The Efficacy of Cyclosporin in Patients with Severe Atopic Dermatitis

Jong Hee Lee, M.D., Kyu Han Kim, M.D., Kyung Chan Park, M.D.,
Jin Ho Chung, M.D., Dae Hun Suh, M.D.

Department of Dermatology, Seoul National University College of Medicine, Seoul, Korea

Background: **Cyclosporin A (CsA), a potent immunosuppressant, has been reported to be effective in the treatment of severe atopic dermatitis (AD).**

Objective: **The aim of this study was to evaluate the efficacy and side-effects of CsA in Korean patients with severe AD.**

Materials and methods: **16 patients with recalcitrant AD took CsA for at least 6 weeks. Among them, 11 patients were followed up for more than 16 weeks. Initial dose was 5mg/kg/day (maximum 300 mg/day) and the dose was reduced according to their therapeutic responses. SCORAD (Scoring AD) was used to evaluate clinical efficacy of CsA. During the 1st month of therapy, the therapeutic efficacy and side-effects were evaluated every 2weeks and after 1 month, every month. We checked blood pressure and laboratory abnormalities including liver function test, blood urea nitrogen (BUN), creatinine (Cr) and urinalysis at each visit in addition to observing clinical adverse effects.**

Results: **Significant reduction of SCORAD was noted in 15 patients after 6 weeks of CsA therapy. Only one patient stopped CsA therapy because of the elevation of blood pressure. Three patients showed albuminuria, which disappeared after CsA dose reduction.**

Conclusion: **CsA can be used effectively and safely in severe Korean AD patients. Albuminuria seems to be a peculiar side-effect in Korean patients.**

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Key Words: Cyclosporin A, Therapeutic efficacy, Side-effects

Severe atopic dermatitis (AD) inevitably causes distress to patients and greatly impairs their quality of life[1,2]. In the treatment of AD, some individuals are resistant to conventional therapies or even more, develop unacceptable side-effects, which require an additional effective treatment modality. Cyclosporin A (CsA), a potent immunosuppressant, may be the treatment of choice in crisis interventions[2-4]. The aim of our study was to evaluate the therapeutic efficacy and side-effects of CsA in patients with AD refractory to other treatments including topical corticosteroids, oral antihistamines, thymopentin, and interferon gamma.

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Reprint request to : Kyu Han Kim, M.D., Department of Dermatology Seoul National University Hospital 28 Yongon-dong, Chongno-gu Seoul 110-744, Korea
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PATIENTS AND METHODS

1. Patient

Sixteen patients (M:F=10:6) with their ages ranging from 12 years to 43 years (Mean age $\pm$SD; 24.1$\pm$7.6), attending AD clinic at Seoul National University Hospital were enrolled. All the subjects had severe, disabling AD which were resistant to conventional therapies. Patients with hypertension, renal impairment, hepatic dysfunction, or history of malignancy were excluded from

our study.

2. Methods

1) Treatment schedules

The initial dose of CsA was 5mg/kg daily (maximum 300 mg/day), which lasted usually for 4-6 weeks and then slowly tapered generally by decreasing 1mg/kg/day every 2 weeks. Dose tapering schedule was adjusted according to the therapeutic responses. In cases of unwanted side-effects, the dose was reduced rapidly or the administration of drugs discontinued. Adjunctive therapeutic regimens including topical steroids and oral antihistamines were allowed during the course of CsA therapy.

2) Assessment of therapeutic efficacy

The therapeutic efficacy was monitored by evaluating SCORAD[5](Scoring AD) values at their base-line, 2 weeks, 4 weeks and 6 weeks, respectively. For 11 patients the follow-up period was extended to 16 weeks. SCORAD consists of 3 components and is defined as extent/5 + 7 x intensity /2 +subjective symptom. Disease extent (percent area involved) is estimated using the conventional 'rule of nines' . For disease intensity, the values consist of six clinical indices including erythema, edema/papulation, oozing/crust, excoriation, lichenification and dryness, with their scales ranging from 0 to 3. Subjective symptoms - pruritus and sleep loss for the last 3 days previous to visit - are assessed by a visual analog scale (0-10).

3) Safety Evaluation

During the 1st month of therapy, side-effects were evaluated every 2 weeks and after 1 month, every month. At each visit, subjects were questioned about adverse effects such as headache, tremor, hirsutism, gingival hyperplasia and GI discomfort. Blood pressure was also monitored along with laboratory work-ups of liver function test, blood urea nitrogen (BUN), creatinine (Cr), and urinalysis.

4) Statistical Analysis

Comparison of the SCORAD values at baseline with those after treatment was done by using Wilcoxon signed rank test. p-values less than 0.05 were regarded as statistically significant.

RESULT

One patient discontinued CsA therapy due to the elevation of blood pressure after the first 2 weeks of treatment. Fifteen patients were followed up for at least 6 weeks. Eleven patients were followed up for more than 16 weeks. In 15 patients there were no adverse effects such as the elevation of blood pressure, headache, tremor, hirsutism, gingival hyperplasia and GI discomfort, which are well known side-effects of CsA therapy. For laboratory work-ups, no abnormal laboratory findings were found in 12 patients. Three patients had to reduce the dose of CsA rapidly due to their (1+) albuminuria, which disappeared after dose tapering. However, serum creatinine levels of 15 patients were within normal limits and no patients showed 30% or more increase of creatinine levels comparing to the baseline levels.

SCORAD values of 15 patients at pretreatment (mean±SD; 55.0±20.9) were significantly higher than those at 6 weeks after treatment (mean±SD; 30.5± 16.0) (p=0.002). In comparing of SCORAD at pretreatment with those of 2 weeks, 4 weeks, and 6 weeks posttreatment, significant decreases were noticed at 2 weeks (p=0.035), at 4 weeks (p=0.001), and at 6 weeks (p=0.002), respectively (Table 1). In 11 patients with more than 16 weeks of follow-up, significant decrease of

Table1. Change of SCORAD values (mean ± SD) in AD patients treated with CsA

	0	2 wk	4 wk	6 wk[a]	8 wk	12 wk	16 wk[b]
SCORAD	55.0±20.9	43.9±13.8	32.4±12.1	30.5±16.0	26.0±15.1	23.8±13.8	20.8±13.3
Extent	50.9±30.9	41.3±28.5	29.8±18.5	25.3±22.2	23.4±22.9	14.6±11.7	15.4±14.3
Intensity	9.5±3.3	8.4±2.3	6.3±2.4	6.3±2.7	5.5±2.4	5.0±2.9	4.1±2.6
Subjective Symptom	10.9±5.6	7.0±5.6	4.9±4.5	4.9±4.4	4.3±3.9	3.4±4.1	2.5±3.4

[a]Data analysed in 15 patients

[b]Data analysed in 11 patients

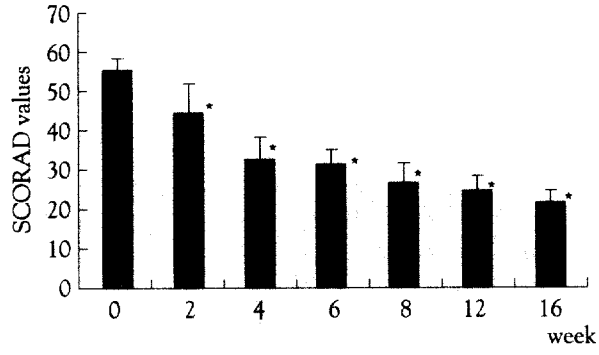

Fig. 1. Change of SCORAD values(mean±SD) in 11 patients according to the treatment period of cyclosporin A. *statistically significant compared to baseline level($p<0.05$).

SCORAD values from 55.2±22.2 at baseline to 20.8± 13.3 at 16 weeks was also noticed ($p=0.004$) (Fig.1). Although the overall SCORAD values decreased significantly 6 weeks after CsA therapy, the SCORAD values of 3 patients did not decrease significantly. In fact these 3 patients were not satisfied with CsA treatment at all.

At baseline, the mean body area affected by eczema was 50.9%. This decreased to 41.3% 2 weeks later, 29.8% 4 weeks later, and 25.3% 6 weeks later. These were all statistically significant ($p<0.05$). For 11 patients with 16 weeks follow-up, the extent of disease also showed statistically significant decrease 16 weeks after CsA therapy.

Further analysis revealed a significant decrease ($p<0.05$) both in the intensity and in the subjective symptoms (9.5 versus 6.3 in intensity, and 10.9 versus 4.9 in subjective symptoms). Subjective symptoms such as pruritus and sleep loss improved much. In comparison of the subjective symptoms at pretreatment with that at 6 weeks and at 16 weeks, statistically significant decrease was observed ($p<0.05$). All patients showed satisfaction especially with the decrease of pruritus. Even the patient who could not continue CsA therapy due to the elevation of blood pressure, was content with the reduction of pruritus when he visited 2 weeks after CsA therapy started.

DISCUSSION

In the 1980' s CsA was thought to be highly effective for the treatment of psoriasis and many inflammatory dermatoses as well as for the immunosuppression after an organ transplantation, especially kidney, and began to be used in severe psoriasis[6-8]. In the early 1990' s evidence was accumulating that CsA is beneficial in crisis intervention for AD[9-12]. Many studies have been performed about the efficacy of CsA on AD in adult and children patients. All reports revealed the efficacy of CsA in severe AD[11-14].

The mechanism of beneficial effect of CsA on AD is not clearly known. The main action of CsA is the inhibition of the activated T cells by blocking IL-2 production. In the skin lesions of AD, most of the infiltrated lymphocytes are CD4+ cells, and IL-2 receptors and HLA-DR are expressed on most of the CD4+ cells. Inhibition of the production of IL-2 by CsA makes the infiltrated T helper cells inactivated with the decreased production of IL-5 and the lesions of AD improved[15,16]. Another hypothesis of CsA effect on the AD is that CsA inhibits production of the pruritogenic cytokines and this reduces pruritus in patients of AD[17]. Thus itch of AD resolves and the lesions of AD improve. Some support the latter hypothesis but it is not known what exactly pruritogenic cytokines are. Others[18] showed evidences that CsA might exert its therapeutic efficacy by inhibiting mast cell activation and by affecting the interaction between mast cells and nerves.

This is the first report about CsA treatment in Korean patients with AD. In our study, almost all the patients with severe AD showed remarkable improvement both for the symptoms and severity index.

We must pay attention to nephrotoxicity of CsA in its use. Many reports[2,11] showed significant increase of serum Cr and this made reduction of the CsA dose. We did not find significant increase of Cr, but albuminuria was detected in 3 patients, which disappeared with dose reduction. Albuminuria was hardly mentioned in western reports. In Asia, there is only one report about CsA treatment in AD, which is a 3 patient-case report in China[19]. These cases also showed no elevation of BUN and Cr. Although there are very few reports in Asian patients, we thought the different pattern of CsA side-effects might exist between Asian and Caucasian patients. CsA is metabolized mainly in the liver and we know well cytochrome P-450 mediated metabolism is different between Asian and Caucasian[8]. In this context, there might be a different

side-effect profile in our patients, especially for the albuminuria. Except for albuminuria, CsA was generally well tolerated by our patients.

Another problem with the use of CsA in the dermatological field is its immunosuppression[8]. Until now, no specific side-effect associated with immunosuppression has been detected. As described above[8], CsA was initially used in renal transplantation as an immunosuppressive agent. When used in renal transplantation, its dose is 15 mg/kg/day. The dose of CsA used in AD is much smaller, usually 5mg/kg/day. Eczema herpeticum and other skin infections are more common in AD patients than in normal subjects, but during or after CsA treatment, there were no reports that the prevalence of infectious disease actually increases in AD patients. The potential hazard of developing malignancy by immunosuppression has not been confirmed. The history of using CsA in AD was short, only about 10 years. So its long term side-effects have not been established yet.

Our study showed that CsA can be used effectively and safely in severe Korean AD patients. Our study also suggested that side-effects might be different between Caucasian and Asian. More studies with more patients and longer follow-ups should be needed.

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