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ORIGINAL ARTICLE

Cyclosporin Treatment of Atopic Dermatitis: Is It Really Associated with Infectious Diseases?

Shin Woo Kim, M.D., Young Woon Park, M.D., In Ho Kwon, M.D.[1], Kyu Han Kim, M.D.

Department of Dermatology, Seoul National University College of Medicine, Seoul, [1]Hallym University College of Medicine, Anyang, Korea

Background: Patients with severe atopic dermatitis (AD) can benefit from cyclosporin (CSA) treatment. Some studies reported that CSA can cause infectious diseases as side effects. **Objective:** To investigate the possible association of CSA treatment in AD patients with infectious diseases. **Methods:** We performed a case-controled study on 202 patients with AD, 101 of whom were taking CSA and 101 who were not. Retrospective medical record review was held, and the incidence of infectious disease in both groups was compared. **Results:** The total number of infectious diseases in the CSA group was slightly lower than in control group but that was not statistically significant. Similarly, the incidence density was almost the same in the two groups. In both groups, eczema herpeticum was the most common infection. **Conclusion:** Our results suggest that CSA therapy in AD does not increase the incidence of infectious disease. **(Ann Dermatol 22(2) 170～172, 2010)**

-Keywords-
Atopic dermatitis, Cyclosporin, Infectious disease

INTRODUCTION

Atopic dermatitis (AD) is a pruritic disease of unknown origin which usually starts in early infancy; it is characterized by pruritus, eczematous lesions, dry skin, and lichenification. AD has enormous morbidity, and the incidence and prevalence appears to be increasing[1]. Although there is no cure for AD, it can be controlled under preventive measures and medical treatments. Treatment helps to stop the rash from recurring and controls itching. Generally, a combination of topical corticosteroid and moisturizers is used. Cyclosporine (CSA) is considered for treatment of patients with severe disease in whom conventional therapy is ineffective.

By inhibiting T-cell production of cytokines, CSA is demonstrated to be helpful in a variety of skin disorders. Several studies reported that the short-term use of CSA effectively decreases the severity of AD in patients for whom conventional topical therapies could not adequately control the course of their disease[2-4]. However, the treatment may be associated with a number of potential adverse events. Adverse events of CSA include nephrotoxicity, hepatotoxicity, high blood pressure, gastrointestinal symptoms, infections, paresthesia and headaches[5].

Herein, we focused on infectious diseases. In several studies, infectious diseases were observed in up to 1.5 per person-years of CSA treatment[6]. However, there is no case-control study regarding the influence of CSA on infectious diseases. The current study attempted to ascertain the association between CSA and infectious diseases, by reviewing the medical records of AD patients treated with CSA and those of controls.

MATERIALS AND METHODS

The medical records at Seoul National University Hospital from January 2000 through December 2008 were reviewed to identify AD patients who had been treated with CSA (cases). Patients who had been treated for more than 2 weeks were included, their age ranging from 10 to 50 years. Patients suffering from diseases other than AD and receiving any systemic immunosuppressive treatment ex-

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Corresponding author: Kyu Han Kim, M.D., Department of Dermatology, Seoul National University College of Medicine, 28 Yeongeon-dong, Jongno-gu, Seoul 110-744, Korea. Tel: 82-2-2072-2410, Fax: 82-2-747-0611, E-mail: kyuhkim@snu.ac.kr

cept CSA and anti-histamines were excluded from this study. The case group was composed of 101 patients, with a mean age of 26.7 years.

Controls included moderate-to-severe AD patients who were not treated with CSA. All controls were individually matched with cases for age and sex. Patients visiting our clinic continuously (shorter than 4 weeks intervals) for 3 months or more were included in the control group. Patients suffering from diseases other than AD and receiving any systemic treatment except anti-histamines were excluded. The mean age of the control group is also 26.7 years.

Relevant data collected included age, sex, treatment period of CSA (in case group), observation period (in control group), dose of CSA, and information about infectious diseases. The number of infectious diseases was counted, and the names recorded. Then, incidence density was calculated as a total number of infectious diseases/a total treatment or observation period (person-year). The study was approved by the Institutional Review Board at Seoul National University Hospital.

Statistical analysis

Analysis was carried out using the SPSS (version 15.0) software packages. A total number of infectious diseases and the incidence density of the CSA group were compared with those of the control group, according to the Mantel-Haenszel χ^2 test. All *p*-values were two-sided and $p<0.05$ was considered statistically significant.

RESULTS

The study included 101 patients and 101 controls. The male:female ratio of both groups was 1.89:1 (66:35). The total treatment period of CSA was 35.7 years and the average was 0.35 ± 0.2 years. Initial CSA dosages were in the range of 3 to 5 mg/kg body weight, and dosages were tapered, depending on the severity of the disease. The total observation period in the control group was 44.9 years, and the average was 0.44 ± 0.39 years.

As shown in Table 1, the total numbers of infectious diseases in cases and controls were 15 and 16, respectively.

Table 1. Comparison between cases and controls

	Cases (n=101)	Controls (n=101)
Total number of infectious diseases	15	16
Incidence density of infectious diseases (/person-year)	0.42	0.36

The total number of infectious diseases in controls was higher than that of cases, but the difference was not statistically significant. The incidence density of cases was higher than that of controls (0.42 per person-year vs. 0.36 per person-year), but the difference was also statistically insignificant.

Table 2 shows the classification of infectious diseases observed in this study. In both groups, eczema herpeticum was the most common infection. Only one non-skin infectious disease (tonsillitis) was detected in case group.

DISCUSSION

AD is a chronically relapsing skin disease; therefore, successful treatment of AD requires a systematic, multipronged approach, incorporating skin hydration, pharmacologic therapy, and identification and elimination of flare factors. In patients refractory to conventional forms of therapy, alternative anti-inflammatory and immunosuppressive agents may be necessary.

CSA is a potent immunosuppressive drug that acts primarily on T cells by suppressing cytokine transcription. Multiple studies demonstrated that patients with severe AD can receive benefit from short-term CSA treatment[2-4]. Meanwhile, some studies reported that CSA can cause infectious diseases as a kind of side effects[7-9]. Harper et al.[7] reported that one event (folliculitis) occurred in 40 patients treated with CSA, and Atakan and Erdem.[8] found 1 furuncle and 1 herpes labialis among the 22 patients in their study. Berth-Jones et al.[9] enrolled 65 patients and investigated the efficacy and safety of CSA over the course of 48 weeks. In their study, 48 infectious diseases (21 skin sepsis, 5 herpes simplex lesions, 4 warts and 18 non-skin infectious diseases) were reported. The previous studies only showed a link, not a causal relationship, between in-

Table 2. The classification of infectious diseases observed in the study

	Cases	Controls	Total
Skin diseases			
Eczema herpeticums	6	5	11
Herpes simplex lesions*	4	3	7
Superficial fungal infections	2	3	5
Cellulitis	-	3	3
Warts	1	1	2
Herpes zoster lesion	1	-	1
Folliculitis	-	1	1
Non-skin disease			
Tonsillitis	1	-	1
Total	15	16	31

*Excluding eczema herpeticum.

fectious diseases and CSA. Furthermore, there was no study comparing AD patients treated with CSA with controls. As a result, we do not know if CSA really increase the incidence of infectious diseases.

At first thought, CSA seemed to induce infectious diseases because CSA inhibits the transcription of interleukin 2 and several other cytokines, leading to an inhibition of the activation of T cells. However, we found almost the same incidence of infectious diseases in controls and cases, and the difference in incidence is not statistically significant. We do not believe that infectious disease is not a possible side effect of CSA, however, AD can be complicated in itself by various skin infections that may reflect local defects in the function of T cells, especially when AD is severe. CSA reduces disease severity significantly, and it is conceivable that CSA may also accordingly lower the possibility of skin infections in AD.

There are some limitations to the study. Firstly, it is a retrospective study, leading to the second limitation: there is a chance we missed some actual infectious diseases which were not recorded in medical charts (not noted by the medical staff nor mentioned by the patients). Further, we could not conduct laboratory tests for all patients to confirm the said infectious diseases. Lastly, there is still a chance we misdiagnosed.

In conclusion, this is the first case-control study regarding the influence of CSA on infectious diseases. Our results suggest that CSA therapy in AD does not increase the incidence of infectious disease. However, a prospective double-blind controlled study, including a long-term follow-up would be necessary to confirm these results.

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