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

Maria L. Pacor, M.D.,* Gabriele Di Lorenzo, M.D.,# Nicola Martinelli, M.D.,* Pasquale Mansueto, M.D.,# Simonetta Friso, M.D.,* Maria Esposito Pellitteri, M.D.,# Gaetana Di Fede, M.D.,# GiovamBattista Rini, M.D.,# and Roberto Corrocher, M.D.* (Italy)

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 sulfate–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 sulfate–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 (vehicle). 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 sulfate–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 tolerance to their therapeutic effect are significant drawbacks to the use of this drug and justifies the search for better therapeutic alternatives.[1]

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.[2–4]

Currently, there is available evidence regarding the potential use of tacrolimus ointment in a range of dermatological disorders. Moderate-to-severe atopic dermatitis, a helper T cell type 2 (Th2)–mediated disease, significantly improves with tacrolimus 0.03 and 0.1% ointment compared with vehicle in both adult and pediatric patients. The 0.1% concentration is likely to be more effective than the 0.03% concentration. Skin burning and itching at the application site are the most common side effects and these events are generally of short duration and of mild or moderate intensity.[5–10] Furthermore, other interesting studies regarded the use of tacrolimus ointment in the treatment of facial psoriasis,[11] oral lichen planus,[12–15] pyoderma gangrenosum,[16,17] and steroid-induced rosacea.[18,19]

Recently, some anecdotal studies, with few patients, have established the efficacy of immunomodulators in the treatment of ACD, a Th1-mediated disorder.[20–25] The aim of this study was to evaluate the efficacy and safety of tacrolimus ointment 0.1% in treating nickel sulfate–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 sulfate–induced ACD based on clinical history (hand 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.

*From the *Dipartimento di Medicina Clinica e Sperimentale, Università degli Studi di Verona, Italy, and #Dipartimento di Medicina Clinica e delle Patologie Emergenti, Università di Palermo, Italy*
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Address correspondence and reprint requests to Gabriele Di Lorenzo, M.D., Dipartimento di Medicina Clinica e delle Patologie Emergenti, Via del Vespro, 141 90127 Palermo, Italy
E-mail address: [illegible]

A total of 28 volunteer patients, of both genders (24 women and 4 men), aged from 17 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, pregnant or lactating women. A randomized, 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 (total, 100 mg) was mixed with 100 g of hydrophilic petrolatum (white petrolatum composed of 8% bleached beeswax, 3% stearyl alcohol, and 3% cholesterol). The placebo ointment of tacrolimus was only made of 100 g of hydrophilic petrolatum without tacrolimus.[7] 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 antihistamines (levocetirizine, Xyzal). No other medication was permitted during the trial.

The treatment started after a 7-day run-in period. Then, the enrolled patients were randomly divided in 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 −7 (begin of the run-in period), 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; and 3, severe erythema. Oozing was scored as follows: 0, no oozing; 1, mild oozing; 2, moderate oozing; and 3, severe oozing. Scaling was scored as follows: 0, no scaling; 1, mild scaling; 2, moderate scaling; and 3, severe scaling. Itching was scored as follows: 0, no itching; 1, mild itching; 2, moderate itching; and 3, severe itching. The final value of eczema symptoms for each patient was given by the sum of the scores 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 appropriated). 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 for 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 period, both in groups A and B.

In group A, during the treatment with tacrolimus, the scores for all four considered symptoms were significantly improved than those of the other trial phases ($p < 0.001$ by Kruskal-Wallis with all pairwise comparisons). During tacrolimus treatment, ~65% of days were reported as free from symptoms (more precisely, 65.7% as free from erythema, 67.6% as free from oozing, 68.6% as free from scaling, and 67.6% as free from itching), whereas during the run-in period patients recorded 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-

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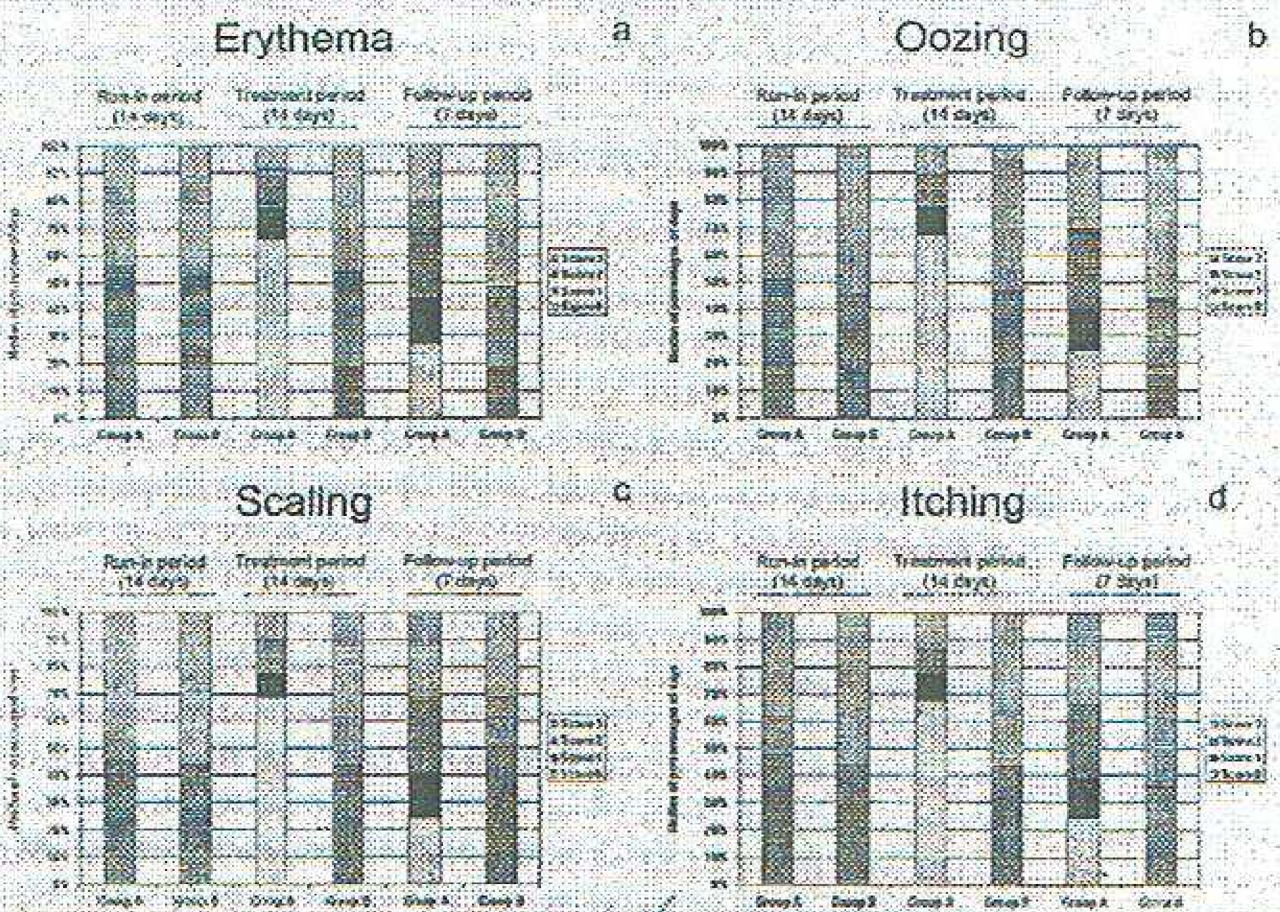

Figure 1. A significant difference was established between the run-in/treatment period and the follow-up period in group A (tacrolimus group, $p < 0.001$ by Kruskal-Wallis with all pairwise comparisons) and from treatment period in group B (placebo group, $p < 0.001$ by Mann-Whitney test).

Wallis with all pairwise comparisons). During the follow-up period ~25% of days was recorded as free from symptoms, but ~50% of days presented, again, moderate-to-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 moderate-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 (erythema, $p = 0.266$; oozing, $p = 0.130$; scaling, $p = 0.919$; itching, $p = 0.362$ [by Mann-Whitney test]), whereas 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 (1.8 [95% CI, 1.2–2.4] versus 4.2 [95% CI, 3.5–5.0]; $p < 0.0001$) 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, 4.6–6.5]; $p < 0.0001$). 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, 3.4–4.5]; $p < 0.0021$). 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, 3.5–5.0] versus 4.0 [95% CI, 3.4–4.5]; $p = 0.5$).

The investigator's global assessment showed the following: at the end of the treatment period in the tacrolimus group, remarkable improvement in 8 patients (57.1%) and complete remission of dermatitis in 6 patients (42.8%); in the placebo group, no improvement in 10 patients (71.5%) and mild improvement in 4 patients (28.5%). Local adverse events (burning/itch-

ing at the application site), in the tacrolimus-treated group, were experienced by 4/14 (28.6%) patients and were transient and well tolerated.

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 in few patients and were transient and well tolerated. No patients withdrew because of 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 emollients for alleviation of symptoms. Allergen identification, through patch testing, and allergen avoidance are the keys to preventing recurrences of this disease.[1]

Tacrolimus, a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*, has been shown to inhibit T-lymphocyte activation. This agent inhibits the activation of calcineurin, an enzyme important for the translocation of the pluripotent transcription factor, a nuclear factor of activated T cell, 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 rubrae, osteoporosis, and adrenal suppression.[1–4] 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 dermatological disorders.[20–28]

The safety and efficacy of tacrolimus ointment in the treatment of moderate-to-severe atopic dermatitis was evaluated in some vehicle-controlled, randomized clinical trials. In addition, more recent studies provided further support of the safety and efficacy profile of tacrolimus ointment in children ≥2 years of age. No significant adverse effects were indicated in all of these studies. The more frequent effects were infections, pyrexia, burning, pruritus, erythema, and papules in the application area. In most long-term treated patients, skin burning was mild to moderate in severity and decreased rapidly after the 1st week of treatment. There was no increase in the incidence of infections or malignancies.[5–10]

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, bilateral 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 eliciting 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 30% of patients on the placebo-treated site.[23] Another trial evaluated the ability of tacrolimus ointment 0.1%, under occlusion for 48 hours, to suppress nickel-elicited ACD in a randomized, petrolatum- and mometasone furoate 0.1% ointment-controlled, double-blind, intraindividual study, which included 28 women volunteers. The treatment with tacrolimus showed a significantly greater improvement of both the eczema reaction and the degree of erythema.[24]

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% efficaciously inhibits moderate-to-severe nickel sulfate–induced steroid-resistant ACD, in the specific site of clinical manifestations (hand eczema), when compared with placebo (vehicle), both as patient's and investigator's 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 brief 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/haptens that can not be avoided, and some of them could show steroid resistance, a nonsteroidal drug that could be efficaciously 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

1. Hachem JP, De Paepe K, Vanpee E, et al. Efficacy of topical corticosteroids in nickel-induced contact allergy. Clin Exp Dermatol 27:47–50, 2002.
2. Tocci MJ, Matkovich DA, Collier KA, et al. The immunosuppressant FK506 selectively inhibits expression of early T cell activation genes. J Immunol 143:718–726, 1989.
3. Panthans-Groß A, Novak N, Kraft S, et al. Human epidermal Langerhans cells are targets for the immunosuppressive macrolide tacrolimus (FK506). J Allergy Clin Immunol 107:343–352, 2001.
4. Wollenberg A, Sharma S, von Bubnoff D, et al. Topical tacrolimus (FK506) leads to profound phenotypic and functional alterations of epidermal antigen presenting dendritic cells in atopic dermatitis. J Allergy Clin Immunol 107:519–525, 2001.
5. Cheer SM, and Plosker GL. Tacrolimus ointment. A review of its therapeutic potential as a topical therapy in atopic dermatitis. Am J Clin Dermatol 2:389–406, 2001.
6. Ruzicka T, Bieber T, Schopf E, et al. A short-term trial of tacrolimus ointment for atopic dermatitis. European Tacrolimus

Multicenter Atopic Dermatitis Study Group. N Engl J Med 337:816–821, 1997.
7. Kang S, Lucky AW, Pariser D, et al. Long-term safety and efficacy of tacrolimus ointment for the treatment of atopic dermatitis in children. J Am Acad Dermatol 44(suppl 1):S58–S64, 2001.
8. Kapp A, Allen BR, and Reitamo S. Atopic dermatitis management with tacrolimus ointment (Protopic). J Dermatol Treat 14(suppl 1):5–16, 2003.
9. Pacor ML, Di Lorenzo G, Martinelli N, et al. Comparing tacrolimus ointment and oral cyclosporine in adult patients affected by atopic dermatitis: A randomized study. Clin Exp Allergy 34:639–645, 2004.
10. Reitamo S, Ortonne JP, Sand C, et al. European Tacrolimus Ointment Study Group. A multicentre, randomized, double-blind, controlled study of long-term treatment with 0.1% tacrolimus ointment in adults with moderate to severe atopic dermatitis. Br J Dermatol 152:1282–1289, 2005.
11. Yamamoto T, and Nishioka K. Topical tacrolimus: An effective therapy for facial psoriasis. Eur J Dermatol 13:471–473, 2003.
12. Hodgson TA, Sahni N, Kaliakatsou F, et al. Long-term efficacy and safety of topical tacrolimus in the management of ulcerative/erosive oral lichen planus. Eur J Dermatol 13:466–470, 2003.
13. Lener EV, Brieva J, Schachter M, et al. Successful treatment of erosive lichen planus with topical tacrolimus. Arch Dermatol 137:419–422, 2001.
14. Nazzaro G, and Cestari R. Topical tacrolimus ointment in ulcerative lichen planus: An alternative therapeutic approach. Eur J Dermatol 12:321, 2002.
15. Morrison L, Kratochvil FJ III, and Gorman A. An open trial of topical tacrolimus for erosive oral lichen planus. J Am Acad Dermatol 47:617–620, 2002.
16. Richter-Hintz D, Schuppe HC, Homey B, et al. Topical tacrolimus (FK 506) is effective in the treatment of pyoderma gangrenosum. J Am Acad Dermatol 42:304–305, 2000.
17. Reich K, Vente C, and Neumann C. Topical tacrolimus for pyoderma gangrenosum. Br J Dermatol 139:755–757, 1998.
18. Bamford JT, Elliott BA, and Haller IV. Tacrolimus effect on rosacea. J Am Acad Dermatol 50:107–108, 2004.
19. Goldman D. Tacrolimus ointment for the treatment of steroid-induced rosacea: A preliminary report. J Am Acad Dermatol 44:995–998, 2001.
20. Nakada T, Iijima M, and Maibach HI. Eyeglass frame allergic contact dermatitis: Does tacrolimus prevent recurrences? Contact Derm 53:219–221, 2005.
21. Anderson BE, Marks JG Jr, and Mauger DT. Efficacy of tacrolimus ointment in the prevention and treatment of contact dermatitis. Dermatitis 15:158–159, 2004.
22. Queille-Roussel C, Graeber M, Thurston M, et al. SDZ ASM 981 is the first non-steroid that suppresses established nickel contact dermatitis elicited by allergen challenge. Contact Derm 42:349–350, 2000.
23. Saripalli YV, Gadzia JE, and Belsito DV. Tacrolimus ointment 0.1% in the treatment of nickel-induced allergic contact dermatitis. J Am Acad Dermatol 49:477–482, 2003.
24. Alomar A, Puig L, Gallardo CM, et al. Topical tacrolimus 0.1% ointment (protopic) reverses nickel contact dermatitis elicited by allergen challenge to a similar degree to mometasone furoate 0.1% with greater suppression of late erythema. Contact Derm 49:185–188, 2003.
25. De Rie MA, Meinardi MM, and Bos JD. Lack of efficacy of topical cyclosporin A in atopic dermatitis and allergic contact dermatitis. Acta Derm Venereol 71:452–454, 1991.
26. Bieber T, Cork M, Ellis C, et al. Consensus statement on the safety profile of topical calcineurin inhibitors. Dermatology 211:77–78, 2005.
27. Del Rosso J, and Friedlander SF. Corticosteroids: Options in the era of steroid-sparing therapy. J Am Acad Dermatol 53(suppl 1):S50–S58, 2005.
28. Fonacier L, Spergel J, Charlesworth EN, et al. American College of Allergy, Asthma and Immunology; American Academy of Allergy, Asthma and Immunology. Report of the Topical Calcineurin Inhibitor Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 115:1249–1253, 2005.