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ORIGINAL ARTICLE

Cyclosporine A combined with medium/low dose prednisone in progressive IgA nephropathy

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Abstract The aim of the present study was to evaluate the efficacy of cyclosporine A (CsA) combined with medium/low dose prednisone in the treatment of progressive immunoglobulin A nephropathy (IgAN). Ninety-six patients who satisfied the inclusion criteria were enrolled in a prospective controlled clinical study. They were assigned into two groups and initially given either 0.6–0.8 mg/kg/day prednisone (maximum 40 mg/day) plus 3 mg/kg/day CsA (CsA group), or 1 mg/kg/day prednisone (maximum 60 mg/day) alone (steroid group). During therapy, the dose of prednisone was reduced in both groups and the dose of CsA was gradually tailed off over the first 3 months and maintained at 2 mg/kg/day in the CsA group. Urinary protein excretion, serum biochemical indexes, clinical efficacy and side effects of CsA were assayed. A significant decline in mean 24-hour urinary protein excretion ($p < 0.05$) was observed 1 month after treatment in patients in the CsA group, which was observed 2 months after treatment in the steroid group. The decline in mean 24-hour urinary protein excretion in the CsA group was more significant than in the steroid group. Serum albumin level increased significantly in the CsA group 2 months after therapy ($p < 0.05$). Moreover, at the end of the course, a higher remission rate was observed in patients with Lee's Grade III IgAN after combined treatment with prednisone and CsA ($p < 0.05$). No significant difference in clinical efficacy was observed in patients with Lee's Grade IV and Grade V IgAN between the two groups ($p > 0.05$). CsA at a dose of 2–3 mg/kg/day in combination with medium/low dose prednisone was effective in inducing remission of IgAN, especially for patients with Lee's

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Grade III IgAN, and is a safe and effective choice for short-term treatment of patients with progressive IgAN.

Introduction

Immunoglobulin A nephropathy (IgAN) is recognized to be the most common type of primary glomerulonephritis worldwide [1,2]. Some IgAN patients have stable renal function over several decades, whereas others develop hypertension, nephrotic syndrome, and chronic renal failure [3]. A variety of mechanisms have been demonstrated to be involved in the pathogenesis of IgAN, of which, immune abnormalities including activation of T lymphocytes play important roles, and secondary inflammation caused by abnormal growth factors and cytokines participate mainly in mesangial proliferation and sclerosis [4]. Therefore, early diagnosis and intervention are important for IgAN treatment. Recent studies suggest that urine protein $>$ 1.0 g/24 hour is an independent risk factor for IgAN progression [4]. Thus, actively reducing urinary protein and delaying IgAN progression are currently the focus of treatment. Active treatment using corticosteroids, immunosuppressants, angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockers (ARBs) is advocated for patients with initial proteinuria ($>$1 g/day) accompanied with hypertension, and patients with progressive IgAN as indicated by diagnostically confirmed renal dysfunction, glomerular sclerosis, crescent formation, interstitial fibrosis, and vascular sclerosis [4]. Studies have reported that prednisone can reduce urinary protein, protect renal function, and delay the progress of IgAN [5]. However, many patients with IgAN are not sensitive to corticosteroid therapy as clinically manifested as urinary protein sustainably greater than 1 g/24 hour or decreased less than 25% after 12 weeks of prednisone treatment. In addition, these patients generally have Lee's Grade III or higher IgAN in renal biopsy. Therefore, they are generally treated with immunosuppressants besides prednisone therapy.

Cyclosporine A (CsA), a potent, highly selective immunosuppressant, has been widely used to treat patients with organ transplantation and autoimmune diseases. Compared with other immunosuppressive agents, CsA selectively acts on T lymphocytes without affecting bone marrow myeloid and erythroid cells. Many clinical studies have indicated that CsA has good clinical efficacy in the treatment of minimal change nephrosis, focal segmental glomerulosclerosis, as well as idiopathic membranous nephropathy-induced nephrotic syndrome. However, its application in the treatment of progressive IgAN is rarely reported. Therefore, we selected inpatients who were diagnosed by renal biopsy to have Lee's Grade III or higher IgAN and used prospective, controlled clinical studies to explore the clinical efficacy and safety of joint treatment with CsA and medium/low-dose prednisone in patients with progressive IgAN.

Methods

Patients

From June 2005 to May 2012, a total of 96 inpatients who met the following criteria were enrolled in the present study: (1) renal pathology proved to be IgAN by renal biopsy; (2) Lee's Grade III–V; (3) serum creatinine (Scr) $<$150 μmol/L or estimated glomerular filtration rate (eGFR) $>$ 60 mL/minute; and (4) urinary protein excretion rate 1.0–3.5 g/24 hour. Patients were excluded or exited from the trial regardless of efficacy if: (1) they had an infection, liver and systemic disease, diabetes mellitus, or neoplasms; (2) they were pregnancy or during lactation; or (3) they had allergic purpura, ankylosing spondylitis, systemic lupus erythematosus, Sjogren's syndrome, psoriasis, or other secondary IgAN. End points of the study were: (1) end of follow-up; (2) Scr concentration doubled, or eGFR reduced by $>$50%; and (3) serious adverse events. The treatment protocol was approved by the Institutional Review Board of Taian Central Hospital and was consistent with all of the patients. Informed consent was obtained from each participant. Ethical approval for this study was obtained from the Medical Ethical Committee of Taian Central Hospital, Taian. China.

Experimental group

Patients including 24 males and 24 females with a mean age of 35.4 $\pm$ 7.3 were assigned to CsA group. 48 cases in steroid group including 28 males and 20 females with the average age of (34.5 $\pm$ 8) years old.

Patients in the CsA group were given oral CsA (Oral Cyspin; Hangzhou Zhongmei-Huadong Pharmacentical Co. Ltd., Hangzhou, China) at 3 mg/kg/day in the first 3 months, then maintenance with 2 mg/kg/day for 9 months for patients who had clinical improvement. CsA administration was stopped promptly if patients had suspected CsA-associated nephrotoxicity or when no clinical improvement occurred after 4–6 months of treatment. The dose of CsA was adjusted to ensure the concentration was maintained at 100–150 ng/ml. Prednisone (Shandong Xinhua Pharmaceutical Co. Ltd., Zibo, China, 0.6–0.8 mg/kg/day maximum, 40 mg/day) was given to patients in the CsA group every morning for 6–8 weeks. The dose was then gradually reduced by 5 mg every 2 weeks to 10 mg/day during. Patients in the steroid group were given prednisone (1.0 mg/kg/day maximum, 60 mg/day) every morning for 8–12 weeks. The dose was then gradually reduced by 5 mg every 2 weeks to 20 mg/day, and then by 2.5 mg every 2 weeks to 10 mg/day. This was the maintenance dose for 1 year.

The target blood pressure was ≤140/90 mmHg in both groups. All patients were given ARB (Valsartan 80—160 mg/day; Beijing Novartis Pharma Ltd, Beijing, China) and hypertension was controlled with ARB and/or nifedipine and/or diuretics.

Measurement of laboratory indexes

All patients were followed-up twice in the 1st month, once in the 2nd month, and thereafter once every 4—6 months. Serum albumin, Scr, blood urea nitrogen, cholesterol, triglyceride, uric acid, fasting blood glucose, eGFR, and 24-hour urinary protein excretion rate were examined. Remission rate and drug side effects were closely observed and confirmed with repeat examination of 24-hour urinary protein excretion rate and serum albumin.

Efficacy was defined as complete remission (CR) and partial remission (PR). CR was defined as proteinuria <0.5 g/24 hours, serum albumin > 35 g/L, and normal Scr. PR was defined as proteinuria reduced by >25% but still higher than 0.5 g/24 hours, and stable Scr. Invalid was defined as proteinuria reduced <25% or worsening of renal function [6].

CsA level (C_0) were monitored by high performance liquid chromatography (HPLC) (CsA standard: The Control of Pharmaceutical and Biological Products of China; Cyclosporine D (CsD) the internal standard: North China Pharmaceutical Research Institute) weekly for 1 month and thereafter monitored monthly. Methanol and acetonitrile (Tianjin Siyou Chemical Reagent Factory, Tianjin, China, analytic reagent); Ether (Tianjin Tianda Chemical Experiment Factory, Tianjin, China); N-hexane (Tianjin Chemical Reagent Factory, Tianjin, China, analytic reagent). HPLC was developed using acetonitrile-methanol-water (60:20:20 by volume) as mobile phase, Polaris C18 column (250 mm × 416 mm, 5 μm) and 214 nm wavelength detection. The flow rate was 0.5 ml/minute and the column temperature was 70°C. One millimeter of CsD (dissolved in methanol, concentration of 500 ng/ml) was added to 1.5 ml blood samples. Then 1.5 ml 0.1 mol/ml NaOH and 5 ml ether were added to the mixture. The mixture was stirred and extracted for 3 minutes, and centrifuged at 3000 r/minute for 5 minutes. Then the supernatant was put in a 40°C water bath and dried by nitrogen. The residue was dissolved by 0.3 ml n-hexane. After that, 80 μl mobile phase was added, stirred and extracted for 1 minute, centrifuged at 3000 r/minute for 5 minutes, then 20 μl lower mobile phase was taken as the sample.

Statistical analysis

Statistical analyses were performed using SPSS for Windows version 12.0 (SPSS Inc., Chicago, IL, USA). Data were represented as mean ± standard deviation. The data were analyzed with repeated measures one-way analysis of variance and application of comparison for paired data analysis and for two-group variance analysis. Cumulative proportions of patients with CR and/or PR in the two groups were compared using the χ^2 test. Statistical significance was set at the level of $p < 0.05$.

Results

Patient characteristics

Patients in the two groups had similar baseline demographic, clinical, and laboratory characteristics (Table 1). Their baseline sex and age distributions were similar. Their systolic, diastolic, and mean blood pressure showed no significant differences. The number of patients with blood pressure higher than 140/90 mmHg at baseline was also similar in the two groups: 10 (20.8%) in the steroid group and 12 (25%) in the CsA group ($p > 0.05$). The mean proteinuria values at baseline were 2.01 ± 0.8 g/day (range: 1.03—3.47 g/day) in the steroid group and

Table 1 Baseline demographic, clinical and laboratory characteristics of patients.

		Steroid group (n = 48)	CsA group (n = 48)	T (or Z) value	p
Male/female		28/20	24/24	$x^2 = 0.671$	0.413
Age (y)		34.5 ± 8.0	35.4 ± 7.3	0.576	0.566
SBP (mmHg)		131.3 ± 17	134.7 ± 14	1.070	0.288
DBP (mmHg)		80.2 ± 11.5	83.2 ± 10.7	1.323	0.189
MAP (mmHg)		95.5 ± 10.2	96.8 ± 9.7	0.640	0.524
Patients with BP > 140/90 mmHg [n (%)]		10 (20.8)	12 (25)		
Serum albumin (g/L)		33.93 ± 7.6	33.96 ± 6.5	0.021	0.984
Proteinuria (g/d)		2.01 ± 0.8	2.07 ± 0.9	0.345	0.730
Serum creatinine (μmol/d)		87.3 ± 22.05	89.9 ± 19.87	0.607	0.545
Lee's Grade	II	36	32	Z = 0.918	0.359
	III	8	10		
	IV	4	6		
Uric acid (mg/dL)		5.3 ± 1.7	5.4 ± 1.2	0.333	0.740
Cholesterol (mmol/L)		6.77 ± 2.91	6.56 ± 3.29	0.421	0.712
Triglyceride (mmol/L)		2.74 ± 1.52	2.63 ± 1.0	0.318	0.674
FBG (mmol/L)		5.1 ± 0.7	4.9 ± 0.7	0.299	0.712
eGFR (mL/min)		76.7 ± 23.8	75.1 ± 24	0.594	0.213

BP = blood pressure; CsA = cyclosporine A; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FBG = fasting blood glucose; MAP = mean arterial pressure; SBP = systolic blood pressure.

2.07 ± 0.9 g/day (range: 1.11–3.36 g/day) in the CsA group ($p > 0.05$). Lee's classification at the time of biopsy was III, IV, and V in 36 patients, eight patients, and four patients, respectively, in the steroid group and in 32 patients, 10 patients, and six patients, respectively, in the CsA group. Renal function, estimated by Scr and eGFR, was similar in the two groups. Information in Table 1 also suggested no significant differences in serum albumin, uric acid, cholesterol, triglyceride, and fasting blood glucose between the two groups.

Primary outcomes

Table 2 lists the clinical findings in the patients in the two groups. There was a marked difference in urinary protein excretion between different times and groups by repeated measure with analysis of variance (times: $F = 112.435$, $p < 0.0001$; Groups: $F = 37.87$, $p < 0.0001$), and in serum albumin (times: $F = 42.022$, $p < 0.0001$; Groups: $F = 5.57$, $p = 0.02$). However, as shown in Table 2, Scr, serum uric acid, mean arterial pressure, serum cholesterol, serum triglyceride, fasting blood glucose, and eGFR did not change significantly from baseline to the end of the study in both groups. For patients in the CsA group, urinary protein excretion decreased significantly from 2.07 ± 0.9 g/day to 1.22 ± 0.5 g/day after 1 month of treatment, and proteinuria was reduced to 0.53 ± 0.4 g/day ($p < 0.01$) after 12 months of follow-up. Similar outcomes were also observed in patients in the steroid group. In addition, proteinuria differed significantly between the two groups after 2 months and 6 months of therapy ($p < 0.05$), but not after 12 months of therapy. Serum albumin concentration increased significantly after 2 months of treatment with CsA combined with prednisone. Compared with the steroid group, serum albumin increased significantly after 2–12 months of combined therapy, and these changes were more significant after 12 months of therapy. Although serum albumin level also increased in patients treated with prednisone alone, this increase did not reach statistical significance. The time of action time for CsA was 21.3 ± 6.7 days. Serum CsA concentration was 132.5 ± 55.1 ng/mL in patients who reached complete remission and had an average CsA dose of 2.64 ± 0.57 mg/kg/day. Despite the satisfactory changes in serum albumin concentration and urinary protein excretion, we noticed no improvement of renal function or alteration in renal creatinine concentration during combined treatment with CsA and steroid.

Table 3 shows the clinical efficacy of the two treatments. Complete remission occurred in 12.5%, 37.5%, 41.7%, and 52.1% patients after 1 month, 2 months, 6 months, and 12 months of combined treatment with CsA and steroid, respectively. Although the efficacy of the two treatments did not differ significantly after 6 months, it differed significantly after 12 months. In addition, the complete remission rate of patients in the CsA group was significantly higher than that of patients in the steroid group after 2 months of treatment ($p < 0.05$ or $p < 0.01$).

Table 4 shows the clinical efficacy of the two treatments for IgAN patients with different Lee's Grade. Patients with Lee's Grade III in the CsA group had a CR rate of 56.25% and

Table 2 Comparison in clinical findings following treatment of two groups.[a]

Group	Time	Proteinuria (g/d)	Serum albumin (g/L)	Serum creatinine (μmol/L)	Uric acid (mg/dL)	MAP (mmHg)
Steroid	0.5M	1.96 ± 0.6	33.90 ± 6.5	87.3 ± 21.5	5.3 ± 1.2	95.3 ± 10.3
	1M	1.85 ± 0.3	34.01 ± 7.0	87.0 ± 22.3	5.3 ± 1.6	95.1 ± 11.2
	2M	1.52 ± 0.4*	34.11 ± 6.5	86.9 ± 21.8	5.2 ± 1.1	96.3 ± 10.6
	6M	1.23 ± 0.5*	34.12 ± 5.9	87.1 ± 20.3	5.3 ± 1.2	96.7 ± 10.4
	12M	1.01 ± 0.6*	35.69 ± 7.1	86.3 ± 19.8	5.3 ± 1.1	96.8 ± 10.9
Cs A	0.5M	1.97 ± 0.9	34.01 ± 7.2	89.9 ± 18.5	5.4 ± 1.1	96.8 ± 9.7
	1M	1.22 ± 0.5*	34.65 ± 5.2	87.2 ± 17.8	5.4 ± 1.5	97.2 ± 9.3
	2M	0.87 ± 0.6**, ***	38.49 ± 5.4*, ***	87.6 ± 15.3	5.4 ± 1.1	97.2 ± 9.1
	6M	0.72 ± 0.3**, ***	39.72 ± 5.9*, ***	88.4 ± 18.4	5.3 ± 1.8	96.7 ± 10.2
	12M	0.53 ± 0.4**	39.51 ± 6.4*,***	88.7 ± 16.6	5.3 ± 1.6	96.2 ± 11.5

Group	Time	Cholesterol (mmol/L)	Triglyceride (mmol/L)	FBG (mmol/L)	eGFR (ml/min)	CsA concentration (C_0)
Steroid	0.5M	6.76 ± 1.98	2.75 ± 1.61	5.1 ± 0.5	76.4 ± 21.4	–
	1M	6.73 ± 1.82	2.77 ± 1.39	5.2 ± 0.8	78.9 ± 26.2	–
	2M	6.75 ± 1.77	2.76 ± 1.69	5.0 ± 0.6	78.4 ± 24.9	–
	6M	6.72 ± 1.80	2.76 ± 1.46	4.9 ± 0.5	77.5 ± 30.1	–
	12M	6.69 ± 1.79	2.75 ± 1.37	4.7 ± 0.7	78.6 ± 27.8	–
CsA	0.5M	6.62 ± 2.97	2.69 ± 1.14	4.9 ± 0.7	75.6 ± 27.3	102.7 ± 18.4
	1M	6.71 ± 1.82	2.69 ± 1.31	4.8 ± 0.8	74.8 ± 23.6	108.6 ± 14.9
	2M	6.71 ± 1.73	2.67 ± 1.49	4.5 ± 0.5	75.1 ± 20.9	111.4 ± 13.7
	6M	6.72 ± 1.91	2.65 ± 1.35	4.3 ± 0.7	76.4 ± 21.7	106.7 ± 20.1
	12M	6.71 ± 1.76	2.65 ± 1.41	4.7 ± 0.5	77.3 ± 25.4	107.3 ± 15.2

*$p < 0.05$.
**$p < 0.01$ compared to the indexes prior to treatment in the same group.
***$p < 0.05$ simultaneous comparison of indexes between two groups.
[a] Statistical analysis used one-way analysis of variance with t test. $n = 48$ for CsA group and $n = 48$ for steroid group.

Table 3 The comparison of efficacy between two groups.[a]

Group	*n*	Time	CR (%)	PR (%)	CR + PR (%)
Steroid	48	0.5 m	0 (0)	14 (29.2)	14 (29.2)
		1 m	2 (4.2)	28 (58.3)	30 (62.5)
		2 m	6 (12.5)	28 (58.3)	34 (70.8)
		6 m	10 (20.8)	26 (54.2)	36 (75)
		12 m	10 (20.8)	26 (54.2)	36 (75)
CsA	48	0.5 m	0 (0)	18 (37.5)	18 (37.5)
		1 m	6 (12.5)	28 (58.3)	34 (70.8)
		2 m	18 (37.5)**	22 (45.8)	40 (83.3)
		6 m	20 (41.7)*	22 (45.8)	42 (87.5)
		12 m	25 (52.1)**	19 (39.6)	44 (91.7)*

*$p < 0.05$.
**$p < 0.01$.
CR = complete remission; CsA = cyclosporine A; PR = partial remission.
[a] Statistical analysis used χ^2 test. Simultaneous comparison between two groups.

PR + CR rate of 100%, which were significantly higher than those of patients with Lee's Grade III in the steroid group ($p < 0.05$). The remission rates of patients with Lee's Grade IV and V IgAN were similar between the two groups ($p > 0.05$). In addition, the remission rate of patients with Lee's Grade III IgAN in the CsA group was significantly higher than that of patients with Lee's Grades IV and V in the same group ($p < 0.05$).

Several complications were observed in patients in the CsA group. (1) Hypertension was found in four patients, who were treated with antihypertensive therapy. (2) Liver damage was found in three patients, who were successfully managed by adjusting blood CsA concentration. (3) Overgrowth of body hair and gingiva were observed in nine patients and five patients, respectively. These symptoms disappeared after tapering off the CsA dose. No infection, leukopenia, renal impairment, hair loss, or other adverse reactions were found. In the steroid group, six patients had infection, five patients had hypertension, and eight patients had abnormal blood glucose. They all recovered after appropriate therapies. All patients in the steroid group completed the trial. Two patients were lost to follow-up after 3 months and 4 months treatment, respectively, and two participants stopped using CsA after 6 months of follow-up due to no clinical improvement.

Table 4 Comparison of clinical effect of different classification of CsA on IgAN.[a]

Group	*n*	Lee's Grade	CR (%)	PR (%)	CR + PR
CsA	48	III (32)	19 (59.38)*,**	13 (40.63)	32 (100)*
		IV (10)	5 (50.0)	4 (40.0)	9 (90)
		V (6)	1 (16.67)	2 (33.33)	3 (50)
Steroid	48	III (36)	8 (22.22)	23 (63.89)	31 (86.11)
		IV (8)	2 (25.0)	2 (25)	4 (50)
		V (4)	0 (0)	1 (25)	1 (25)

*$p < 0.05$, comparison in different classification in the same group.
**$p < 0.05$, comparison between two groups.
CR = complete remission; CsA = cyclosporine A; IgAN = IgA nephropathy; PR = partial remission.
[a] Statistical analysis used χ^2 test.

Discussion

Recent data have indicated that IgAN is a widespread type of glomerulonephritis with relatively poor renal outcome. Up to 40% of IgAN patients reach end-stage renal disease within 20 years [1,2]. Several studies have proved that steroids, angiotensin-converting enzyme inhibitors, fish oil, cytotoxics, immunosuppressants, tonsillectomy, and vitamin E are beneficial to IgAN patients [7–12]. However, consensus about therapy is still lacking. CsA has no doubt become the first-line therapy in organ transplantation since the late 1970s. Its efficacy has led to its use in a variety of immune-mediated glomerular diseases such as minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, membranoproliferative glomerulonephritis, and lupus nephritis.

Shin et al. [13] used CsA to treat patients with severe Henoch–Schönlein nephritis with nephrotic syndrome for an average of 5.5 years. They found declined urinary protein/24 hours, increased serum albumin, and significantly decreased activity index at the second renal biopsies in all patients after CsA therapy, but no decline in chronicity index and tubulointerstitial scores, suggesting that CsA may be beneficial to a subset of Henoch–Schönlein nephritis patients with nephrotic syndrome. Tao et al. [14] found that low-dose CsA treatment of adult patients with nephrotic syndrome complicated with idiopathic membranous nephropathy for at least 6 months was safe and effective, and all patients maintained CR without relapse.

However, the efficacy of CsA in IgAN patients remains poorly studied. Shin et al. [15] treated 14 children with CsA and steroids, and found the mean duration of CsA therapy was 10.9 ± 1.9 months. They believe that CsA may be effective in reducing proteinuria and regressing renal pathology in a subset of children with IgAN. Rasić et al. [16] have demonstrated that a high percentage of adult patients with primary nephrotic syndrome associated with IgAN achieve remission after CsA treatment. However, due to limited experience, CsA treatment of IgAN was not approved in the Last Summary of Therapeutic Options published by Galla [17]. Lai et al. [18] published a small study in 1987 in which CsA administered for 3 months significantly reduced proteinuria, and this effect persisted in some of the patients during a subsequent 12 weeks of observation. The decrease in proteinuria was accompanied by a reduction in glomerular filtration, which nevertheless was not sufficient to explain the decrease in proteinuria.

The mechanisms of action of CsA are unclear, but may involve the following: (1) immunomodulation by T-cell-mediated cytokines, resulting in restoration of glomerular basement membrane charge selectivity [19,20]; (2) inhibition of vascular permeability factors [21]; and (3) nonspecific alteration of renal hemodynamics, reducing proteinuria through functional renal insufficiency.

Our study showed that CsA treatment was effective in reducing proteinuria and elevating serum albumin. The

combination of CsA and medium/low-dose prednisone was more effective in reducing proteinuria and elevating plasma albumin compared with the steroid group, suggesting a synergistic effect between CsA and prednisone. Although no significant improvement of renal function was observed after treatment, we did observe a trend towards improvement of renal function. The outcome could have been due to the short duration of the trial. In addition, no significant differences in CR rate and effective rate were observed 15 days after treatment, but CR rate at 2 months and 6 months and the effective rate at 12 months in the CsA group were higher than those in the steroid group ($p < 0.05$ or $p < 0.01$). Despite the effective rate after 6 months therapy not differing significantly between the two groups, the CR rate in the CsA group was higher than that in the steroid group. Thus, we conclude that the combined treatment of CsA and medium/low dose of prednisone is superior to prednisone pulse therapy alone in IgAN. We also found that a higher remission rate could be achieved in patients with Lee's Grade III IgAN after combined treatment with prednisone and CsA, indicating that these patients could benefit more from CsA. No significant difference in clinical efficacy was observed in classification Lee's IV andVpatients between the two groups. In our opinion, the results may be relevant for small samples, short time of observation, and in patients with serious histological changes.

We also found no difference in cholesterol, triglyceride, and blood sugar after treatment with CsA. Although there were complications in some patients during therapy, they all recovered by appropriate therapy. Our study indicated that short-term combination of CsA and prednisone in patients with IgAN is safe.

Many studies have demonstrated the clinical effect of CsA in kidney disease. However, its toxicity, especially its nephrotoxicity, has limited its application. The current study showed that CsA therapy was effective in regressing renal histological changes in a subset of patients with IgAN (~50%). Although there were no serious complications of CsA therapy during the study, it is important to use the lowest effective dosage of CsA and monitor the CsA level closely. In addition, this study had several limitations such as small sample size, not being a randomized double-blind clinical trial, lack of repeat biopsy, and relatively short length of treatment and follow-up.

In summary, our study suggests that CsA combined with steroid is effective in reducing proteinuria and elevating serum albumin in patients with progressive IgAN. The patients with Lee's Grade III IgAN would benefit more from combination of CsA and prednisone than those with Lee's Grade IV and V IgAN. The efficacy in our study was limited to only 1 year of treatment and short-term follow-up, which is not the final goal of patient management. More evidence is needed to conclude that the combination of CsA and prednisone may have better long-term effects (compared with 1 year's treatment). Further studies are required to continue to clarify whether combined therapy is effective in the advanced stage of IgAN and to confirm whether it actually improves renal outcome over the long term.

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