Med* 1982; 306: 451-454.
- 6 Shalhoub RJ. Pathogenesis of lipoid nephrosis. A disorder of T Cell function. *Lancet* 1974; ii: 556-560.
- 7 Meyner A, Simon P, Perret GP. Remission of Idiopathic nephrotic syndrome after treatment with Cyclosporine A. *Br Med J* 1986; 292: 789-792.
- 8 Brodeh J, Hoyer PF. Cyclosporine treatment of Idiopathic nephrotic syndrome in children. *In* Cyclosporine in Autoimmune Disease. Ed Schmdler R. 1st International Symposium, Berlin Springer, 1985; p 329.
- 9 Tejani A, Butt MK, Trachtman H. Cyclosporine A induced remission of relapsing nephrotic syndrome in children. *Kidney Int* 1988; 33: 729-734.
- 10 International Study of Kidney Disease in Children. Early identification of frequent relapsers among children with minimal change nephrotic syndrome. *J Pediatr* 1982; 101: 514-518.
- 11 International Study of Kidney Disease in Children. Primary nephrotic syndrome in children. Clinical significance of histopathologic variants of minimal change and of diffuse mesangial hypercellularity. *Kidney Int* 1981; 20: 765-771.

12. Cyclosporine Task Force. Critical issues in cyclosporine monitoring. Report of the task force on cyclosporine monitoring. *Clin Chem* 1987; 33:1269-1288.
 13. Meyrier A. Antiproteinuric and immunological effects of Cyclosporin A in the treatment of glomerular diseases. *Nephrol Dial Transplant* 1992; 7(Suppl 1): 80-84.
 14. Bunjes D, Hardt C, Rollinghoff M. Cyclosporine A mediated immunosuppression of primary cytotoxic T-Cell response by impairing the release of interleukin-1 and interleukin-2. *Eur J Immunol* 1981; 11: 657-659.
 15. Hulton SA, Neuhaus TJ, Dillon MJ. Long term Cyclosporin A treatment of minimal change nephrotic syndrome of childhood. *Pediatr Nephrol* 1994; 8: 401-403.
 16. Habib R, Niaudet P. Comparison between pre-treatment and post-treatment renal biopsies in children receiving cyclosporine for idiopathic nephrosis. *Clin Nephrol* 1994; 42:141-144.
 17. Yoshikawa N, Tanaka R, Kitano Y. Long term cyclosporine in steroid dependent nephrotic syndrome: *In: Cyclosporine in the Therapy of Renal Disease*. Ed. Tejani A. Basel Karger 1985; pp 19-27.
 18. Niaudet P. Cyclosporine in the treatment of idiopathic nephrosis. *Indian Pediatrics* 1995; 32:1317-1321.
 19. KIM MS, Grupe WE. The management of primary glomerular disease: Alternatives to steroid therapy. *In: Pediatric Kidney Disease*. Eds. Edelmann CM. Boston, Little Brown and Company, 1992; p 1363.
 20. Capodicasa G, Desanto NG, Nuzzi F. Cyclosporine A in nephrotic syndrome of childhood: A 14-month experience. *Int J Pediatr Nephrol* 1986; 7: 69-72.
 21. Lagrue C, Laurent J, Belghiti D, Robeva R. Cyclosporine and idiopathic nephrotic syndrome. *Lancet* 1986; 2: 692-693.
 22. Tune BM, Liebermann E, Mendoza SA. Steroid-resistant nephrotic focal glomerulosclerosis: A treatable disease. *Pediatr Nephrol* 1996; 10: 772-778.
 23. Ingulli E, Singh A, Baqi N, A Hadi, Tejani A. Aggressive, long term Cyclosporine therapy for steroid-resistant focal glomerular sclerosis. *J Am Soc Nephrol* 1995; 5: 1820-1825.
-