Tacrolimus ointment in nickel sulphate-induced steroid-resistant allergic contact dermatitis

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ABSTRACT

Tacrolimus ointment is a topical immunomodulator. Currently, there is available evidence regarding the potential use of topical tacrolimus in a range of dermatological disorders. The aim of this study was to evaluate the efficacy and safety of tacrolimus ointment 0.1% for the nickel sulphate-induced steroid-resistant allergic contact dermatitis (ACD) A randomized, double-blind, placebo-controlled, parallel-group study design was performed in a total of 28 patients affected by nickel sulphate-induced steroid-resistant ACD after a 14-day run-in period. Then, the enrolled patients were randomized into two subgroups. Group A was treated with tacrolimus for 14 days and finally observed for a 7-day follow-up period; Group B instead, was treated with placebo ointment. Four major symptoms (erythema, oozing, scaling, and itching) were considered as outcomes during the different phases of the study. In group A, during the treatment period with tacrolimus, a significant improvement was observed in all four considered symptoms. On the other hand, no improvement in symptoms was observed in the placebo-treated group B. Local adverse events in the tacrolimus-treated group, such as burning/itching at the application site, were transient and well tolerated. No patients withdrew because of burning/itching. In our study, tacrolimus ointment 0.1% appeared to be both effective and safe in the treatment of nickel sulphate-induced steroid-resistant ACD.

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Today, topical corticosteroids are the mainstay of therapy for allergic contact dermatitis (ACD), but the need for potent formulations carries an associated risk of local adverse effects and systemic absorption. In addition, the development of tachyphylaxis or intolerance to their therapeutic effect are significant drawbacks to the use of this drug and justifies the search for safer topical alternatives.

Tacrolimus ointment is usually the first choice among an ample variety of topical immunomodulators. Tacrolimus inhibits calcineurin, an important intracellular phosphatase, and thereby T-lymphocyte activation.

Currently, there is available evidence regarding the potential use of tacrolimus ointment in a range of dermatological disorders. The objective of this study was to evaluate the efficacy and safety of tacrolimus ointment 0.1% in treating nickel sulphate-induced steroid-resistant ACD with a randomized, ointment-controlled study.

MATERIALS AND METHODS

Patients

Patients were selected from a database of the Dipartimento di Medicina Clinica e Sperimentale, University of Verona (Italy), with known moderate to severe nickel sulphate-induced ACD based on clinical history (chronic eczema) and prior patch testing at our department. All patients were treated with topical corticosteroids and showed a resistance to the treatment. In particular, some patients totally failed to respond, and others still had residual eczema.

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A total of 28 volunteer patients, of both genders (24 women and 4 men), aged from 14 to 58 years, were enrolled and gave their informed consent to the study. The main exclusion criteria were treatment with systemic corticosteroids, cytotoxic agents or phototherapy within 6 weeks before participation in the study, previous treatment with tacrolimus, and finally pregnancy or lactation. A double-blind, placebo-controlled, parallel-group study design, approved by the human subjects committee of our institutional review board, was used.

Patients received the following treatments:
1. The 0.1% tacrolimus ointment given twice a day.
2. Placebo given twice a day.

To prepare the 0.1% ointment, the content of tacrolimus capsules (100 mg) was mixed with 100 g of hydrophilic petrolatum (white petrolatum composed of 3% bleached beeswax, 3% stearyl alcohol, and 3% cetearyl esters). The placebo content of tacrolimus was made of 100 g of hydrophilic petrolatum without tacrolimus. The test compounds were contained in opaque syringes and the treatment was not distinguishable from placebo and was blinded for both investigator and patients. Rescue medication for the itching included oral antihistaminus (cetrizinehydrochloride, Xyzal).

No other medication was permitted during the trial.

The treatment started after a 7-day run-in period. The enrolled patients were randomly divided into two subgroups. Group A (13 women and 1 man; age 29.3 ± 7.3 years) and the group B (11 women and 3 men; age 31.3 ± 10.4 years) were treated with tacrolimus and placebo, respectively, for 14 days and finally observed for a 14-day follow-up period. Each patient underwent five visits on days 0, 14, 21, and 28 for clinical evaluation.

Patient's Assessment of Symptoms

Patients were instructed to record their symptoms daily on a diary card. Eczema symptoms included erythema, oozing, scaling, and itching. Erythema was scored as follows: 0, no erythema; 1, mild erythema; 2, moderate erythema; 3, severe erythema. Oozing was scored as follows: 0, no oozing; 1, mild oozing; 2, moderate oozing; 3, severe oozing. Scaling was scored as follows: 0, no scaling; 1, mild scaling; 2, moderate scaling; 3, severe scaling. Itching was scored as follows: 0, no itching; 1, mild itching; 2, moderate itching; 3, severe itching. The final value of the score for each symptom was given by the sum of the score of the four symptoms considered.

Investigator's Global Assessment of the Therapy

The investigator's global assessment of the results of the therapy was recorded as follow: 0, no improvement; 1, mild improvement; 2, remarkable improvement; and 3, complete remission of dermatitis.

Safety Assessment

Safety assessment consisted of monitoring and recording all adverse events by their severity and potential relationship to the study drug.

Statistical Analysis

Statistical analysis was performed with the SYSTAT 10 software package (SPSS, Inc., Chicago, IL). The analyses for age and sex distribution between the two subgroups of patients were performed by t-test and Fisher's exact test, respectively. The data of symptoms score (erythema, oozing, scaling, and itching) were expressed as proportions of the patients prevalence of different day scores during each phase of the trial and, because considered as an ordinal score, were analyzed by nonparametric tests (Mann-Whitney or Kruskal-Wallis with all pairwise comparisons when appropriate). A value of p < 0.05 was considered significant.

The use of rescue medication during the study was expressed as mean and 95% confidence intervals (95% CI) of the number of tablets taken during the run-in and treatment periods and analyzed with ANOVA and Bonferroni's comparisons. A value of p < 0.05 was considered significant.

RESULTS

The two subgroups of patients were not statistically different for age (group A, 29.3 ± 7.3 years versus group B, 31.3 ± 10.4 years) and from sex distribution (group A, 1/14 men versus group B, 3/14 men). All patients completed the study. Figure 1: a-d shows the distributions, as percentages of daily scores for erythema, oozing, scaling, and itching during run-in, treatment, and follow-up periods, both in groups A and B.

In group A, during the treatment with tacrolimus, the scores for all four considered symptoms were significantly improved as compared to those of the other trials (p < 0.001 by Kruskal-Wallis with all pairwise comparisons). During tacrolimus treatment, 65.8% of days were reported as free from symptoms (more precisely, 65.8% as free from erythema, 67.6% as free from oozing, 65.6% as free from scaling, and 67.6% as free from itching), whereas during the run-in period patients scored always moderate-to-severe symptoms and no day was reported as free from symptoms.

Remarkably, also, during the follow-up period, immediately after tacrolimus treatment, the scores for all four considered symptoms were significantly lower than during the run-in period (p < 0.001 by Kruskal-Wallis with all pairwise comparisons), but higher than during tacrolimus treatment (p < 0.001 by Kruskal-
Figure 1. A significant difference was established between the run-in treatment period and the follow-up period in group A (bacitracin group; \( p < 0.001 \)) by Kruskal-Wallis with all pairwise comparisons) and from treatment period in group B (placebo group; \( p < 0.001 \)) by Mann-Whitney test.

Walls with all pairwise comparisons). During the follow-up period, 25% of days was recorded as free from symptoms, but 75% of days presented, again, moderate-severe symptoms.

In contrast, in the placebo-treated group B, no improvement in symptom scores was noted. During placebo treatment, as well as during the run-in period, patients recorded always mild-to-severe symptoms, and no day was reported as free from symptoms.

There were no differences in mean symptom scores between groups A and B during the run-in period (erythematous, \( r = 0.266 \); itching, \( r = 0.133 \); scaling, \( r = 0.706 \); itching, \( r = 0.922 \) (by Mann-Whitney test). However, mean symptom scores were significantly lower in group A versus group B both during treatment (\( p < 0.001 \) by Mann-Whitney test) and follow-up period (\( p < 0.001 \) by Mann-Whitney test).

The mean (95% CI) of the number of tablets of antihistamine taken as rescue medication was significantly lower in the group treated with tacrolimus at the end of the treatment period versus the same group at the end of the run-in period (2.8 [95% CI, 1.2–2.4] versus 1.2 [95% CI, 0.6–2.8]; \( p < 0.0001 \)) and versus the placebo group at the end of the treatment period (1.8 [95% CI, 1.2–2.4] versus 5.5 [95% CI, 4.6–6.4]; \( p < 0.0001 \)). On the contrary, the mean was significantly higher in the placebo group at the end of the treatment period versus the same group at the end of the run-in period (5.5 [95% CI, 4.6–6.5] versus 4.0 [95% CI, 3.4–4.6]; \( p < 0.0021 \)). However, no significant differences were found between the tacrolimus group and the placebo group at the end of the run-in period (4.2 [95% CI, 3.6–4.8] versus 4.0 [95% CI, 3.4–4.6]; \( p = 0.5 \)).

The investigator’s global assessment showed the following: at the end of the treatment period in the tacrolimus group, remarkable improvement in 8 patients (67.4%) and complete remission of dermatitis in 6 patients (50.0%). In the placebo group, no improvement in 10 patients (71.4%) and mild improvement in 4 patients (28.6%). Local adverse events (burning/itch-
CONCLUSIONS

In our study, tacrolimus ointment 0.1% appeared to be both effective and safe in the treatment of nickel sulfate-induced, steroid-resistant ACD. Local adverse events (burning/itching at the application site) were experienced by 47/14 (28.6%) patients and were transient and well tolerated. No patients withdrew due to burning/itching.

Treatment of nickel sulfate-induced ACD has until now centered around the use of corticosteroids, with the adjunct of antihistamines, wet dressings, and excellent for alleviation of symptoms. Allergens identification, through patch testing, and allergen avoidance are the keys to prevention of recurrence. Topical corticosteroids have been widely used for the treatment of ACD. However, in severe cases, the severe systemic side effects of systemic corticosteroids have been noted, such as mild to moderate weight gain, hypertension, corticosteroid-induced diabetes, and Cushing’s syndrome. These systemic side effects have limited the use of systemic corticosteroids in ACD.

Tacrolimus (PROTACRIMUS) ointment has been shown to inhibit T-lymphocyte activation. The agent inhibits the activation of calcineurin, an enzyme important for the translocation of the protein transcription factor, a nuclear factor of activated T cells, from the cytoplasm to the nucleus, where it "turns on" a number of proinflammatory cytokines associated with T-cell activation. Furthermore, tacrolimus does not have the many side effects of steroids, such as cutaneous atrophy, striae, cataracts, and adrenal suppression. The introduction of tacrolimus ointment marked the event of a new, nonsteroidal drug class—topical immunomodulators or topical calcineurin inhibitors—for the management of inflammatory dermatologic disorders.

The safety and efficacy of tacrolimus ointment in the treatment of moderate-to-severe atopic dermatitis was assessed in a vehicle-controlled, randomized, controlled trial. The results of this study provided further support of the safety and efficacy profile of tacrolimus ointment in children aged 2 years or younger. No significant adverse events were observed in all of these studies. The more frequent events were infections, pruritus, burning, pruritus, erythema, and papules in the treated areas. In most long-term-treated patients, skin burning was mild to moderate and decreased rapidly after the first week of treatment. There was no increase in the incidence of infections in the long-term patients.

More recent studies focused on the efficacy and safety of tacrolimus ointment use in the treatment of nickel sulfate-induced ACD. A small, double-blind, randomized, vehicle-controlled, placebo-paired comparison study was performed in 19 subjects to assess safety and efficacy of tacrolimus ointment 0.1% in the treatment of nickel sulfate-induced ACD. Efficacy was evaluated through patch testing of both upper inner arms. On the tacrolimus-treated site, 80% of patients had an improvement in the investigator’s global assessment score versus 20% of patients on the placebo-treated site. Another trial evaluated the ability of tacrolimus ointment 0.1%, under occlusion for 48 hours, to suppress nickel-chelated ACD in a randomized, petrolatum- and metronidazole ointment 0.1% ointment-controlled, double-blind, intrasubject study, which included 28 women volunteers. The treatment with tacrolimus showed a significantly greater improvement of both the clinical reaction and the degree of erythema.

Our findings complement and amplify these studies, because we showed, with a randomized, double-blind, placebo-controlled, parallel group study design, that treatment with topical tacrolimus 0.1% efficiently inhibits moderate to severe nickel sulfate-induced steroid-resistant ACD in the specific sites of clinical manifestations (hand, elbow, and finger), which are not treated with placebo (vehicle), both as patients and physicians' global assessment and rescue medication use. Overall, in 10/14 (71.4%) patients' topical tacrolimus 0.1% appeared to be both effective and safe. Local adverse events, such as burning/itching at the application site, experienced in a minority of patients, were transient and well tolerated. However, the principle limitations of our study are the small number of patients treated and the short duration of the follow-up period to identify possible adverse effects caused by long-term use of the drug.

Because many patients affected by ACD are exposed continually to external allergens/agents that can not be avoided, and some of them could show steroid resistance, a nonsteroidal drug that could be effectively and safely used on a long-term basis, without the risk of significant side effects, would be beneficial both to these patients and to the practitioners.

REFERENCES
