

Cyclosporin A in refractory idiopathic nephrotic syndrome: 5 years clinical experience

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Summary: The use of cyclosporin A (Cy A) in idiopathic nephrotic syndrome, particularly lesions of focal segmental glomerular sclerosis, is controversial. A retrospective study of 10 adult patients with nephrotic syndrome treated with Cy A was performed. Histological diagnosis was established in all patients: focal segmental glomerular sclerosis ($n = 6$), focal global sclerosis ($n = 1$), mesangial proliferative glomerulonephritis ($n = 1$), focal proliferative glomerulonephritis ($n = 1$) and minimal change disease ($n = 1$).

All patients had previously received immunosuppressive therapy (duration of steroids 1–76 months; 35.0 ± 12.1 , mean \pm SEM). Cy A in a dose of 3–5 mg/kg/day, reduced proteinuria from 16.85 ± 6.67 to 3.37 ± 1.48 g/24 hours ($P = 0.008$), with an associated increase in serum albumin from 15.2 ± 2.6 to 34.3 ± 2.5 g/l ($P < 0.001$).

In six patients steroid therapy was discontinued. Cy A was well tolerated for up to 5 years. There was no significant nephrotoxicity.

In conclusion, Cy A was effective treatment of refractory idiopathic nephrotic syndrome, including those cases with focal segmental glomerular sclerosis.

Introduction

The management of refractory idiopathic nephrotic syndrome remains a significant problem. It is a debilitating condition as infection may supervene and progression of the disease can lead to terminal renal insufficiency.

'Idiopathic' nephrotic syndrome encompasses two main forms of glomerular disease, namely minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS). MCD is primarily a disease of children, which generally responds to steroids.¹ Patients may develop dependence on steroids and require repeated or continuous treatments, which inevitably leads to features of glucocorticoid toxicity. Resistance to steroids can occur. Alkylating agents such as cyclophosphamide and chlorambucil have also been shown to induce remission,^{2,3} however, the potential side effects, particularly gonadal toxicity, have limited their use. Nephrotic syndrome accompanied by lesions of FSGS carries a poor prognosis, with only 20% of cases responding to steroids.⁴ Up to 50% of patients with the FSGS lesion will have developed end-stage renal failure within 10 years.⁵

In recent years, cyclosporin A (Cy A) has been used in the treatment of nephrotic syndrome, both in adults and children.^{6–11} Reports confirm favourable response rates in cases of steroid-dependent MCD of up to 70% and disappointing response rates of 20% in FSGS.⁹ This report examines the clinical experience of Cy A therapy in cases of refractory nephrotic syndrome.

Patients and methods

A retrospective study was performed to examine patients with refractory nephrotic syndrome commenced on Cy A. The patients had either become resistant to conventional treatment or had developed features of marked toxicity. All patients treated with Cy A were included in the study. Ten patients (nine male, one female) with an age range of 23–68 years were studied. Histological examination was performed on renal biopsies from all patients. Six patients had FSGS, one patient focal global sclerosis, one patient mesangial proliferative glomerulonephritis, one patient focal proliferative glomerulonephritis and one with MCD. All patients had previously received immunosuppressive therapy (duration of steroid treatment between 1 and 76 months; 35.9 ± 12.21 ; mean \pm SEM), including four patients who had also received either

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cyclophosphamide or azathioprine. Cy A was given in addition to maintenance steroids in a dose of 3–5 mg/kg/day. Levels were maintained at 50–150 µg/l. Blood Cy A levels were measured by standard radioimmunoassay. The pre-Cy A range of proteinuria was from 3 to 60 g/24 hours (mean \pm s.e.m. 16.85 ± 6.67). Proteinuria, serum albumin, serum creatinine and clinical course were monitored. Immunosuppressive regimes were altered according to clinical response. The patients' characteristics are shown in Table I.

Definitions

Nephrotic range proteinuria: greater than 3 g/24 hours. Complete remission: proteinuria < 1 g/24 hours. Partial remission: a significant fall in proteinuria, associated with a rise in serum albumin and improvement in clinical condition.

Statistical methods

Paired *t* tests were used. *P* values < 0.05 were taken as significant. Results are expressed as mean \pm SEM.

Results

There was a highly significant reduction in proteinuria with the introduction of Cy A therapy. The mean daily protein excretion fell from 16.85 ± 6.67 to 3.37 ± 1.48 g/24 hours ($P = 0.008$). This was associated with an increase in serum albumin from 15.2 ± 2.62 to 34.3 ± 2.49 g/l ($P < 0.001$) (Table II). Seven patients achieved full remission and three patients partial remission (reduction of proteinuria from 60.0–14.0, 16.2–8.0, 24.0–7.0 g/24 hours).

Sustained responses of between 12 to 60 months were seen in eight patients. One patient relapsed

after 4 months, and required manipulation of corticosteroids and Cy A dose to induce a sustained remission. One patient responded well to treatment but did not comply with treatment. This was confirmed by unrecordable Cy A levels on occasion of relapse. In six patients it was possible to withdraw steroids completely. The treatment was well tolerated (Table III). In three patients (nos. 6–8), who had significantly impaired renal function prior to treatment, there was an improvement in serum creatinine with the introduction of Cy A and the reduction of diuretic therapy. In three patients there was an increase in serum creatinine to just above the normal range (nos. 1,4,10). The remaining patients continued to have serum creatinine within the normal range for a period of up to 60 months on treatment. Cy A did not have to be discontinued in any patient due to nephrotoxicity.

Mild increases in blood pressure were noted in three patients. These patients were managed easily with anti-hypertensive therapy. Two patients had myocardial infarcts following 24 and 48 months of treatment.

Discussion

This study demonstrates the effectiveness of Cy A in patients with severe idiopathic nephrotic syndrome. Six patients with FSGS responded to treatment, three of whom obtained complete remission.

FSGS is often resistant to treatment, with less than 20% of patients attaining complete remission with corticosteroids.⁴ A recent large study by Meyrier *et al.* demonstrated that, in 50% of 'steroid-sensitive' cases, Cy A reduced proteinuria. In steroid-resistant cases only 20% obtained remission.⁹ The current study of a small number of

Table I Patient characteristics

Patient no.	1	2	3	4	5	6	7	8	9	10
Age (years)	33	23	32	29	50	68	60	66*	30	52
Years since diagnosis	4	21	4	12	5	3	11	6	28	3
Renal histology	FSGS	Focal global sclerosis	FSGS	FSGS	Mesangial proliferative	FSGS	Focal proliferative	FSGS	MCD	FSGS
Duration of steroid therapy (months)	5	75	3	72	5	1†	76	24	75	3
Previous cytotoxic therapy	–	+	–	+	–	–	+	–	+	–

*Only female patient; †steroid-induced hyperosmolar state.

Table II Efficacy

Patient no.	1	2	3	4	5	6	7	8	9	10
Proteinuria (G/24 hours)										
Pre-	60	4	20	16.2	9	24	4	13.6	3.5	14.7
Post-	14	0	1	8	1	7	1	0.8	0.1	0.8
Serum albumin										
Pre-	9	21	12	2	24	4	17	17	19	27
Post-	20	42	31	27	39	26	37	40	42	39
Steroid therapy	+	-	+	-	-	-	+	-	-	+
Duration of response (months)	4	60	Variable compliance	12*	48	36	12	48	48	24

*Lost to follow-up.

Table III Toxicity

Patient no.	1	2	3	4	5	6	7	8	9	10
Serum creatinine ($\mu\text{mol/l}$)										
Pre-	100	78	84	86	94	340	135	146	67	107
Post-	146	90	80	125	98	190	122	90	100	129
Blood pressure	-	+	-	-	+	-	-	-*	+	-*

*Suffered myocardial infarction.

patients observed for 1–5 years demonstrates a very good response with a moderate dose of Cy A.

The mechanism of action of Cy A in nephrotic syndrome is yet to be fully elucidated. It has been postulated that any glomerular insult (so far undefined) may lead to the production of lymphokines, including interleukin 1 and 8, which are chemotactic for macrophages and T cells, causing a brisk inflammatory response resulting in focal glomerulosclerosis and declining renal function.¹² Cy A is one of a family of cyclic peptides produced by the fungus *Tolyocladium inflatus* Gams. It inhibits the production and release of interleukins and gamma interferon, and is thus a potent immunosuppressor.¹³

An alternative, non-immunological, mechanism for reduction of proteinuria is by alteration of intrarenal haemodynamics, as Cy A is recognized to cause intrarenal vasoconstriction, probably of the afferent arteriole, associated with a decrease in glomerular filtration rate.⁷ More recent work has suggested that Cy A restores charge selectivity to the glomerular basement membrane, thereby reducing the membrane permeability.¹⁴

Cy A-related nephrotoxicity is well recognized¹⁵ and it is important to consider the potential

nephrotoxic effects, particularly in patients with already low glomerular filtration rates secondary to FSGS. In our experience, the following guidelines should be considered. The dose of Cy A should not exceed 5 mg/kg/day in adults. Blood levels should be checked one month following the introduction of treatment and, providing these are satisfactory, at two-monthly intervals thereafter. Trough levels are used and levels ranging between 50 and 150 $\mu\text{g/l}$ attained. Certain drugs may lead to increased nephrotoxicity if given concomitantly with Cy A. For example, non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors and antibiotics, including erythromycin, should be used with caution.

Serum creatinine, similarly, should be measured at 1 month, then at 2-monthly intervals, and dosage of Cy A adjusted if serum creatinine increases significantly above the baseline. The drug should be avoided or discontinued in patients with a serum creatinine which is above 200 $\mu\text{mol/l}$.

Conversely, improvements in serum creatinine may be seen in those patients obtaining a response to treatment, which permits a reduction in diuretic requirements. A trial of therapy should be discontinued if a significant reduction in proteinuria is not

achieved within 2–3 months. It is encouraging that none of the patients in the study developed severe nephrotoxicity. Similarly, only moderate elevations of blood pressure were observed.

In conclusion, Cy A is an effective and well-tolerated treatment of refractory idiopathic nephrotic syndrome, including those patients with FSGS.

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