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Importance of concomitant topical therapy in moderate-to-severe atopic dermatitis treated with cyclosporine

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ABSTRACT: Cyclosporine (CS) is widely used in patients with refractory atopic dermatitis (AD). During CS treatment, many patients have a tendency to decrease their adherence to topical agents as their disease improves. Our aim was to compare the efficacy and relapse rate of CS treatment combined with topical therapy and CS monotherapy. This prospective, randomized, 6 month study involved 60 patients with moderate-to-severe AD who were randomly assigned to two groups, one receiving CS and topical agents and the other, CS only. Clinical outcomes were based on investigators' global assessment (IGA) scores, eczema areas and severity index scores, and trans-epidermal water loss. If a patient achieved treatment success (IGA score ≤ 2) during the study period, CS was stopped. Relapse rate and time to relapse were evaluated during the 3 months after discontinuation of CS. The treatment success rate was significantly higher in the combination group ($p = 0.028$). The combination group had a shorter median time to response ($p = 0.040$), a lower cumulative dose ($p = 0.041$), and a longer time to relapse ($p < 0.01$) than the monotherapy group. Although CS monotherapy is effective against AD, topical agents should be used concomitantly.

KEYWORDS: atopic dermatitis, cyclosporine, eczema, therapy – topical, topical agents

Introduction

Atopic dermatitis (AD) is an inflammatory skin disease characterized by severe pruritus and a chronic relapsing course. Topical agents including corticosteroids and calcineurin inhibitors are the mainstays of treatment regardless of clinical severity. In the case of patients with severe recalcitrant AD, cyclosporine (CS) is now commonly used (1).

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CS, which selectively inhibits T-cell activation, is an effective systemic medication for moderate-to-severe AD. In addition to inhibiting T-cell activation, CS inhibits keratinocyte hyperproliferation and release of histamine from mast cells. Also, CS down-regulates the expression of adhesion molecules on capillary endothelium in the dermis (2). As the atopic lesions improve during CS treatment, patient adherence to topical treatment often decreases. However, evidence concerning the influence of topical agents in addition to systemic treatments is limited.

The aim of this study was to evaluate the importance of topical treatment concomitant with CS in

moderate-to-severe AD patients. We compared the treatment efficacy, relapse rate after cessation of CS, and safety profile between the combination treatment group and the CS-only group.

Methods

Patients

This study was conducted with 60 patients who visited the Department of Dermatology of Hanyang University Hospital in Korea between March 2013 and March 2014. Patients of any age diagnosed with moderate-to-severe AD (eczema area and severity index (EASI) score ≥ 16) were enrolled (3). A washout period of up to 4 weeks was required for patients taking oral medication, and up to 2 weeks for patients receiving topical medication. The main exclusion criteria were: (i) receipt of other systemic treatments (systemic immunosuppressive therapy, antibiotics, phototherapy, etc.); (ii) uncontrolled chronic disease (diabetes mellitus or hypertension); (iii) other clinically relevant systemic diseases (abnormal renal or liver function, history of malignancy, etc.); (iv) pregnancy or lactation. The study was approved by the Institutional Review Board of Hanyang University Hospital, and informed consent was obtained from all participants.

Study design

This prospective, randomized study consisted of two phases. The first phase lasted up to 6 months to evaluate the treatment success rate during CS treatment. Patients visited the outpatient clinic every 2 weeks for the first month and every 4 weeks for the following 5 months until they achieved treatment success. The second phase was the following 3 months to assess relapse rate in patients who achieved treatment success during the first phase.

The patients were randomly assigned to two groups. The combination group (group A) was treated with oral CS and topical agents, while CS monotherapy group (group B) was treated with oral CS only. The topical agents used in group A were medium potency topical corticosteroids (methylprednisolone aceponate, Topisol[®], Kolon Pharma, Korea) on the trunk and extremities, or topical calcineurin inhibitors (0.1% tacrolimus ointment, protopic[®], Astellas Pharma, Japan) on the face. The patients were instructed to apply these topical medications twice a day until the lesions improved. Application of the same moisturizer twice a day was permitted throughout the study period in both groups. All patients began on

a CS dose of 4–5 mg/kg per day (Cipol-N[®], 100 mg, 25 mg/cap, Chongkundang, Korea), which could be tapered by 1–1.5 mg/kg at each visit according to treatment response. All patients were instructed to take CS before meals to enhance the absorption and efficacy of CS.

Treatment success was defined as investigators' global assessment (IGA) score of 2 or less (4). IGA was scored from 0 to 5 based on investigators' assessment of patients' skin (0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe; 5, very severe disease) (5). CS treatment was discontinued if patients achieved treatment success at any time during the first phase. After discontinuing CS, the patients were observed for 3 months after cessation of CS (the second phase). During the second phase, the patients in both groups used topical agents intermittently when skin lesions appeared. Oral antihistamine and γ -linoleic acid were permitted, if necessary, throughout the study period in both groups.

Assessment of clinical outcomes

Clinical outcomes were based on IGA scores, EASI scores, and trans-epidermal water losses (TEWL) at each visit. IGA scores and EASI scores were evaluated by independent, blinded, dermatologists.

EASI scores were based on severity of erythema, swelling, abrasion, and lichenification in four different body parts (head and neck, upper extremity, trunk, and lower extremity) (3). TEWL was measured twice on the antecubital fossa in a climate-and-humidity-controlled room (room temperature 20–24°C; humidity 28–38%). The average of the measurements was reported.

Assessment of adverse effects and relapse

Possible adverse effects such as headache, hypertrichosis, infection, dizziness, and so forth were checked at each visit, as was blood pressure. Laboratory tests, including complete blood cell count, liver function test, kidney function test, electrolyte levels, and urine analysis were performed initially at 4 weeks and every 12 weeks thereafter. Relapse was defined as an IGA score of 3 or more and was assessed during the second phase of the study (4).

Statistical analysis

All analyses were performed using the statistics program SPSS package ver. 21.0. Differences between the two groups in median time to response, cumulative dosage, and time to relapse were analyzed using the independent samples *t*-test and the

Table 1. Baseline demographic data for the two groups

	Group A (n = 30)	Group B (n = 30)	p-value
Age (years)	22.63	23.43	0.767
Sex			
Male	15 (50.0%)	19 (63.3%)	0.297
Female	15 (50.0%)	11 (36.7%)	
Duration of disease (years)	5.47	5.97	0.655
Initial EASI	22.45	24.41	0.066
IgE (IU/mL)	1738.12	1919.88	0.404
Eosinophil count	459.48	406.03	0.647

EASI, eczema area and severity index.

Mann–Whitney test. The chi-square test and Fisher's program SPSS package ver. 21.0. Differences, adverse effects, and rates of treatment success, and repeated measures ANOVA was used to compare EASI scores. A *p* value ≤ 0.05 was considered statistically significant.

Results

Demographic data

A total of 60 patients were enrolled. Group A comprised 15 males and 15 females with a mean age of 22.6 years. Group B comprised 19 males and 11 females with a mean age of 23.4 years. There were no statistically significant differences between the groups in terms of age, sex, duration of disease, initial EASI score, total serum IgE level, or serum eosinophil count. The demographic characteristics of the patients are summarized in Table 1.

Comparison of the clinical efficacy of CS monotherapy and combination treatment

Treatment success rates. The patients who dropped out due to lack of compliance (group A: *n* = 2, group B: *n* = 1) and adverse effects (group A:

n = 1) were excluded from analysis of treatment success rate. The average daily dosage of CS during the first 4 weeks was 3.61 mg/kg/day (group A: 3.54 mg/kg/day, group B: 3.68 mg/kg/day). In group A, 27 patients finished the study protocol, 23 (85.2%) of whom achieved treatment success during the first phase of the study. In group B, 17 (58.6%) of 29 patients achieved treatment success during the first phase. The difference in the rate of treatment success between the groups was statistically significant (*p* = 0.028).

Median times to response and cumulative dosages. In group A, 23 patients achieved treatment success, after a mean treatment duration of 12.1 ± 5.7 weeks; in group B, 17 patients achieved treatment success, after a mean treatment duration of 16.1 ± 6.1 weeks (*p* = 0.040; Table 2). The largest number of patients achieved treatment success between the 6th and 12th week in group A, and between the 18th and 24th week in group B. The distributions of numbers of patients who achieved treatment success according to the treatment period are shown in FIG. 1A.

The mean total cumulative dose for patients who achieved treatment success was 235.1 ± 121.8 mg/kg in group A, and 319.54 ± 129.18 mg/kg in group B (*p* = 0.041; Table 2).

EASI scores and TEWL in successfully treated patients. In both groups, the mean EASI scores of successfully treated patients showed statistically significant decreases after treatment success compared to the baseline (*p* < 0.01, respectively). The difference in the reductions in EASI scores between the two groups was not statistically significant (*p* = 0.136).

Also, for both groups, there was a statistically significant decrease in TEWL after treatment (*p* < 0.01, respectively). The TEWL of group A showed more significant reductions than those of group B (*p* = 0.041; FIG. 1B).

Table 2. Treatment response and relapse in the two groups

		Group A (n = 23)	Group B (n = 17)	p-value
Efficacy	Median time to response (weeks)	12.13	16.12	0.040*
	Cumulative dosage (per weight, mg/kg)	235.13	319.54	0.041*
Relapse	Relapse rate	6/23 (26.09%)	9/17 (52.94%)	0.083
	Time to relapse (weeks)	10.67	6.22	<0.01*

*(*p* < 0.05).

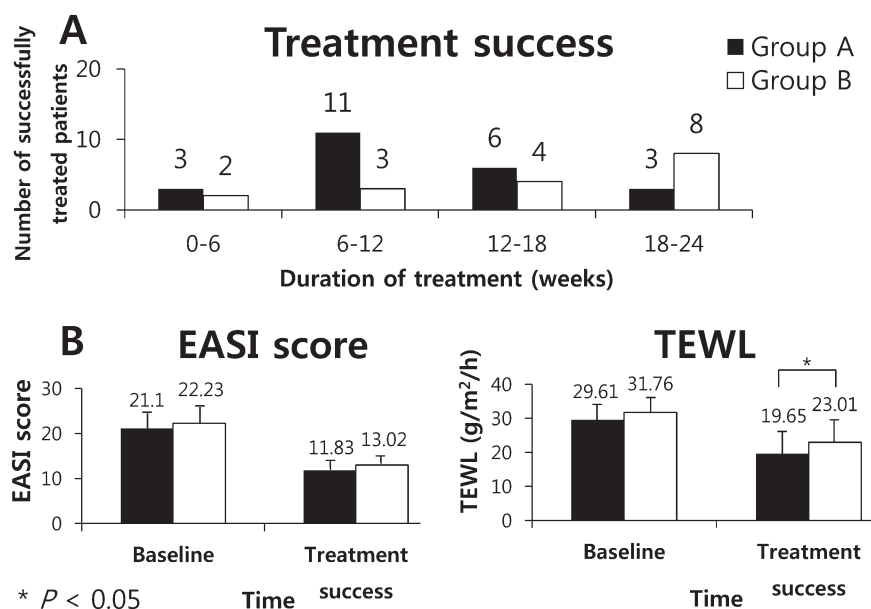


FIG. 1. (A) Numbers of successfully treated patients according to treatment duration. (B) Changes in EASI scores and TEWL in successfully treated patients.

Relapse rate and time to relapse. The 40 patients who achieved treatment success were followed up for 3 months after discontinuation of CS (the second phase). Relapse occurred in 6 of 23 patients (26.1%) in group A after a mean duration of 10.67 weeks, and in 9 of 17 patients (52.9%) in group B after a mean duration of 6.22 weeks. There was a statistically significant difference between the two groups in the time to relapse ($p < 0.01$), but not in the relapse rate ($p = 0.083$; Table 2).

Adverse effects

There were 17 adverse events (group A: 8, group B: 9) associated with CS. Most were mild and resolved after reduction of dosage or discontinuation of CS. One patient developed a severe abscess on the hip after 3 months of treatment and CS was stopped. Meanwhile, adverse event related to topical agents was not reported. There was no significant difference in adverse effects between the two groups.

Discussion

Topical treatments including corticosteroids and calcineurin inhibitors have been the mainstay of therapy for AD for many years. The issue of patient compliance with topical agent treatment is especially significant in AD, which is a chronic inflammatory skin disorder. Several complicated factors, including treatment response and steroid phobia, may result in nonadherence and unsatisfactory treatment (6). Furthermore, the increase

of using CS which is relatively effective and safe may be a factor for decreasing adherence to topical agent regimens.

According to the American Academy of Dermatology Guidelines for Care committee, CS is recommended for the treatment of severe and refractory AD (7). Most patients improve significantly within 2–6 weeks of starting CS treatment (2), and, in fact, rapid improvement can actually induce nonadherence to topical agent regimens. Similarly, previous reports showed that patients with AD or psoriasis adhere better to oral treatment than to topical treatment (8,9). One of the reasons might be patient faith in CS efficacy. When the patients who were resistant to topical monotherapy improved during CS treatment, they tended to attribute the success to CS efficacy and misunderstand the necessity of topical therapy. Another reason might be the difference in convenience between oral and topical treatments. However, no reports have addressed the importance of concomitant topical treatment in AD patients receiving CS treatment.

In the present study, we compared the efficacy, relapse rate, and safety of combination CS and topical treatment (group A) with those of CS monotherapy (group B). Although both groups improved clinically, the treatment success rate was higher among patients who also received topical agents in addition to CS (group A). Furthermore, four patients in group B did not improve clinically during CS treatment despite increasing the dose. Because topical corticosteroids and calcineurin inhibitors exert anti-inflammatory effects by

reducing epidermal hyperproliferation (1), they might provide effects additional to those stemming from CS treatment. These effects of topical corticosteroids might also be responsible for the difference of reduction in TEWL between the two groups of successfully treated patients. This suggests appropriate short-term treatment with topical corticosteroids not only improves inflammation, but also normalizes skin barrier function (10–12). However, prolonged and continuous use of topical corticosteroids can induce skin barrier abnormalities and increase TEWL (13). In contrast to the observed TEWL differences, reductions in EASI scores were not significantly different between the two groups of successfully treated patients.

In addition to clinical efficacy, there were differences in median time to response and cumulative dosage between the two groups. One possible reason for these differences was the difficulty of reducing the CS dose in group B. As a result, a longer duration of CS and a higher dose may have been required because of a relative lack of efficacy. Topical treatment not only overcomes some of the drawbacks of CS dose reduction, but also reduces the median time to response and cumulative dose of CS.

Another aim of this study was to investigate whether combining CS with topical agents would prolong remission. Because discontinuation of CS may result in rapid relapse of AD, treatments that can reduce the relapse rate and median time to relapse are important (1). In this study, relapse occurred in 15 of the 40 (37.5%) patients in both groups. This relapse rate was lower than in a number of other studies (14–17). According to Granlund et al., (14) recurrence was observed in 80% of patients by 6 weeks after discontinuation of CS treatment. Because the criteria for recurrence varied between studies, it is difficult to compare our relapse rate directly with those in other studies. Some previous studies defined relapse as a greater than 75% increase in severity compared to baseline score or when the investigator or patient felt that further systemic therapy was required (14–16). In our study, we defined relapse as an IGA score of 3 or higher. Although we used a different method of evaluating relapse, the definition was similar to that in previous studies in terms of the condition of requiring systemic therapy. Although the actual relapse rates were not significantly different between the two groups, we found a significantly higher “time to relapse” in group B than in group A. Because of our small sample size, a larger randomized study will be needed to compare relapse rates more adequately.

Overall, the adverse events in our study were smaller in number and milder than those in other reports (18). We found that 30.4% (17/56) of patients experienced adverse events associated with CS treatment. Adverse events related to topical agents have not been reported. Gastrointestinal symptoms including dyspepsia, nausea, and abdominal pain were the most common adverse events in our study, and this result agrees with the previous report (19). Except in the case of one severe abscess, most of the adverse events were mild, and were reversed after dosage reduction or discontinuation of CS. One patient in group A developed a severe abscess on the hip after CS treatment. This might have been related to CS treatment because the patient not only had no history of previous abscess, but also experienced no recurrent episodes after discontinuation of CS. However, when considering that the patient was an immunocompetent young man, it was difficult to confirm a direct association between abscess and CS treatment.

One of the limitations of our study is the small number of patients and the limited duration of follow-up. The observational periods in previous reports ranged from 3 to 24 months (14–17). Although our observational period was relatively short compared with other studies, a 3-month follow-up seemed sufficient because relapse was most likely to occur in the first 6 weeks. Another limitation is the absence of a vehicle-only placebo for the topical corticosteroids and calcineurin inhibitors to reduce bias. Nevertheless, it might be difficult to evaluate the additive effect of topical agents when using a placebo, because the vehicle of the placebo might also have a moisturizing effect. Therefore, this study design was appropriate to evaluate the pure additive effects of topical agents during CS treatment.

This is the first study to evaluate the clinical importance of concomitant topical agents in the CS treatment of AD patients. We conclude that topical treatments can reduce the duration of CS treatment and cumulative dose, and also achieve better clinical results and more prolonged remission. Therefore, it is indicated for dermatologists to encourage and educate patients about the importance of maintaining treatment with topical agents.

Conflicts of interest

None.

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