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Treatment of Lichenified Atopic Eczema with Tacrolimus Ointment

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Sir,

At present, topical corticosteroids are the mainstay for treatment of atopic dermatitis. In long-term use, however, corticosteroids induce tolerance and some patients may become allergic to these steroids (1). Areas such as lichenified lesions may be resistant to corticosteroid treatment. The atrophogenicity of corticosteroids further limits their use on areas of the skin that are thin, such as the face and neck and flexure regions.

Tacrolimus ointment is the first potential new topical therapy for atopic dermatitis since the introduction of corticosteroids some 40 years ago. Short-term studies in adults and children have shown that tacrolimus ointment is effective and safe in the treatment of atopic dermatitis (2–9). Unlike topical corticosteroids, tacrolimus ointment does not cause skin atrophy (10).

In atopic dermatitis itch, erythema and vesiculation are the first symptoms and signs showing response to treatment, while lichenification takes more time to heal. In the present placebo-controlled, randomized study, we assessed whether 0.1% tacrolimus ointment is also effective on lichenified lesions. We also wanted to measure the effect of tacrolimus on the barrier function in flexure regions, which are vulnerable to thinning and atrophy, when treated with potent topical corticosteroids. Consequently, lichenified elbow flexure regions were selected for treatment.

PATIENTS AND METHOD

Atopic dermatitis patients aged 18 to 60 years were eligible for entry. Patients were required to have a confirmed diagnosis of moderate to severe atopic dermatitis according to Rajka & Langeland (11). Patients had to have a lichenified area on each elbow flexure region of at least 12 cm^2 and with a lichenification score of at least 2 on a scale from 1 to 3. Patients were allocated 0.1% tacrolimus or a vehicle control (tacrolimus ointment base) based on a 1:1 randomization for a treatment period of 2 weeks. Patients were instructed to apply the ointment to the selected treatment area of the elbow flexure twice daily, with each application separated by about 12 h. The investigator, patient, and study monitor were unaware of the treatment allocation. No concurrent treatment other than emollients or bath oil was allowed during the study.

Assessment was done at baseline and after 3 to 4 days, 7 days and 14 days of treatment and 14 days post-treatment. The investigator graded the treated areas on a scale of 0 to 3 for the severity of erythema, oedema, oozing/crust, excoriation and lichenification of involved skin, and dryness of non-involved skin. The patient graded pruritus of the selected treatment area on a 10-cm visual analogue scale. The primary efficacy endpoint was the change in the combined score for pruritus, erythema, oedema, oozing/crust, excoriation, and lichenification of involved skin, dryness of non-involved skin and pruritus. The pruritus grading was converted to an ordinal scale of 0 to 3 before being added to the combined score. The extent of affected skin at the elbow regions was measured at the same intervals. At the end of the treatment phase, a global assessment of the treated area was made (completely resolved, markedly improved, moderately improved, slightly improved, no change, or worse).

Transepidermal water loss (TEWL) was measured at the treated elbow flexure as described previously (12), and superficial blood flow was measured using a laser Doppler flowmeter (Periflux PF3, Perimed, Sweden). Measurements were taken on days 3, 7, 14 and 28. Skin thickness (the distance between the stratum corneum to lower dermis) of treated lichenified elbow regions was measured with a high-frequency ultrasound device (DUB20-S, taberna pro medium, Lüneburg, Germany) (13). Purified water was used as the transmitting medium for the ultrasound, at a frequency of 30 MHz. The skin thickness was assessed as the average of 4 measurements taken at 1 mm intervals.

Percentage changes between baseline and days 7, 14 and 28 were calculated for each patient. Descriptive statistics are based on these values. Treatment group comparisons were made using the Wilcoxon rank sum test.

RESULTS

Of 16 patients screened, 14 were randomized to receive either 0.1% tacrolimus (6 patients) or vehicle control (8 patients). No major differences in demographics or baseline characteristics of the patients were seen between the groups.

The percentage decrease in the combined symptom score between baseline and the end of the treatment period was significantly greater in the 0.1% tacrolimus group (68.5%) than in the vehicle control group (13.4%) ($p = 0.002$). The difference

in reduced itch was even more pronounced, with a decrease of 80% in the tacrolimus group, but with no reduction in the vehicle group. The area of symptomatic skin decreased by 45.6% in the 0.1% tacrolimus group and by 2.9% in the vehicle control group.

In the global assessment of treated areas, all patients who received 0.1% tacrolimus (6/6, 100%) were assessed as markedly improved at the end of treatment. However, none of the patients in the vehicle group achieved a marked improvement; 4/8 patients (50%) showed moderate improvement, 2/8 (25%) slightly improved, and 2/8 (25%) showed no change.

No significant difference in skin thickness measured by ultrasound was observed in the 0.1% tacrolimus group compared to the vehicle control group after 7 or 14 days of treatment ($p = 0.478$ for each period). The decrease in skin thickness at day 14 was 5.8% and 1.1% in the tacrolimus and vehicle group, respectively.

During treatment, TEWL was reduced to a similar extent on tacrolimus- and vehicle-treated sites (−60 and −42%, respectively). Measured by laser Doppler, the superficial blood flow decreased in the tacrolimus-treated area (−55%), while it increased slightly on the vehicle side (4%). Fourteen days after cessation of treatment, both TEWL and superficial blood flow returned to the baseline values in both groups.

DISCUSSION

This study demonstrated that 0.1% tacrolimus ointment is an effective treatment for lichenified elbow lesions of atopic dermatitis patients and showed that this treatment is not associated with skin thinning. The significant reduction in pruritus alone suggests that the action of topical tacrolimus is highly specific, as pruritus is considered a primary symptom of atopic dermatitis. Pruritus is also a major factor in causing lichenification in atopic dermatitis.

Skin burning is a specific side effect of topical tacrolimus and can influence blinding of the study. However, as patients are informed about this side effect prior to the study, patients on placebo have also reported this side effect in previous studies (8), it is possible to keep the study blinded.

TEWL measurement showed similar reductions for both tacrolimus- and vehicle-treated sites, suggesting that both treatments had a restorative effect on barrier function. The relatively high reduction of TEWL also in the vehicle group could be explained by the occlusive properties of the ointment base. In contrast, the reduction in superficial blood flow was much greater in tacrolimus-treated than vehicle-treated sites, indicating a specific treatment effect on erythema, also shown in the reduction of erythema in these patients.

The absence of skin thinning on treated regions as determined by ultrasound was corroborated by a comparative study performed in parallel in these patients and healthy volunteers to determine the effects of 0.1% tacrolimus ointment, betamethasone-valerate ointment, and a vehicle control on asymptomatic skin (10). The results from that study showed a significant reduction of skin thickness only on sites treated with betamethasone-valerate. Measurements of collagen synthesis markers PICP and PINP (the C- and N-terminal split products of procollagen I) and PIIINP (N-terminal split product of procollagen III) from blister fluids showed significant decreases in these markers after 7 days on sites treated with betamethasone-valerate ($p < 0.001$, Friedman's test), whereas 0.1% tacrolimus did not affect collagen synthesis.

We conclude that 0.1% tacrolimus ointment is effective also in the treatment of lichenified lesions of atopic dermatitis. The significant efficacy in the absence of skin thinning observed with tacrolimus ointment suggests a treatment effect similar to that of potent corticosteroids but without risk of skin atrophy. Further study is warranted to determine whether effective maintenance can be achieved with once daily or even twice weekly applications.

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