CYCLOSPORIN A PLUS PREDNISONE TREATMENT OF STEROID – SENSITIVE FREQUENTLY RELAPSING NEPHROTIC SYNDROME IN CHILDREN*

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SUMMARY: Aksu N, Türker M, Erdoğan H, Özinel S, Kansoy S. (Department of Pediatric Nephrology, Social Security Tepecik Teaching Hospital, Yenişehir-İzmir, Turkey). Cyclosporin A plus prednisone treatment of steroid-sensitive frequently relapsing nephrotic syndrome in children Turk J Pediatr 1999; 41: 225-230.

Recently, there have been numerous reports on the use of cyclosporin A (CyA) in children with nephrotic syndrome (NS). In this prospective study, we wanted to evaluate the efficacy of CyA together with prednisone therapy in children with steroid-sensitive frequently relapsing NS.

A total of 11 children (7 boys, 4 girls) with steroid-sensitive NS were included in this study. The patients ranged in age from 3.5 to 15 years (average 8.45 ± 4.26 years). Renal biopsy showed minimal change disease in five, mesangial proliferation in four, focal glomerulosclerosis in one and membranous glomerulonephritis in one. The NS had lasted from 13 to 113 months (average 50.27 ± 38.60 months). The number of relapses varied from three to 10 episodes with an average of 5.9 ± 3.3 episodes. Patients received 5 mg/kg CyA daily in two divided doses for five months and prednisone for a total of eight weeks (30 mg/m² daily for 4 weeks followed by 30 mg/m² on alternate days for 4 weeks). After the completion of the treatment protocol, no therapy was given unless a relapse was observed.

Mean follow-up period was 14.9 ± 5.99 months with a range from six to 26 months. Before this combined treatment, there was a mean relapse rate of 0.144 ± 0.05 relapses month with a range from 0.088 to 0.238. After discontinuation of therapy, the relapse rate dropped to a mean of 0.0179 ± 0.031 with a range of 0 to 0.083.

In conclusion, it would appear that a combination of CyA and prednisone is effective, sustaining the remission in steroid-sensitive NS. Corticosteroids in combination with CyA may be a better approach than conventional steroid treatment in such patients.
Key words: cyclosporin A, prednisone, frequently relapsing nephrotic syndrome, children.

Children with nephrotic syndrome (NS) are usually treated with corticosteroids alone or in combination with immunosuppressive agents[1-5]. It is well known that steroid-sensitive, frequently relapsing nephrotic syndrome is still an important clinical problem in pediatric renal clinics. Although conventional steroid treatment is effective, the steroid-sensitive frequently relapsing cases are complicated by steroid dependency and secondary complications with this treatment. These side effects of the drugs limit their use[6-8]. Recently, several papers have reported

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that cyclosporin A (CyA) might be beneficial in these situations[9, 10]. Although CyA could be used alone in treatment of NS, a combination of CyA and corticosteroids has also been reported[11, 12], with better results obtained in steroid-sensitive nephrotic syndrome[13, 14]. In this prospective study, we wanted to evaluate the efficacy of CyA together with prednisone therapy in children with steroid-sensitive frequently relapsing nephrotic syndrome.

Material and Methods

A total of 11 children (7 boys, 4 girls) under 15 years of age with steroid-sensitive nephrotic syndrome were included in this study. The patients ranged in age from 3.5 to 15 years (average 8.45 ± 4.26 years). The definitions of NS, remission, relapse and frequent relapsers were the same as used by the International Study of Kidney Disease in Children (ISKDC)[15]. Five had biopsy-proven minimal change disease, four had mesangial proliferation, one had focal glomerulosclerosis and one had membranous glomerulonephritis. The NS had lasted from 13 to 113 months (average 50.27 ± 38.60 months). The age at which the patients initially presented with NS varied from one to 12.5 years (mean 4.27 years) and the number of relapses varied from three to 10 episodes, with an average of 5.9 ± 3.3 episodes (Table I). All patients had previously received oral prednisone alone or incombination with cyclophosphamide upon each episode.

Table I: Clinical Data for Patients with Nephrotic Syndrome

No.	Patient	Age (y)	Sex	Age at Onset of NS (y)	Biopsy	Duration of NS (mo)	No of Episodes
1	K.A.	10	M	3.5	MCD	81	10
2	A.K.	4.5	F	2	MGN	28	3
3	E.Ö.	3.5	F	2.5	MCD	13	3
4	F.B.	8	M	7	MCD	13	3
5	O.Ç.	15	M	12.5	MCD	30	4
6	K.H.	5.5	F	3	Mes. Pro	29	3
7	E.E.	10.5	M	1	Mes. Pro	111	10
8	B.İ.	4	M	2.5	MCD	21	5
9	V.K.	14	M	4.5	FGS	113	10
10	C.T.	13	M	6	Mes. Pro	82	10
11	E.İ.	5	F	2.5	Mes. Pro	32	4
						X^2	5.9
						SD	± 3.3

MCD: minimal change disease; MGN: membranous glomerulonephritis; Mes. Pro: mesangial proliferation; FGS: focal glomerulosclerosis; y: year(s); mo: month(s); NS: nephrotic syndrome.

After informed consent was obtained, patients received 5 mg/kg CyA daily in two divided doses for five months and prednisone for a total of eight weeks (30 mg/m^2 daily for 4 weeks followed by 30 mg/m^2 on alternate days for 4 weeks). After the completion of the treatment protocol no therapy was given unless a relapse was observed. During the course of treatment no other drugs except diuretics were administered. During the course of the therapy, renal functions, liver functions, serum electrolytes, blood pressure and cyclosporin levels were monitored weekly in the first month, and monthly thereafter. Cyclosporin A CyA whole blood levels were measured 12 hours after the last CyA intake and determined by radioimmunoassay (RIA) method. The response to treatment was assessed in the conventional manner by clinical examination, determination of 24 hour urinary protein excretion andrenal function profiling which included serum albumin and cholesterol concentrations. Statistical evaluation was made using Chi-square and t test.

Results

All children completed the full trial. All patients came into full remission with a complete loss of proteinuria. The patients showed definite improvement and normalization of serum protein, albumin, triglyceride and cholesterol levels. Serum urea concentrations slightly increased during the treatment but returned to pre-treatment levels after CyA was discontinued. Serum creatinine concentrations remained normal (Table II). The mean blood levels of CyA were 136 ± 57.33 ng/ml. The relapse rates in the eleven patients were calculated as relapses per month. Mean follow-up period was 14.9 ± 5.99 months with a range from six to 26 months. Before the combination of CyA and prednisone treatment, there was a mean relapse rate of 0.144 ± 0.05 relapses/month with a range from 0.088 to 0.238. After discontinuation of therapy, the relapse rate dropped to a mean of 0.0179 ± 0.031 with a range of 0 to 0.083 (Table III).

Table II: Laboratory Parameters of Patients Before and After Treatment (Mean ± SD)

Parameters	Before	After	p
Serum protein (g/dl)	4.21 ± 0.36	7.03 ± 0.54	< 0.001
Serum albumin (g/dl)	1.69 ± 0.26	4.51 ± 0.45	< 0.001
Serum cholesterol (mg/dl)	486.6 ± 135.8	154.4 ± 28.7	< 0.001
Serum triglyceride (mg/dl)	389.7 ± 184.9	142.2 ± 75.3	< 0.001
Serum urea (mg/dl)	29.90 ± 6.52	34.18 ± 3.81	< 0.05
Serum creatinine (mg/dl)	0.62 ± 0.17	0.67 ± 0.20	> 0.05

Table III: Relapse Rates of Patients Before and After Treatment

	Pre-Treatment			Post-Treatment		
No.	No of Episodes	Relapse* Rate (rel/mo)	Follow-up Period (mo)	No of Episodes	Relapse*Rate (rel/mo)	Mean CyA Levels (ng/ml)
1	10	0.123	19	1	0.052	125.3
2	3	0.107	16	1	0.062	99
3	3	0.230	16	–	0.000	158.6
4	3	0.230	26	–	0.000	106.3
5	4	0.133	19	–	0.000	194.5
6	3	0.103	15	–	0.000	64.4
7	10	0.090	19	–	0.000	267.8
8	5	0.238	8	–	0.000	97
9	10	0.088	8	–	0.000	146.5
10	10	0.121	12	1	0.083	151.7
11	4	0.125	6	–	0.000	89.1
X^2	5.9	0.144	14.9	0.272	0.0179	136.38
SD	± 3.3	± 0.05	± 5.99	± 0.467	± 0.031	57.33

* Significance of relapse rates between pre- and post-treatment periods ($p < 0.005$).
rel: relapse; mo: month(s); CyA: cyclosporin A.

Hypertrichosis was recognized in five patients, but was not so disturbing. Gingival hyperplasia was seen in three patients. Chicken-pox occurred in one patient at the fifth month of treatment, but it is questionable whether or not this was related to the combined treatment.

Discussion

It is well known that steroid-sensitive frequently relapsing nephrotic sydrome is still a major unsolved clinical problem. These steroid-sensitive frequently relapsing nephrotic cases are complicated by steroid dependency and secondary complications by long-term use of corticosteroids[6, 7, 16].

The pathophysiology of nephrotic syndrome is still obscure. Recently, a variety of lymphokines have been identified in patients with nephrotic syndrome. It is known that on contact with a specific antigen, sensitized lymphocytes secrete these active lymphokines. It has been suggested that these lymphokines lead to the alteration of glomerular anionic sites resulting in increased capillary permeability to proteins[7, 10, 17]. This notion led to trials of CyA in the treatment of nephrotic syndrome. cyclosporin A CyA is a specific modulator of T cell function. The drug acts on T cells and specifically inhibits production of lymphokines (interleukin-2) from activated T helper cells, and reduces the release of interleukin-1 from the macrophages. Because of this specific action, it has

been suggested to extend the indications for CyA treatment to therapy of nephrotic syndrome which is thought to be T-cell mediated[18-20].

Cyclosporin A CyA in combination with corticosteroids has been proposed as a better approach in steroid-sensitive nephrotic patients. Cyclosporin A CyA duplicates the efficacy of steroids in nephrotic syndrome. This effect is possibly related to the similarities of action between these two drugs[11]. Our use of CyA together with corticosteroids in this study was an attempt to obtain a synergistic effect between the two drugs. Using this combined therapy, all patients showed a full remission with a complete loss of proteinuria. The patients showed definite improvement and normalization of nephrotic parameters. The duration of remission was significantly longer than that before initiation of combined treatment. There was a significant reduction in the relapse rate and the majority of patients did not experience any relapse with this treatment. Before the combination of CyA and prednisone therapy, there was a mean relapse rate of 0.144 ± 0.05 relapses/month with a range from 0.088 to 0.238. After discontinuation of this combined treatment, the relapse rate dropped to a mean of 0.0179 ± 0.031 with a range of 0 to 0.083 (Table III).

Clinical side effects of CyA treatment are reported as frequent, but of minor intensity. Side effects included renal insufficiency, gastrointestinal disturbances, hypertrichosis, mild hypertension, and gum hypertrophy in occasional cases[14, 21]. In our study, mean serum urea concentrations slightly increased during the treatment but returned to pre-treatment levels after CyA was discontinued. Mean serum creatinine concentrations remained normal. Slight hypertrichosis was observed in five patilents, but did not require any treatment. Gingival hyperplasia was seen in three patients. Chicken-pox occurred in one patient at the fifth month of treatment, but it is questionable whether this complication was primarily related to the combined treatment or to the natural course of the nephrotic syndrome.

In conclusion, it would appear that a combination of CyA and prednisone is effective in sustaining the remission in steroid-sensitive nephrotic syndrome. Corticosteroids in combination with CyA may be a better approach than conventional steroid treatment in such patients.

REFERENCES

1. Niaudet P, Tete MJ, Broyer M, Habib R. Cyclosporine and childhood idiopathic nephrosis. Transplant Proc 1988; 20 (Suppl): 265-268.
2. Brandis M, Burghard R, Leititis J, Zimmerhackl B, Hildebrandt F, Helmchen U. Cyclosporin A for treatment of nephrotic syndromes. Transplant Proc 1988; 20 (Suppl): 275-279.
3. Ehrich JH, Brodehl J. Long versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children. Eur J Pediatr 1993; 152: 357-361.
4. Chan MK, Cheng IK. Cyclosporin A in steroid-sensitive nephrotic syndrome with frequent relapses. Postgrad Med J 1987; 63: 757-759.

5. Tune BM, Lieberman E, Mendoza SA. Steroid-resistant nephrotic focal segmental glomerulosclerosis: a treatable disease. Pediatrr Nephrol 1996; 10: 772-778.
6. Tirelli AS, Paterlini G, Ghio L, et al. Renal effects of cyclosporin A in children treated for idiopathic nephrotic syndrome. Acta Paediatr 1993; 82: 463-468.
7. Meyrier A, Condamin MC, Simon P. Treatment with cyclosporine of adult idiopathic nephrotic syndrome resistant to corticosteroids and other immunosuppressants. Transplant Proc 1988; 20 (Suppl): 259-261.
8. Niaudet P, Broyer M, Habib R. Treatment of idiopathic nephrotic syndrome with cyclosporin A in children. Clin Nephrol 1991; 35 (Suppl): 531-536.
9. Meyrier A. Treatment of glomerular disease with cyclosporin A. Neprol Dial Transplant 1989; 4: 923-931.
10. Ponticelli C, Rivolta E. Cyclosporine in nephrotic syndrome. Transplant Proc 1988; 20 (Suppl): 253-258.
11. Tejani A, SuthanthiranM, Pomrantz A. A randomized controlled trial of low-dose prednisone and cyclosporine versus high-dose prednisone in nephrotic syndrome of children. Nephron 1991; 59: 96-99.
12. Niaudet P. Treatment of childhood steroid-resistant idiopathic nephrosis with a combination of cyclosporine and prednisone. J Pediatr 1994; 125: 981-986.
13. Niaudet P, Habib R. Cyclosporine in the treatment of idiopathic nephrosis. J Am Soc Nephrol 1994; 5: 1049-1056.
14. Brodehl J, Hoyer PF, Oemar BS, Helmchen U, Wonigeit K. Cyclosporine treatment of nephrotic syndrome in children. Transplant Proc 1988; 20 (Suppl): 269-274.
15. International Study of Kidney Disease in Children. Early identification of frequent relapsers among children with minimal change nephrotic syndrome. J Pediatr Nephrol 1982; 101: 514-518.
16. Hulton SA, Neuhaus TJ, Dillon MJ, Barratt TM. Long-term cyclosporin A treatment of minimal-change nephrotic syndrome of childhood. Pediatr Nephrol 1994; 8: 401-403.
17. Nyrop M, Olgaard K. Cyclosporin A treatment of severe steroid resistant nephrotic syndrome in adults. J Intern Med 1990; 227: 65-68.
18. Tejani A, Gonzalez R, Rajpoot D, Sharma R, Pomrantz A. A randomized trial of cyclosporine with low-dose prednisone compared with high-dose prednisone in nephrotic syndrome. Transplant Proc 1988; 20 (Suppl): 262-264.
19. Garin EH, Orak JK, Hiott KL, Sutherland SE. Cyclosporine therapy for steroid resistant nephrotic syndrome. Am J Dis Child 1988; 142: 985-988.
20. Brodehl J, Brandis M, Helmchen U, et al. Cyclosporin A treatment in children with minimal change nephrotic syndrome and focal segmental glomerulosclerosis. Klin Wochenschr 1988; 66: 1126-1137.
21. Hulton SA, Jadresic L, Shah V, Trompeter RS, Dillon MJ, Barratt TM. Effect of cyclosporin A on glomerular filtration rate in children with minimal change nephrotic syndrome. Pediatr Nephrol 1994; 8: 404-407.