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Originals

Combination Therapy Consisting of Low-dose Cyclosporin A, Low-dose Prednisolone and Enalapril in Children with Steroid-Sensitive Nephrotic Syndrome

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SUMMARY

To evaluate the extent to which combined low-dose cyclosporin A (CsA), low-dose glucocorticoid and enalapril would permit decreasing 1) steroidal toxicity, 2) the frequency of relapse of nephrotic syndrome and 3) adverse effects due to CsA, in children with steroid-dependent nephrotic syndrome. Eight children with steroid-dependent nephrotic syndrome underwent CsA therapy (mean : 2.7 mg/kg/day) for more than 24 months. Renal biopsy was performed at 24 months of CsA treatment. Height development was assessed by comparing with normal level. The changes in prednisolone dosage, as well as in the frequency of relapse, were studied. Prednisolone dosage significantly ($p < 0.05$) decreased to 0.20 ± 0.14 mg/kg/day after start of CsA therapy, being 0.64 ± 0.35 mg/kg/day before it. The frequency of relapse significantly ($p < 0.05$) decreased to 0.13 ± 0.12 times per month after start of CsA therapy, its initial frequency being 0.48 ± 0.11 times per month. There were no severe histological abnormalities. The height development delay was progressed in only one patient. There were no adverse effects of CsA. It may be safely said that low-dose CsA (2.5～3.0 mg/kg) was effective in pediatric steroid-dependent nephrotic syndrome and that the trough levels of CsA of 100 to 150 ng/ml were not necessary when combined with low-dose prednisolone which would not induce major side effects.

Key Words : cyclosporin A, enalapril, steroid-dependent nephrotic syndrome, children

INTRODUCTION

Cyclosporin A (CsA) has been reported to be effective for steroid-dependent nephrotic syndrome, decrease the frequency of relapse and reduce adverse effects due to steroid such as short stature, obesity, bone fracture, epidermal lipomatosis, and so on [1～4]. However, there are two major problems in CsA treatment : one is CsA nephrotoxicity [5～8] and the other is the relapse of nephrotic syndrome after withdrawal of CsA [9, 10]. In most of reports, CsA had been used at 5 mg/kg body weight or more in oder to gain a trough level of 100 ng/ml. At these dose, nephrotoxicity often occurs : histological abnormalities have been reported in 30 to 50% of patients in 1 to 2 years of treatment [5～8]. In addition, the relapse of nephrotic syndrome has been reported after CsA short-term 1 to 2 years CsA treatment [9, 10]. Thus, this study was designed for the purpose of minimizing nephrotoxicity of CsA and the frequency of relapse, using CsA at low dose and enalapril in children with steroid-dependent nephrotic syndrome for long term.

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Table 1 Summary of patient characteristics

Patient number	sex	Age at onset of NS (year)	Response of steroids	Parthology	Age at onset of CsA therapy (year)	Duration of CsA treatment (months)
1	F	6.5	FR	MCNS	10.5	44*
2	M	2.9	FR	MCNS	3.6	35*
3	M	3.5	NFR	MCNS	14.6	54**
4	F	10.7	FR	MCNS	11.5	29*
5	M	2.7	FR	ND	3.5	36**
6	M	2.6	FR	ND	3.2	38**
7	M	4.2	NFR	MCNS	13.2	26**
8	F	4.1	FR	MCNS	5.7	26***

CsA, cyclosporin ; F, female ; M, male ; NS, nephrotic syndrome ; FR, frequent relapser ; NFR, non frequent relapser ; MCNS, minimal change nephrotic syndrome ; ND, renal biopay was not done ; *, all medications were completed ; **, CsA was continued ; ***, drop out

PATIENTS AND METHODS

Patients having proteinuria greater than 40 mg/m^2/hr, hypoalbuminemia (2.5 g/dl or less) and edema were diagnosed to have nephrotic syndrome. The reduction in urinary protein level below 4 mg/m^2/hr (Albustix, 0 or trace) for 3 days was judged as a remission. Where proteinuria returned to 40 mg/m^2/hr or greater and remained at these level for 3 days after remission, the condition was defined as a relapese. Steroid dependence was defined as recurrence of proteinuria when the glucocorticoid dose was reduced or within 2 weeks of discontinuation of glucocorticoid therapy. The condition that relapse repeated 3 times or more in 6 months or 4 times or more in 1 year was defined as frequent relapse.

There were 8 children with nephrotic syndrome, 5 boys and 3 girls, who had been treated with CsA for more than 2 years since June, 1994 to July, 2002, in Iwakuni Medical Center. Their age was 2.6 to 10.7 years (4.7 ± 2.8 years) at the onset of disease and 3.2 to 14.6 years (8.2 ± 4.7 years) at the initiation of CsA therapy. Six of these eight patients were frequent relapsers and the remaining patient (No. 4 and 8) was a non-frequent relapser who had a short stature (height : −2.3 S.D. and −1.7 S.D., respectively) probably due to a long-term use of prednisolone. Three patients received cyclophosphamide before entry in the study (patients No. 1, 2, and 4). Enalapril, an angiotensin converting enzyme inhibitor (ACE-I), was used in combination with CsA in all the seven patients. Patient profiles are summarized in Table 1.

CsA (Sandimmun) therapy was started at about 2.5 mg/kg (2.66 ± 0.57 mg/kg) a day, divided into 2 times, after disappearance of proteinuria on prednisolone. The trough level of CsA was measured by monoclonal antibody fluorescence polarization immunoassay every 3 to 4 months. The initial dose level of CsA was maintained in all patients, except for one patient (No. 3) in whose dose was increase from 1.9 mg/kg to 2.2 mg/kg because of relapse occurring twice in 3 months after initiation of CsA therapy. Enalapril was used at 1.25 mg/kg in combination with CsA in all patients, expecting its protective effects against CsA-toxicity on the kidney. Prednisolone was administered alternate-day in combination with CsA. Its dosage was gradually tapered to the withdrawal within 3 months. If relapse occurred on CsA treatment, prednisolone was administered at 1 mg/kg/day for 2 to 3 weeks, followed by the alternate-day dosing schedule of prednisolone. The dose of alternate-day prednisolone was more gradually tapered off than the first tapering off. Prednisolone was withdrawn in patient having no relapse occurred for 6 months. If no relapse occurred for one year after the withdrawal of prednisolone, CsA dose was gradually decreased to the withdrawal.

Follow-up renal biopsy was performed in 7 patients (No. 1, 2, 3, 5, 6, 7 and 8) at 24 months of CsA treatment. Patient 4 did not have the follow-up renal biopsy, because tapering CsA had already begun at the time. The difference in height from normal level was assessed and other adverse effects of prednisolone and CsA were evaluated. The Wilcoxon signed-ranks test was used for statistics comparison of the relapse frequency and the dose level of prednisolone. P value less than 0.05 was considered as statistically significant levels.

Table 2 Dose of prednisolone during CsA treatmernt for every 6 months (mg/kg body weight/day)

Patient number	During 6 months before initiation of CsA	0 – 6 m	7 – 12 m	13 – 18 m	19 – 24 m	25 – 30 m	31 – 36 m	37 – 42 m	43 – 48 m
1	0.50	0.37	0.29	0.26	0.20	0.11	0.08	0.00	0.00
2	0.71	0.12	0.00	0.00	0.11	0.13	0.12	0.00	0.00
3	0.28	0.05	0.00	0.00	0.18	0.04	0.00	0.09	0.12
4	0.51	0.13	0.13	0.09	0.03	0.02	0.00	0.00	
5	0.67	0.46	0.08	0.04	0.06	0.08	0.68		
6	0.66	0.20	0.27	0.15	0.25	0.26	0.16		
7	0.35	0.19	0.04	0.12	0.08	0.08			
8	1.41	0.10	0.46	0.25	0.40				

Table 3 CsA dose, trough level, and patient responces

Patient number	Maintenance dose of CsA (mg/kg/day)	Trough level of CsA (mg/ml)	No. of relapse for 6 months before CsA treatmernt	No. of relapse during CsA treatmernt for every 6 months								
				0 – 6 m	7 – 12 m	13 – 18 m	19 – 24 m	25 – 30 m	31 – 36 m	37 – 42 m	43 – 48 m	49 – 54 m
1	2.3	< 20	3	1	1	1	1	1	0	0	0	0
2	3.1	< 20	3	0	0	0	1	0	0	0	0	0
3	2.2	36 - 65	2	0	0	0	2	0				
4	2.2	51 - 93	3	1	1	0	1	0	0	0		
5	2.7	30 - 43	3	2	1	0	1	0	3			
6	3.2	29 - 35	3	1	1	2	4	3	1			
7	3.2	28 - 48	2	2	0	0	1					
8	3.3	61 - 95	4	0	1	1	1					

RESULTS

As of July, 2002, the median duration of CsA treatment is 24 to 54 months (35.8 ± 9.9 months) and 3 of 8 patients have had no relapse for more than 2 years after withdrawal of CsA, one patient (No.8) dropped out because of poor compliance, and the remaining 4 patients are still in CsA. The maintenance dose of CsA, the trough levels and the frequency of relapse on CsA treatment are shown in Table 3. The trough level was below 50 ng/ml in five patients (Nos. 1, 2, 5, 6 and 7) and 51 to 95 ng/ml in the remaining 3 patients. The frequency of relapse was 0.48 ± 0.11 times per month for 6 months before CsA treatment. It significantly ($p < 0.05$) decreased to 0.13 ± 0.12 times per month for 6months after initiation of CsA treatment. The dosage of prednisolone was 0.64 ± 0.35 mg/kg/day for 6 months before initiation of CsA treatment and 0.20 ± 0.14 mg/kg/day for 6 months after initiation of CsA treatment ($p < 0.05$). (Fig. 1 and Table 2)

Renal biopsy revealed no remarkable histological abnormalities, except for one patient (No. 8) showing a mild tubulointerstitial fibrosis (Fig. 2).

Figure 3 shows the changes in difference of height from normal level as expressed in standard deviation score. Steroid induced height development delay was not observed in one patient (No.1). Other adverse effects due to CsA, such as hypertension, hypertrichosis, gingival swelling, neurological abnormality, etc. were not noted.

DISCUSSION

As already recognized, CsA is effective for frequent relapse of nephrotic syndrome or steroid-resistant nephrotic syndrome in children. It is known that favorable therapeutic outcome can be obtained in steroid-sensitive nephrotic syndrome by keeping trough levels of CsA between 100 and 150 ng/ml. To keep such trough level, CsA dose of 5 mg/kg or more is recommended [1~4]. However, at such dose levels of CsA, nephrotoxicity such as tubulointerstitial lesion, focal glomerular sclerosis and arteriolar lesion occurs in 20 – 60% of patients according to recent reports [6~9]. Inoue et al [10]. administered CsA at 100 to 150 mg/m^2/day for the first 6 months of CsA

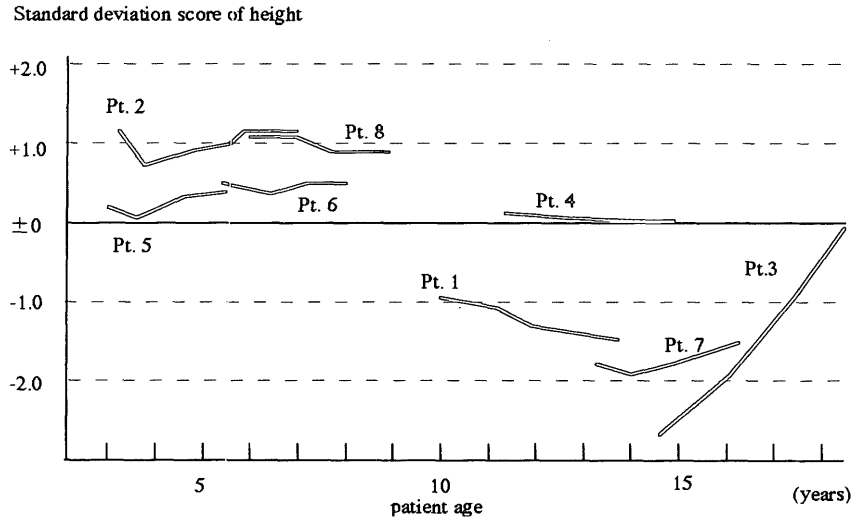

Fig. 1 Mean and S.D. score of the dose of prednisolone for 6 months from 6 months before initiation of CsA to 2 years after then. In all duration, prednisolone dose was significantly reduced comparing with the dose before CsA treatment ($p<0.05$).

Fig. 2 Follow up biopsy specimen of patient 8 showed localized tubular atrophy and mild interstitial fibrosis. Periodic acid - Schiff's reagent stain, × 200.

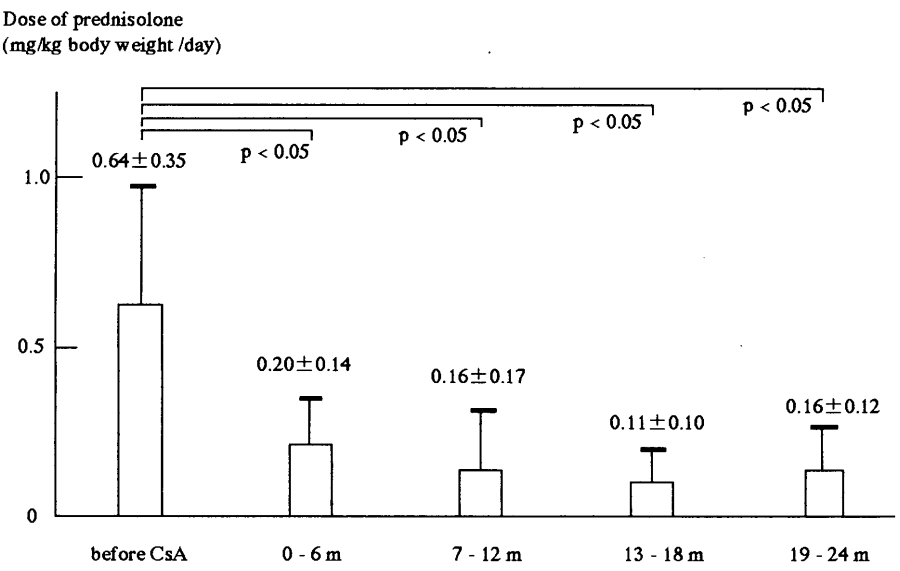

Fig. 3 Height S.D. score changes during CsA treatment. Inspite of concomitant use of the steroid, all patients showed no suppression of height growth except for patient 1.

treatment to keep trough levels of 100 to 150 ng/ml, and for 18 months thereafter, they continued CsA treatment at 75 mg/m^2/day. They reported that this CsA treatment permitted decreasing the frequency of relapse and prednisolone dosage, resulting in a reduction of side effects of glucocorticoids such as obesity, growth retardation, bone fracture, epidermal lipomatosis et al. On the other hand, they reported chronic nephrotoxicity due to CsA in 7 of 13 patients. In our study, low-dose CsA treatment significantly (< 0.05) decreased the frequency of relapse and the dosage of steroid. The height development delay due to steroid was not observed in our patients, except for one patient (No.1), a-10-year-old girl, with established short stature whose epiphyseal line was already closed at the initiation of CsA treatment. She had receipt a high-dose steroid therapy for 4 yeas before entry in the study in other hospital. Delay of initiation of CsA therapy would prevent her catch-up growth. In contrast, a 14-year-old boy (No. 3) showed an excellent catch-up growth on CsA treatment, suggesting that the reduction in steroid dose owing to low-dose CsA prevented growth retardation, and 13-year-old boy (No. 7) also showed catch up height growth and reached 160 cm of height.

As to the relapse of nephrotic syndrome, high dose CsA administration (5 mg/kg or more) can induce complete remission in most cases with steroid sensitive nephrotic syndrome during the period of CsA treatment[2, 4, 9]. Modified method by Inoue et al[10], described above, complete remission could be obtained in 54% of their patients on CsA treatment. In all our patients on low-dose CsA treatment, relapse occurred, indicating that it was difficult to maintain complete remission of nephrotic syndrome with low-dose CsA alone. Although these reports suggest that CsA could prevent the relapse of nephrotic syndrome dose-dependently, Kano et al[11]. showed excellent outcome with low-dose CsA. They performed 2-year administration of CsA to 14 children with steroid-dependent nephrotic syndrome at a low dose (1.6 – 3.1 mg/kg/day), and it effectively induced complete remission without prednisolone use. The reason of discrepancy of results between Kano's report and ours is not known. In their study, all patients had received cyclophosphamide therapy more than 6 months prior to CsA therapy. It is known that some patient with early steroid-resistant minimal change nephrotic syndrome will respond to cyclophosphamide and that subsequent relapses will even become steroid sensitive[12]. It might be neccessary to clarify whether the effects of CsA are influenced by cyclophosphamide or not.

We think that the low-dose CsA treatment was effective in all our patients. The trough level of CsA was below 50 ng/ml in 5 of 7 patients. This suggested that trough level of CsA of 100 to 150 ng/ml were not necessary, when combined with glucocorticoid at low dose or dosing schedule which would not induce major side effects.

Increased dose of CsA is associate with the risk of

nephrotoxicity[13]. It is hypothesized that the constriction of afferent arterioles is a principal manifestation of nephrotoxicity of CsA[14]. The constriction of afferent arterioles thought to be took place through the activation of renin - angiotensin - aldosteron system. Many investigators had been reported that ACE - I could suppress CsA nephrotoxicity in animal models. Emmanuel et al. described that either losartan, an angiotensin II receptor antagonist, or enalapril could prevent the CsA - induced interstitial fibrosis in a salt - dependent rat model[15]. Ishikawa et al. reported the reduction of the renal cortical blood flow and the enlargement of the renin granules in the juxtaglomerular cells were caused by CsA administration in rat model. They proved that temocapril, an ACE - I, prevented the decrease of the renal cortical blood flow [16].

On the other hand, there is less number of reports describing about the clinical protecting effects of ACE - I against CsA nephrotoxicity. Hannedouche et al. treated 25 type 1 diabetes patients with CsA alone or CsA + enalapril. They reported that both CsA - induced decline in GFR and increase in blood pressure were prevented by concomitant using of enalapril, and concluded that chronic angiotensin converting enzyme inhibition could afford some degree of protection against CsA - induced renal dysfunction [17]. Hausberg et al. treated hypertension in renal allograft recipients with quinapril, an ACE - I, or atenolol, a β - blocker. They reported that, compared with atenolol, quinapril had no adverse effects on graft function, and suggested that the relative reduction in albuminuriain patients treated by quinapril could indicate a beneficial effect on long - term graft function[18]. In our patients, neither moderate nor severe nephrotoxicity due to CsA occurred, except for one patient (No.2) showing mild interstitial fibrosis (Fig. 2). It seemed that the decreased dose of CsA mainly contributed to the prevention of CsA nephrotoxicity in addition to the effect of enalapril protecting the kidney against CsA toxicity. However, remains to study the extent to which enalapril participates in reducing CsA nephrotoxicity.

Although we cannot draw a definitive conclusion from the present results obtained in a limited member of patients, we can safely say that CsA is clinically effective at doses (2.5 – 3.0 mg/kg) below its conventional dose in steroid - dependent nephrotic syndrome, and that it sufficiently reduce adverse effects of steroid and nephrotoxicity due to CsA itself decreases satisfactorily.

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