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Cyclosporin in the treatment of idiopathic nephrotic syndrome in children

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Abstract. Thirty-five children (12 girls, 23 boys), aged from 1 year and 5 months to 14 years at the onset of idiopathic nephrotic syndrome, received cyclosporin A (CyA) because of steroid toxicity or failure to respond to steroids. The initial oral dose was 6 mg/kg per day and this was adjusted to obtain trough plasma levels of 50–150 ng/ml. The duration of treatment was between 2 and 8 months. In patients who responded to CyA treatment, the dosage was tapered off; treatment was stopped if found to be ineffective. Of the 35 children, 20 were frequent-relapsing steroid responders who suffered serious side-effects from steroid therapy. Seventeen of them either went into remission or did not relapse despite the withdrawal of prednisone. Prednisone doses could be lowered but not stopped in 1 patient and the remaining 2 patients relapsed when prednisone was tapered off. At the final examination, 10 of the 12 children in whom CyA was tapered off and who had initially responded to CyA had relapsed. A second course was given to these 10 patients and 3 failed to respond. Five children were partial steroid responders and CyA induced a remission in 1 and a partial remission in another. Among the 10 children who were steroid resistant, only 1 responded to CyA, 2 had a partial response and 7 failed to respond to CyA. A reduction of glomerular filtration rate occurred in 8 patients, 7 of whom had either persistent nephrotic syndrome or were in relapse, which suggests that factors other than CyA nephrotoxicity may have been operative. Complete reversal occurred in only 4 patients. Significant histological changes, likely to be related to CyA, were seen in 2 repeat renal biopsies out of the 11 performed.

Key words: Cyclosporin A – Idiopathic nephrotic syndrome – Prednisone – Glomerular filtration rate

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Introduction

One of the major problems in the treatment of idiopathic nephrotic syndrome (INS) is the management of patients who either do not respond to steroid therapy or who have multiple steroid-sensitive 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 alkylating agents. However, the potential side-effects of these drugs clearly limit their use. Recently, several reports 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 [1–5]. We report our experience with CyA in 35 children with INS, including 20 steroid responders, 5 partial steroid responders and 10 steroid non-responders.

Patients and methods

Thirty-five children with INS (12 girls, 23 boys), whose disease had not been well controlled by other forms of therapy, were selected for the study. The diagnosis of INS was based on the presence of nephrotic syndrome and on the results of renal biopsy. All children had received daily prednisone (2 mg/kg) for 1 month, followed by three intravenous boluses of methylprednisolone (1,000 mg/1.73 m^2) if there had been persistent proteinuria at the end of prednisone treatment. Subsequently, the same amount of prednisone (2 mg/kg) was given in a

Table 1. Clinical and pathological features of steroid responders prior to treatment with cyclosporin A (CyA)

Patient no.	Sex	Age at onset of idiopathic nephrotic syndrome (INS) (years)	Duration of INS before CyA (years)	No. of relapses	Immunosuppressive agents before CyA[a]	Pathology[b]	Duration of INS before renal biopsy (years)
1	F	3.8	3.9	10	CHL	MCD	3.9
2	F	1.8	3.1	12	CHL, HN-2	FGF	3.1
3	F	4.2	6.11	10	CHL	MCD	6.9
4	M	1.5	9.0	11	HN-2	MCD	8.9
5	M	1.7	0.8	3	–	MCD	0.8
6	F	1.6	4.3	20	–	FSGS	4.3
7	M	3.9	10.3	12	HN-2	MCD	1.1
8	F	3.8	9.9	20	CHL, HN-2	DMP	0.7
9	M	3.0	14.5	17	CHL, HN-2	MCD	3.4
10	M	2.6	5.2	16	CHL, HN-2	MCD	0.1
11	M	2.7	13.9	17	CHL, HN-2	MCD	13.9
12	M	4.2	8.5	20	Cy	MCD	0.1
13	M	2.2	7.2	14	CHL, HN-2	FSGS	7.1
14	M	2.2	13.3	29	CHL, Cy	MCD	13.3
15	M	3.1	4.9	14	–	MCD	4.9
16	F	6.0	2.0	6	–	MCD	2.0
17	M	12.0	0.7	3	HN-2	MCD	0.7
18	M	2.8	7.2	8	–	MCD	7.2
19	M	2.1	9.5	20	CHL, HN-2	MCD	0.1
20	M	4.8	0.3	2	–	MCD	0.3

[a] CHL: chlorambucil; HN-2: mechlorethamine; Cy: cyclophosphamide
[b] MCD: minimal change disease; FGF: focal and global sclerosis; DMP: diffuse mesangial proliferation; FSGS: focal and segmental glomerulosclerosis

Table 2. Clinical and pathological features of the partial steroid responder patients prior to CyA treatment

Patient no.	Sex	Age at onset of INS (years)	Duration of disease (years)	Immunosuppressive agents before CyA	Pathology	Duration of INS before renal biopsy (years)
21	M	5.9	0.1	–	MCD	0.1
22	M	5.5	0.5	–	MCD	0.5
23	M	2.0	2.0	CHL	DMP	1.2
24	F	10.5	1.7	–	FSGS	0.9
25	M	6.3	0.9	HN-2	MCD	0.1

For abbreviations, see Table 1

Table 3. Clinical and pathological features of steroid non-responders prior to CyA treatment

Patient no.	Sex	Age at onset of INS (years)	Duration of disease (years)	Immunosuppressive agents before CyA	Pathology	Duration of INS before renal biopsy (years)
26	F	13.0	1.0	CHL, HN-2	MCD	0.1
27	F	13.0	0.2	–	FSGS	0.2
28	M	1.4	0.7	–	MCD	0.7
29	M	6.0	3.0	–	FSGS	3.0
30	M	14.2	1.1	Cy	FSGS	0.1
31	F	4.0	1.5	Cy	MCD	0.4
32	F	2.6	0.8	Cy	FSGS	0.1
33	F	5.7	2.7	Cy	FGF	2.7
34	M	1.4	1.6	CHL	MCD	1.0
35	M	2.9	3.3	CHL, HN-2	Not done	

For abbreviations, see Table 1

single dose on alternate days for 2 months and the dosage was decreased by 0.5 mg/kg every 2 weeks. Patients who relapsed during the tapering period were treated with an alternate-day prednisone therapy regimen for several months at the minimal dose which maintained the remission.

Twenty children had had a complete remission after steroid therapy. Seventeen of them had experienced multiple relapses (>6) with serious side-effects as a result of steroid therapy and three had relapsed two or three times as soon as alternate-day prednisone was started. These patients will be referred to as "steroid responders". The clinical and pathological features of these patients are summarized in Table 1.

Five patients had had a partial response to steroid therapy with disappearance of the nephrotic syndrome but persistence of proteinuria. These patients were considered to be "partial responders". Their clinical and pathological features are summarized in Table 2.

Eight patients who did not respond to the initial steroid treatment were considered to be "early non-responders". Two patients, although they had initially been steroid responders, had failed to respond to steroid therapy during a subsequent relapse. These patients were considered to be "late non-responders". The clinical and pathological features of the non-responders are summarized in Table 3.

Renal biopsies. A total of 48 renal biopsy specimens were available for examination. All patients but one (patient no. 35) had undergone at least one biopsy prior to CyA treatment and a subsequent biopsy was performed in 11 patients 2–13 months after the initiation of CyA (mean, 7 months). Immunofluorescence microscopy (IF) was performed on all but 4 biopsy specimens. An electron microscopy (EM) study of the second specimen was performed in 7 of the 11 patients who had repeat biopsies.

Cyclosporin therapy. CyA treatment was initiated after informed consent had been obtained from the parents. Patients who had either a creatinine clearance below 50 ml/min per 1.73 m^2 or impaired liver function, and those who had received immunosuppressive agents within the past 2 months, were not included in the study. The patients initially received 6 mg/kg body wt. in two daily oral doses and the dose was adjusted in order to obtain trough plasma levels between 50 and 150 ng/ml as measured by radioimmunoassay [6]. Regular evaluation of renal and liver functions was performed. CyA was given at full dose for periods ranging from 2 to 8 months. If found to be ineffective the treatment was stopped; this was usually after 3 months. If patients responded, CyA was tapered off and stopped within 2–3 months. In steroid responders, prednisone was tapered off and stopped within 1–4 months after initiation of CyA (Table 4).

Results

We analysed the results of CyA treatment in the three groups of patients defined above according to their response to steroid therapy.

Steroid responders

Histological findings. The examination by light microscopy of renal biopsy specimens obtained at various times (see Table 1) after the onset of the disease and before the initiation of CyA gave the following results: 16 were classified as having minimal change disease (MCD), 1 showed diffuse mesangial proliferation (DMP), 2 had lesions of focal and segmental glomerular sclerosis (FSGS) and 1 of focal global fibrosis (FGF). In 2 patients a biopsy performed 2 years 9 months and 11 years 3 months earlier had shown MCD.

A second specimen was obtained in 8 patients aged from 3 months to 12 years after the initial biopsy and 4–13 months after the initiation of CyA. The pattern of glomerular involvement was unchanged in 6 patients (nos. 8, 9, 11, 13, 16, 20) but 2 patients who had shown MCD in previous biopsy specimens obtained 5 years 10 months and 8 years 9 months earlier had progressed to FSGS (nos. 10, 12).

IF findings were not available in 3 patients (nos. 2, 5, 7). In the remaining 17, IF was negative in 8, showed IgM mesangial deposits in 6 (nos. 6, 8, 10, 13, 14, 19), mesangial deposits of IgG and C1q in 1 (no. 20), mesangial deposits of IgA in another (no. 18) and scattered granules of C3 in the remaining patient (no. 4).

On repeat biopsies, the IF pattern was unchanged in 4 patients (nos. 8, 9, 16, 20) but patient no. 10, who had IgM mesangial deposits in a biopsy specimen examined 5 years 10 months earlier, had scattered granules of C3. Two patients whose IF was negative 1 year and 8 years 9 months before showed IgM mesangial deposits; and 1 patient who had IgM deposits in the initial biopsy specimen 10 months before also showed heavy mesangial and peripheral deposits of IgG.

In addition to these findings in the glomeruli, granular deposits of C3 in the arteriolar walls were observed in 16 early or late specimens.

Response to CyA therapy. The 20 steroid responders had all had their last relapse while receiving alternate-day prednisone (0.3–2.0 mg/kg) within the 8 weeks preceding CyA treatment. They received CyA for periods of at least 3 months. The dose of CyA varied from 6 to 11 mg/kg during the course of treatment before tapering. Two patients were on daily prednisone treatment (1.5–2.0 mg/kg) when CyA was started; 16 patients were on alternate-day prednisone treatment (0.3–2.0 mg/kg); and 2 patients were no longer receiving prednisone (Table 4). Eight patients were in relapse with proteinuria of more than 50 mg/kg.

Seventeen of the 20 patients either went into remission within 10–30 days (nos. 2, 5, 8, 10, 13, 16) or did not relapse at all during the period of full-dose treatment despite the fact that prednisone was withdrawn. Among the 17 patients, 7

Table 4. Response of steroid responders to CyA treatment

Patient no.	Steroid treatment		CyA treatment				
	Dose at initiation of CyA (mg/kg)	Duration after initiation of CyA (days)	Duration at full dose (days)	Response[b]	Relapse of INS	Dose at relapse or at last examination (mg/kg)	Follow-up at relapse or at last examination (days)
1	1.5[a]	60	160	+	–	7.8	160
2	1.7[a]	78	100	+	–	7.0	100
3	0.8[a]	86	125	+	–	6.8	125
4	0.6[a]	60	185	+	–	5.5	180
5	2.0	55	95	+	–	4.3	110
6	1.5[a]	60	120	+	–	8.9	120
7	0.5[a]	45	95	+	–	0.9	165
8	1.6[a]	60	90	+	+	5.0	150
9	0.75[a]	120	150	+	+	0.7	280
10	–		90	+	+	4.7	120
11	0.6[a]	60	120	+	+	1.1	250
12	–		90	+	+	5.0	120
13	1.2[a]	45	120	+	+	0	200
14	1.3[a]	75	130	+	+	0	200
15	1.0[a]	45	90	+	+	2.6	260
16	0.75[a]	30	100	+	+	0	190
17	1.5	60	90	+	+	4.6	120
18	0.3[a]	90	90	±			
19	0.7[a]	50	90	–			
20	2.0[a]	95	220	–			

[a] Alternate day

[b] +, Remission despite prednisone withdrawal; ±, decrease in prednisone requirements to maintain remission; –, relapse at prednisone tapering

(nos. 1–7) had not relapsed at last examination, but all were still receiving CyA (Table 4). Ten patients relapsed (nos. 8–17): 7 while receiving CyA at tapering doses varying between 0.7 and 5.0 mg/kg, 2 as soon as CyA was stopped, and the remaining patient 2 months after CyA withdrawal.

CyA was ineffective in 2 patients (nos. 19, 20). In the last patient (no. 18), CyA treatment allowed a significant decrease in steroid therapy but the patient relapsed when prednisone was withdrawn. The association of CyA with low-dose prednisone allowed remission to be maintained.

Subsequent behaviour. We were able to evaluate the subsequent behaviour of 8 of the 10 patients who relapsed during the tapering-off phase or the post-treatment phase. The period of follow-up was too short for the remaining 2 patients. In 2 patients (nos. 11, 14), increased doses of CyA induced a remission: within 3 weeks in 1 patient and within 10 days in the other. Daily prednisone therapy, in addition to CyA, induced a remission in 5 patients (nos. 8, 9, 12, 13, 17) but only after methylprednisolone pulses in 2 patients (nos. 8, 13). However, 2 patients (nos. 8, 12) relapsed as soon as alternate-day prednisone was started, despite the continuation of CyA. Patient no. 10 did not respond to prednisone therapy and methylprednisolone pulses in addition to CyA when he relapsed. In this patient, cyclophosphamide treatment induced a significant reduction of proteinuria.

Partial steroid responders

Histological findings. By light microscopy, the patients were classified as MCD (3 cases), DMP (1 case) and FSGS (1 case). IF was negative in 3 patients (nos. 22, 23 and 25) and showed mesangial deposits of IgG and Clq in 2 (nos. 21 and 24). No repeat biopsies were performed in these patients.

Response to CyA. The five patients in this group received CyA at doses ranging from 6 to 8.4 mg/kg in 4 cases and at doses up to 15 mg/kg in 1 case because of low trough plasma levels.

CyA was effective in one patient (no. 21) who went into complete remission and who remains protein free 5 months after CyA withdrawal. CyA was partially effective in one patient (no. 24) who had a decrease of proteinuria with a disappearance of the nephrotic syndrome but who relapsed

Table 5. Response of partial steroid responders to CyA treatment

Patient no.	Steroid treatment		CyA treatment	
	Dose at initiation of CyA (mg/kg body wt.)	Duration after initiation of CyA (days)	Duration of treatment at full dose (days)	Response[b]
21	1.0[a]	60	250	+
22	2.0[a]	30	90	−
23	1.1	45	105	−
24	1.25	55	180	±
25	−		90	−

[a] Alternate day
[b] +, Disappearance of proteinuria despite prednisone withdrawal; ±, decrease but persistence of proteinuria; −, no modification of proteinuria

at CyA withdrawal. CyA was without any effect in the remaining 3 patients (Table 5).

Steroid non responders

Histological findings. No renal biopsy was performed in patient no. 35, a late non-responder. The remaining 9 patients were classified by light microscopy as follows: MCD (4 cases), FSGS (4 cases), FGF associated with DMP (1 case). The pattern was unchanged in the 3 repeat biopsies (patients 28, 29, 32) which were performed after the first biopsy at the end of CyA treatment at 3, 8 and 15 months, respectively.

IF findings were not available in 1 patient (no. 31), were negative in 5 (nos. 26, 27, 30, 32, 34) and showed mesangial deposits of IgG and C1q in 1 patient (no. 28), IgM mesangial deposits in another (no. 29) and scattered granules of C3 in the remaining patient (no. 33). In the second specimen, there were no glomeruli for IF in patient no. 28 and IgM deposits had disappeared in patient no. 29. One patient for whom IF was negative in the previous biopsy specimen (patient no. 32) showed extensive granular deposits of IgG, IgM, C1q and C3. Vascular C3 was observed in 4 specimens.

Response to CyA. Ten patients, including 8 early non-responders and 2 late non-responders, received CyA at doses varying from 5.5 to 17.0 mg/kg. All patients but one were off prednisone during the treatment. One patient (no. 35), a late non-responder, went into complete remission within the 1st month of treatment with CyA and is still in remission 3 months after CyA withdrawal. Another patient (no. 33) had a partial remission with disappearance of the nephrotic syndrome but persistent proteinuria. In 1 patient (no. 32) there was a significant decrease of proteinuria but nephrotic syndrome persisted. In these 2 patients, proteinuria increased up to pretreatment levels when CyA was withdrawn. A transient decrease of proteinuria occurred in 2 patients (nos. 27, 28) but this was

Table 6. Response of steroid non-responders to CyA treatment

Patient no.	Steroid treatment		CyA treatment	
	Dose at initiation of CyA (mg/kg body wt.)	Duration after initiation of CyA (days)	Duration of treatment at full dose (days)	Response[b]
26	−		120	−
27	−		90	−
28	−		220	−
29	0.6[a]	30	60	−
30	−		90	−
31	−		90	−
32	−		160	±
33	−		120	±
34	−		60	−
35	−		170	+

[a] Alternate day
[b] +, Disappearance of proteinuria; ±, decrease but persistence of proteinuria; −, no modification of proteinuria

probably related to a reduction in glomerular filtration rate. Proteinuria remained unchanged in the last 5 patients (Table 6).

Side-effects of CyA

We will describe accompanying symptoms which occurred during CyA treatment, although they might not be related only to CyA.

Renal function. Eight patients experienced impairment of renal function. Among the steroid responders, 1 patient (no. 10) had a transient increase of serum creatinine during a relapse, while trough CyA plasma levels were low and another patient (no. 13) had an increase of plasma creatinine with complete reversal following CyA withdrawal. Among the steroid non-responders, 6 patients had a decrease of creatinine clearance. In 2 such patients (nos. 26, 30) this decrease was transient with complete recovery, despite continuation of CyA in 1 of them (no. 26). In 3 patients (nos. 27, 29, 31), impairment of renal function was only partially reversible. In 1 patient (no. 29) CyA was responsible for this, as demonstrated on repeat biopsy. In 2 patients (nos. 27, 31) CyA is likely to have been responsible for the deterioration of renal function since initial biopsies, performed early in the course of the disease and just prior to CyA treatment, showed minor changes and renal function showed no further deterioration after CyA withdrawal. Finally, in 1 patient (no. 34) renal function was impaired following 2 months of treatment and further deteriorated during the year after CyA withdrawal. This patient was started on haemodialysis 14 months after the end of the treatment. It should be noted that nephrotoxicity was related to high trough CyA plasma levels (>150 ng/ml) in only 2 patients (nos. 13, 34).

Our protocol includes a subsequent biopsy in order to evaluate any changes in the renal parenchyma that are induced by CyA. At present, renal biopsies have only been performed in 11 patients 2–13 months after the initiation of CyA treatment (nos. 8–13, 16, 20, 28, 29, 32). Of these 11 patients, 3 had experienced an impairment of renal function during CyA treatment. The biopsy specimens were examined by light microscopy, by IF and by EM.

There were no significant changes in 6 patients (nos. 8, 9, 11, 13, 16, 20) and a vacuolization of the epithelium of scattered proximal convoluted tubules was observed in 2 patients (nos. 12, 32) together with mild interstitial fibrosis, a few atrophic tubules, and giant mitochondria in patient no. 12. Marked changes were observed in the remaining 3 patients, 1 steroid responder and 2 non-responders. Patient no. 10, whose renal function decreased at the time of a relapse whilst receiving CyA, showed lesions of FSGS in two-thirds of the glomeruli together with mild interstitial fibrosis and marked vacuolization of some convoluted tubules. Patient no. 28, who had normal renal function throughout the whole course of CyA treatment, developed, within 8 months, striped interstitial fibrosis with small foci of inflammatory cells, groups of atrophic tubules and marked vacuolization of some convoluted tubules, although he still had MCD in the second specimen. The most severe changes were observed in patient no. 29, who had a decreased creatinine clearance, which was partially reversible when CyA was stopped. A second biopsy specimen was obtained in this patient 3 months after the first one and there was no extension of FSGS lesions. However, in addition to marked vacuolization of groups of proximal tubules, including the pars recta, this patient showed numerous tubules with extensive calcified necrosis of the epithelial cells surrounded by mild interstitial fibrosis.

By EM, no significant changes were found in 2 patients (nos. 13, 20). In 4 patients (nos. 8, 10, 12, 29), varying amounts of enlarged vacuolar clear lysosomes were observed in proximal tubular cells. The vacuolization was also present in some distal tubules in patient no. 29 and was associated with giant mitochondria and focal dilatation of ergastoplasm in patient no. 12. Poorly differentiated tubular cells and thickening of tubular basement membranes were observed in 2 patients (nos. 28, 29).

Hypertension. Blood pressure was moderately elevated in 6 patients, 4 partial steroid responders who were still receiving prednisone therapy and 2 steroid non-responders who were off prednisone. One of the steroid non-responders had an impairment of renal function (patient no. 31). Only 2 patients were still hypertensive after CyA withdrawal.

Other side-effects. Hypomagnesaemia occurred in 22 patients. Hypertrichosis was frequently observed (21 patients) whereas gingival hyperplasia was seen less frequently (9 patients). Liver function tests (serum transaminase, bilirubin levels) showed no changes except for alkaline phosphatase levels, which were significantly increased in

31 patients. Hyperkaliaemia occurred in 1 patient in conjunction with an impairment of renal function.

Discussion

In the majority of children with INS, renal biopsies show MCD with no significant deposits seen by IF. However, other patterns have been identified, namely FSGS and DMP [7]. In addition, IF has revealed the presence in the mesangial areas of various combinations of immunoglobulins, sometimes isolated, sometimes associated with C1q. In some cases, scattered granules of C3 may be seen. Among the immunoglobulins, the most frequently found is IgM. The clinical significance of these morphological findings has been extensively studied and it has become apparent over the years that there is a clinical overlap among these different patterns and that morphological transformations are not uncommon. Since neither the aetiology nor the pathogenesis of INS is established, it can be considered as a disease with some variants in regard to pathology and clinical characteristics.

CyA was used in 35 children with INS. The treatment was effective in 17 out of 20 steroid responders. These 17 patients did not relapse while on CyA despite prednisone withdrawal. However, most of them relapsed when CyA was tapered off or stopped. Furthermore, some patients did not respond to a second course of CyA although the treatment had at first been effective. Among the remaining 3 steroid responders, CyA reduced prednisone requirements in 1 and was ineffective in 2. Conversely, CyA has been less effective in partial steroid responders and in steroid non-responders. Among the 5 partial steroid responders, 2 patients responded to CyA, including 1 who responded only partially. Only 1 of 10 steroid non-responders went into complete remission under CyA therapy, whereas a partial response was observed in 2 patients and no response in 7.

The response of patients with INS to CyA therapy is thus well correlated to the initial steroid responsiveness as 90% of steroid responders reacted to CyA whereas only 30% of the steroid non-responders did so. Conversely, there is no correlation whatsoever between the response to CyA and the histopathological categories. Our results show that 64% of the patients with MCD or DMP and 66% of the patients with focal lesions (FSGS or FGF) responded to CyA therapy. In addition, initial biopsy showed mesangial IgM deposits in 7 patients, 6 of whom were steroid responders. CyA treatment was effective in 5 patients with IgM deposits, all steroid responders.

Our results are in agreement with those reported by Hoyer et al. [3] and by Capodicasa et al. [4]. Hoyer et al. [3] reported 5 children with frequently relapsing minimal change nephrotic syndrome who responded to CyA with fewer relapses during the treatment and reduced prednisone requirements. Capodicasa et al. [4] gave CyA in combination with steroids to 10 children, including 6 frequent relapsers and 4 steroid non-responders. The treatment was effective in 5 frequent relapsers and in 2 steroid non-responders.

There is no real discrepancy between our results and those reported by Tejani et al. [1] and by Meyrier et al. [2]. These authors have correlated the response to CyA treatment with histopathology rather than with the initial response to steroid therapy. Tejani et al. [1] treated 20 children with INS. They observed 14 complete remissions, including 6 patients out of 9 with FSGS, 6 patients out of 7 with IgM nephropathy and 2 patients out of 4 with MCD. The remaining 6 patients had a partial response to CyA. Meyrier et al. [2] treated 6 adult patients with INS, including 3 with MCD who went into remission within 12–42 days but became CyA dependent and 3 patients with FSGS who responded only partially to CyA.

Conversely, our results differ from those reported by Brandis et al. [5], who treated 4 steroid-resistant children and 1 steroid-dependent patient with CyA and observed complete remission in all cases. These discrepancies may be explained either by a different definition of steroid resistance or by the fact that the course of the disease before initiation of CyA was shorter in their patients.

The major side-effect of CyA is nephrotoxicity. Renal function impairment occurred in 8 of the 35 patients and was completely reversible in only 4 of them. It should be stressed that 7 of these patients either had a persistent nephrotic syndrome or were in relapse when the glomerular filtration rate was noted to be decreased, which suggests that factors other than CyA nephrotoxicity may have been operative.

None of the lesions observed either by light microscopy or by EM in the second specimens obtained post-CyA treatment can be considered, in our experience, as specific for CyA nephrotoxicity except for the numerous calcifications observed in patient no. 29, which most likely represent, calcified necrosis of tubular cells, associated with extensive vacuolization of the pars recta of proximal tubules. However, we were also impressed by the interstitial fibrosis shown in the

second biopsy of patient no. 28, who had MCD on both biopsies performed at an interval of 8 months. It is noteworthy that in this patient no deterioration of renal function occurred during the course of treatment. Such a discrepancy between the histological findings and renal function has already been reported by others [8].

In conclusion, CyA is effective in steroid-responsive INS. It may be of help in those patients who develop serious side-effects of steroid therapy. However, most patients relapse when CyA is withdrawn and further studies are needed to know if the association of low doses of CyA and prednisone may be effective in these patients. Conversely, CyA has been less effective in steroid-resistant and in partially steroid-responsive patients. Furthermore, our data suggest that impairment of renal function is more frequent in steroid non-responders. A controlled trial is needed in order to rigourously establish the effects of CyA in INS.

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