Tacrolimus ointment; An Open study for Effects on Severe Facial Atopic Dermatitis in Korean

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Background: In recent studies, tacrolimus ointment has been shown to be effective for the treatment of atopic dermatitis with an excellent safety profile.

Objective: This study was done to assess the efficacy and side-effects of tacrolimus ointment for the facial atopic dermatitis (AD) in Korean.

Patients and methods: Open-label, non-comparative study with 2 months’ follow-up was done to assess the efficacy and safety of tacrolimus ointment (Protopic® ointment 0.1%, Fuji-sawa, Japan) in moderate to severe facial AD. Patients were instructed to apply it two times daily for 8 weeks. Facial lesions were evaluated at baseline, 4 and 8 weeks of treatment with intensity score by investigator.

Results: In comparing of intensity scores and each clinical score at baseline with those of 4 and 8 weeks of treatment, a significant decrease was noticed at all follow-up periods. Burning sense (54.5%) and pruritus (18.2%) were detected.

Conclusion: Tacrolimus ointment is effective in treatment of severe facial AD and has tolerable mild adverse effects at the site of application in Korean.
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Key Words: Atopic dermatitis, Tacrolimus

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease. Especially facial erythema in AD seriously impairs quality of life in these patients. But topical mid- to high-potency corticosteroids should not be used regularly on the face, neck, and intertriginous areas due to side effects such as skin atrophy, telangiectasia, acne and striae. It is difficult to choose proper treatment in facial AD refractory to topical steroids.

Topical formulation of tacrolimus, a macrolide calcineurin inhibitor, has recently been developed. This study was performed to assess the efficacy and side-effects of tacrolimus ointment for the facial AD in Korean.

PATIENTS AND METHODS

1. Study design and patient selection
Open-label, non-comparative study with 2 months’ follow-up was done to assess the efficacy and safety of tacrolimus ointment in facial AD with moderate to severe degree.

AD patients with moderate to severe facial eczema attending AD clinic at Seoul National University Hospital were enrolled in this study. All patients fulfilled Hanifin and Rajka's criteria for AD, and had refractory facial lesions which were resistant to conventional topical steroid therapies for several years.

The study consisted of a baseline visit before treatment, 4 and 8 weeks after treatment initiation. Facial lesion was evaluated with intensity score by investigator. Tacrolimus ointment (Pro-
Table 1. Changes of intensity scores and each clinical signs at baseline, 4-weeks, 8-weeks of treatment (mean ± SD).

<table>
<thead>
<tr>
<th></th>
<th>Baseline (mean ± SD)</th>
<th>4-weeks (mean ± SD)</th>
<th>8-weeks (mean ± SD)</th>
<th>*p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity</td>
<td>11.52 ± 2.8</td>
<td>6.11 ± 0.5</td>
<td>4.82 ± 2.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Erythema</td>
<td>2.94 ± 0.2</td>
<td>1.17 ± 0.6</td>
<td>0.94 ± 0.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Edema</td>
<td>1.52 ± 0.5</td>
<td>0.88 ± 0.5</td>
<td>0.76 ± 0.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Oozing/crust</td>
<td>0.94 ± 0.9</td>
<td>0.23 ± 0.4</td>
<td>0.05 ± 0.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Excoriation</td>
<td>1.88 ± 0.9</td>
<td>0.64 ± 0.7</td>
<td>0.41 ± 0.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lichenification</td>
<td>1.94 ± 0.6</td>
<td>1.47 ± 0.7</td>
<td>1.17 ± 0.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Dryness</td>
<td>2.29 ± 0.7</td>
<td>1.7 ± 0.7</td>
<td>1.47 ± 0.5</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

(*p-value: compared to baseline, Wilcoxon signed rank test)

Fig. 1. Change of the intensity scores and index clinical signs (mean ± SD) in 17 patients, who completed the 8-weeks of treatment, according to the follow-up periods; A, the intensity score. B, each score of index clinical signs. At all follow-up periods, statistically significant decreases were observed (p-value < 0.01).

topical® ointment 0.1%, Fujisawa, Japan) was applied twice daily to the areas of facial lesion. Patients were instructed to continue application for 8 weeks. In Korea, tacrolimus ointment was commercially not available. So all patients ordered the ointment via on-line pharmacy (www.internationalpharmacy.com). During the study, patients were allowed to take oral antihistamines and apply topical corticosteroids to other body areas.

2. Assessments
Facial lesions were evaluated at baseline, 4 and 8 weeks of treatment with intensity score by investigator. Intensity score was sum of the clinical scores for each clinical sign such as erythema, edema, oozing/crust, excoriation, lichenification and dryness. Each clinical sign was scored as 0(clear state), 1(mild state), 2(moderate state), and 3(severe state). At each visit, subjects were questioned about adverse effects.

3. Statistical analysis
Comparison of the intensity scores at baseline with those at 4-weeks, 8-weeks of treatment was done by using Wilcoxon signed rank test. P-value less than 0.01 was regarded as statistically significant.

RESULTS

1. Summary of patients
A total of 33 patients (18 males and 15 females; age range 18-45 years; mean age 27.6 years old)
were enrolled. Seventeen patients completed 8-weeks of treatment, and 15 patients completed 4-weeks of treatment. One patient discontinued tacrolimus ointment therapy at first week of treatment due to the irritation whenever it was applied.

At baseline, intensity score range was 8 to 17 (11.5±2.4, mean±SD).

2. Efficacy of tacrolimus ointment.

For the assessment of efficacy, we analyzed the data of the patients who completed 8-weeks of

Fig. 2. Representative clinical pictures taken at baseline and 4-weeks of treatment in two patients; A, the clinical pictures of 26 years old man showed that facial erythema significantly decreased after 4-weeks of treatment.; B, the clinical pictures of 19 years old woman showed that inflammatory changes (edema, oozing/crust, and excoriation) in addition to erythema markedly decreased after 4-weeks of treatment.
treatment. In comparing of intensity scores at baseline with those of 4-weeks and 8-weeks of treatment, significant decrease was noticed for all follow-up periods. And in the scores of each clinical sign, significant decrease was also noticed for all follow-up periods (Table 1).

The mean intensity score rapidly decreased after 4-weeks of treatment and slowly decreased in next 4 weeks (Fig. 1A). The mean scores of erythema, oozing/crust, and excoriation relatively rapidly declined after 4-weeks of treatment (Fig. 1B). It was well correlated with clinical features (Fig. 2).

3. Adverse effects.
In 54.5% of the patients (18/33), burning sense was observed. Pruritus was observed in 18.2% of the patients (6/33). But intensity of burning sense and pruritus was mild. These degrees were most severe during a few hours of first application and then decreased. Four cases had mild burning sense lasting for one day. One case had severe burning sense and irritation whenever the ointment was applied on facial lesion and this patient was excluded from the study. After 8-weeks of treatment, burning sense and pruritus were not observed. One patient experienced folliculitis.

DISCUSSION

Tacrolimus ointment has been shown to be effective for the treatment of atopic dermatitis and to have an excellent safety profile in recent studies2-7. Tacrolimus is a 23-member macrolide produced by Streptomyces tsukubaensis, a fungus found in the soil of Mount Tsukuba, Japan1. Tacrolimus, formulated for the treatment of atopic dermatitis, is the first in a class of topical immunomodulatory therapeutic agents. Its mechanism of action is based on competitive inhibition of calcineurin by tacrolimus-immunophilin complex which results in suppression of the T lymphocytes, especially CD4+ cells, and on inhibition of the promoter regions of the genes for the inflammatory cytokines which participate in the early immune response and are postulated to play a role in atopic dermatitis pathogenesis8. Tacrolimus may inhibit the release of mast cell preformed mediators, downregulate interleukin-8 receptor expression, decrease intercellular adhesion molecule-1 and E-selectin expression of lesional blood vessel, and downregulate FcεRI on Langerhans cells9,10. This broad range of inflammatory inhibition mechanisms may decrease antigen recognition and downregulate the entire inflammatory cascade leading to clinical improvement11. Recently, the clinical improvement of AD lesions treated with tacrolimus ointment was accompanied by a reduction in the stimulatory activity of epidermal dendritic cell(DC), phenotypic changes in both the Langerhans' cell and inflammatory dendritic epidermal cell (IDEC) populations of the epidermal DC infiltrate, and a decrease of the IDEC population within the pool of CD1a+ epidermal DCs12,13.

This study demonstrated that treatment with tacrolimus ointment had significant beneficial effects on the refractory facial lesion of AD patients, who were resistant to the conventional topical steroid therapies for a few years in Korean. Improvement in facial lesion was evidenced by statistically significant decrease of intensity score and each score of index clinical signs. And rate of improvement in clinical signs, such as erythema, edema, oozing/crust, excoriation, lichenification and dryness, was grossly rapid compared with conventional therapy. Especially, the erythema, excoriation, oozing/crust decreased most rapidly at 4-weeks.

The erythema score declined rapidly after 4-weeks of treatment and then slowly until 8-weeks of treatment. After 8-weeks of treatment, 23.5%(4/17) of the patients had the clear state of erythema. We suggest that short-term use of tacrolimus ointment showed excellent results with facial erythema of atopic dermatitis in adult patients and effect on the erythema was rapid compared with conventional topical corticosteroid therapy. At a concentration that had an efficacy similar to that of 0.13 percent clobetasol propionate (a superpotent corticosteroid that causes atrophy) in treating an inflammatory reaction in pig skin, topical tacrolimus did not cause atrophy14. However, therapeutic efficacy was slightly reduced after continuous use of the ointment for 2 months. Tacrolimus ointment was less effective on the lichenification and the dryness than other clinical signs.

In our study, most common local side effect was burning sense (54.5%), and pruritus (18.2%). In recent studies, incidence rates of burning sense and pruritus were reported 34-58% and 19-46% respectively14,11. But intensities of burning sense and
pruritus were mild, and durations were a few hours to a day. So the local side effects rarely required discontinuation of treatment. Only one patient stopped the use of ointment for local irritation in every application. In one patient, folliculitis was detected.

In conclusion, tacrolimus ointment is effective in the treatment of severe facial AD and has tolerable and mild adverse effects at the site of application in Korean. It is necessary to follow up more patients and to get data on the safety for a longer period.

REFERENCES