ORIGINAL ARTICLE

Cyclosporin-A Treatment in Steroid Nonresponsive Nephrotic Syndrome

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ABSTRACT Fifteen patients with steroid nonresponsive nephrotic syndrome (NS) aged 4-16 years received oral cyclosporin-A (CyA) for 12 weeks. Nine of the patients were boys. Out of the 15 patients, 7 were frequent relapsers, 3 were steroid dependents, 4 were steroid resistants and one with toxic steroid. After 12 weeks of CyA treatment, 6 patients showed complete remission, 7 showed partial remission, and 2 patients did not respond at all. Side effects observed were slight renal function impairment, gingival hyperplasia, and a hump on the breast; all disappeared gradually after stopping CyA. Patients with total remission experienced relapse 2 to 12 months after discontinuation of CyA, while patients with partial remission experienced relapse 2 weeks to 3 months after CyA was discontinued. A tentative conclusion can be drawn that CyA is a good alternative in the treatment of idiopathic NS, especially in steroid dependent patients who are at risk of developing steroid toxicity. CyA represent a major advance in the treatment selected SN patients who have failed with the conventional modes of therapy. **[Paediatr Indones 1994; 34:1-7]**

Introduction

One of the major problems in the treatment of idiopathic nephrotic syndrome (INS) is the management of patients who do not respond to steroid therapy or who have multiple relapses and may therefore develop serious side-effects as a result of steroid therapy. Several modes of treatment have been proposed in these situations, mainly by the use of alkylating agents. However, the potential side effects of these drugs clearly limit their use. Recently, several investigators have claimed that cyclosporin A (CyA), which has been used for the treatment of several autoimmune diseases, may be effective in the treatment of INS.[1-3] The immunosuppressive effects of CyA are the

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consequence of the inhibition of interleukin-2 (IL-2) and other lymphokine secretion by activated T cells. These effects are rapid in onset, dose dependent, and often quickly reversible on discontinuation of the treatment.[4] CyA does not affect the main macrophage and granulocyte functions, such as phagocytosis, chemotaxis, and the release of most monokines, as this suggests that the drug has a greater selectivity than other immunosuppresants currently used.[4] The objective of this study was to assess the effectiveness and safety of CyA treatment in steroid nonresponder patients with primary nephrotic syndrome.

Methods

The diagnosis of INS was based on the presence of nephrotic syndrome that was non-responsive to steroid treatment. Fifteen children with INS (6 girls and 9 boys), were selected for this study whose disease had not been well controlled by steroid therapy. After steroid therapy 7 patients experienced several relapses and were given cyclophosphamide for 8 to 16 weeks but still had relapses. These patients were referred to as frequent relapsers. Three steroid dependent patients had received alternate day prednisone within three months prior to CyA treatment. Four patients with late nonresponders considered as steroid resistant group were also enrolled in this study. One patient with steroid toxicity because of multiple relapses was also included in this study. Patients who had either a creatinine clearance below 50 ml/min/1.73 m^2 or impaired liver function, and those who had received immunosuppressive agents within the past 2 months, were not included in this study. Informed consent was obtained from parents following explanation of the purpose and nature of the study.

The patients initially received 6 mg/kg body weight of CyA in two daily oral doses, and the dose was adjusted in order to obtain through plasma levels between 100 and 200 mg/ml as measured by monoclonal RIA. Regular evaluation of renal and liver functions was performed. CyA was given at full dose for a period of 12 weeks and if found to be ineffective or serious complications ensued, the treatment was discontinued.

Results

A total of 15 patients with steroid nonresponsive nephrotic syndrome aged 4-16 years received CyA for 12 weeks. Nine children were boys and 6 were girls. Of these 15 patients, 10 patients were biopsied and the histological pictures showed FSGS in 5, MesPGN in 2, and MCNS in 3 patients. The remaining 5 patients were not biopsied. See Table 1.

There were 7 patients with frequent relapses (FR), 3 with steroid dependent (SD), 4 with steroid resistant (SR) and 1 with toxic steroid (TS) NS. See Table 2.

Clinical and laboratory studies revealed 4 patients had anasarca, 9 patients had slight edema, and 3 patients had no edema. Blood pressure was moderately elevated in two patients (patients no 11 and 13), a slight increase of urea in 4 patients (patients no 7, 8, 11, and 15) who also had a moderate increase of serum creatinine. Hepatic function as indicated by SGOT and SGPT were within normal limits (see Table 2). Other liver functions, i.e., total serum bilirubin concentration and alkaline phosphatase were also within normal limits. Serum cholesterol concentration was increased in 12 of the 15 patients with the highest concentration of 1245 mg/dl (Table 3).

After CyA treatment for 12 weeks, of the 15 patients, 6 showed complete remission, 7 showed partial remission, and 2 patients did not respond at all (Table 4). Slight elevation of blood urea was encountered in 4 patients (patients nos 5, 10, 11, and 13) and increased in serum creatinine levels in 2 patients (Table 5).

Table 1. Clinical characteristics and histological changes of 15 patients before treatment with CyA

No	Sex	Age (yrs)	Diagn	Immunosuppr Drug	Duration (wks)	Histology
1.	M	11	FR	-	-	MesPGN
2.	M	13	FR	CPA	4	FSGS
3.	M	5	FR	-	-	MCNS
4.	M	12	FR	-	-	-
5.	F	10	SR	CPA	8	FSGS
6.	M	15	SD	-	-	-
7.	F	8	SR,CRF	CPA	12	FSGS
8.	M	4	SR	CPA	12	MCNS
9.	F	11	SR	CPA	8	FSGS
10.	M	6	FR	-	-	FSGS
11.	F	16	TS	CPA	16	MesPGN
12.	M	6	FR	CPA	4	-
13.	M	4	SD	CPA	8	MCNS
14.	F	15	SD	CPA	8	-
15	F	11	FR	-	-	-

Abbreviations: FR=Frequent relapser; MCNS=Minimal change NS; SR=Steroid resistant; FSGS=Focal segmental glomerulosclerosis; SD=Steroid dependent; TS=Toxic steroid; MesPGN = Mesangial proliferative glomerulonephritis; CRF=Chronic renal failure; CPA=Cyclophosphamide

The renal function was completely reversed to normal upon discontinuation of CyA treatment.

The response to CyA treatment in steroid nonresponsive NS patients according to histological changes is depicted in Table 6.

Of the 6 patients with complete remission, 4 patients were frequent relapsers, one with steroid dependent and the other one with steroid resistant NS. Of the 7 patients with partial remission, 3 patients were frequent relapsers, one was steroid dependent, and the remaining two were steroid resistent NS. The only patient with toxic steroid in this series showed partial remission.

The association between the histological changes and the response to CyA treatment can be seen in Table 7. Side effects observed included slight impairment of renal function in four patients, each in steroid resistant, frequent relapser, steroid toxic, and steroid dependent ones. These side effects occurred in 2 patients with FSGS, and one with MCNS. The increased urea and creatinine levels was completely reversed to normal on withdrawal of CyA. Other side effects were gingival hyperplasia found in one patient and a hump on the left mammae in another patient; all of which disappeared gradually after discontinuation of the treatment.

Patients with total remission after 12 weeks of CyA treatment experienced relapse two to twelve months after discontinuation of the drug. On the other hand, patients who showed partial remission following CyA treatment experienced relapse 2 weeks until 3 months after treatment with CyA was discontinued.

Table 2. Clinical and laboratory characteristics of 15 patients before treatment with CyA

Pts No	BW (kg)	Edema			BP (mmHg)	Urea (mg/dl)	Creatinine (mg/dl)	SGOT/SGPT (g/dl)
		Palpebra	Pretibial	Ascites				
1.	33.0	+	+	±	110/70	22	0.57	25/10
2.	35.0	+	±	-	90/60	29	0.6	9/13
3.	19.0	+	±	-	100/70	18	0.45	17/10
4.	44.0	+	+	+	100/70	21	0.5	6/7
5.	31.5	±	±	-	100/60	38	1.14	16/17
6.	35.5	+	+	-	115/70	22	0.52	-
7.	17.5	+	+	-	100/60	44	0.85	15/9,5
8.	12.0	-	-	-	100/70	51	0.84	9,8/10,5
9.	25.0	+	+	-	100/60	42	0.79	9,2/20,5
10	19.0	+	±	-	100/70	29	0.72	18/19
11	56.0	+	±	-	130/90	60	1.02	53/29
12	17.0	+	+	+	100/60	48	0.83	14/10
13	14.5	-	-	-	120/80	23	0.72	37/50
14	49.5	-	-	-	120/80	27	0.58	23/25
15	21.5	+	+	-	100/70	54	1.25	14/6

Note : BW= Body weight; BP= Blood pressure

Table 3. Laboratory characteristics of 15 patients before treatment with CyA

Pts No	Cholest erol (mg/dl)	Bilirubin (mg/dl)	Alk. Phosph /GGT	Urinalysis			Status of NS
				Protein	WBC	RBC	
1.	651	0.10	11.1/16	++	8-15	4-6	Relapse
2.	233	0.80	156/12	+++	3- 4	2-3	Relapse
3.	443	0.10	10.2/19	++	3-4	0-1	Relapse
4.	482	0.60	105/12	++	1- 2	-	Relapse
5.	1245	0.20	10.2/12	+++	2- 3	-	Relapse
6.	931	-	-	+++	2- 3	-	Relapse
7.	511	0.60	10.2/12	++	4- 5	-	Relapse
8.	296	0.12	10.3/11	+	1-2	-	PR
9.	969	0.13	10.2/11	+++	4- 5	0-1	Relapse
10.	545	0.00	10.2/9	+++	1- 2	-	Relapse
11.	634	0.31	10.4/15	++	4- 5	-	Relapse
12.	664	0.79	- /10	++	1- 2	-	PR
14.	276	0.34	10.5	++	1- 2	-	PR
15.	132	0.06	10.3/10	++	10-12	1-2	Relapse

PR=Partial remission; GGT=Gamma glutamil transpeptidase; WBC = while blood cells;
RBC = red blood cells

Table 4. Results of CyA treatment in 15 patients with steroid nonresponsive nephrotic syndrome

Pts No.	CyA Start mm/dd/yy	Dosage (mg)	CyA Stopped mm/dd/yy	Partial Remission mm/dd/yy	Total Remission mm/dd/yy	BP mmHg
1.	10/12/91	2 x 75	02/24/92		03/03/92	90/70
2.	07/17/91	2 x 90	11/13//91		27/11/91	110/80
3.	02/10/91	2 x 40	05/27//92		06/02/92	110/70
4.	05/29/91	2 x 110	09/06/91	05/29//92		100/70
5.	05/29/91	2 x 75	08/16//91	05/10/92		100/70
6.	02/04/91	2 x 50	05/24/91	04/08/92		120/70
7.	01/11/91	2 x 40	07/01/91			100/70
8.	12/19/90	2 x 25	06/24//91		01/21/92	90/60
9.	12/19/90	2 x 50	05/01//91	01/16/91		90/60
10.	12/21/90	2 x 25	03/11//91	02/11/91		90/60
11.	08/23/90	2 x 100	02/14//91	10/08/91		100/70
12.	04/19/91	2 x 35	09/11//91	05/20/91		100/60
13.	04/01/92	2 x 40	07/08/92			100/70
14.	04/08/92	2 x 125	07/22//92		07/08/92	120/80
15.	01/29/92	2 x 50	07/22//92		03/06/92	130/95

Table 5. Laboratory characteristics in 15 patients with steroid non responsive nephrotic syndrome after treatment with CyA

	CyA plasma	Urea (ng/L)	Creatinine (mg/dl)	SGOT/ SGPT	Bilirubin (mg/dl)	Alk Phosph (IU/L)	GGT
1.	421.79	36	0.86	17/21	0,18	10.6	19
2.	low	22	0.70	16/37	0,60	213.0	5
3.	not done	42	0.82	18/11	0,40	10.2	6
4.	328.14	29	0.50	69/71	-	113.0	15
5.	334.54	49	0.98	14/29	-	14.0	7
6.	not done	20	0.48	-	-	10.2	-
7.	25.8	34	0.74	-	-	-	-
8.	low	27	0.65	17/15	0,27	10.2	4
9.	131.76	32	0.62	15/9	0,23	10.6	9
10.	65.75	82	0.89	-	0,06	12.3	-
11.	450.07	58	1.82	22/13	-	10.2	4
12.	low	27	0.60	13/10	0,50	235.0	7
13.	not done	56	1.40	-	-	135.0	7
14.	not done	41	0.80	14/11	0,80	21,2	17
15.	not done	31	0.71	18/17	0,09	10,3	16