

A Double-Blind Randomized Placebo-Controlled Pilot Study Comparing Topical Immunomodulating Agents and Corticosteroids for Treatment of Experimentally Induced Nickel Contact Dermatitis

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Background: Although topical glucocorticoids are effective for most inflammatory skin disorders, their use is limited by local and systemic side effects. Tacrolimus and pimecrolimus are immunomodulators that provide clinicians with steroid-sparing options in the long-term topical treatment of allergic contact dermatitis.

Objective: To obtain pilot data regarding the relative efficacies of pimecrolimus 1% cream, tacrolimus 0.1% ointment, clobetasol propionate 0.05% ointment, and triamcinolone acetonide 0.1% ointment, as compared to control preparations (Vanicream and petrolatum), for treatment of experimentally induced nickel contact dermatitis.

Methods: Twenty-one volunteers with positive patch test reactions to nickel sulfate 5% at six sites (three on each arm) applied each study medication to one nickel site, respectively, twice daily for 14 days. Study medications were prepared in identical syringes, and the site of application was randomly assigned by a computer-generated randomization schedule. Assessments were performed at 3, 7, 10, and 14 days after randomization.

Results: Most reactions were coded as resolved or as almost resolved by day 14 regardless of treatment. Although most pairwise comparisons were not statistically significant, a clear trend was observed for sites treated with active drug to do better than control sites.

Conclusion: Possible explanations for these results include contamination by neighboring medication sites, timing of assessments, and lack of repeated nickel applications.

THE TREATMENT of choice in many inflammatory skin disorders, including atopic dermatitis and allergic contact dermatitis, has long been topical glucocorticoids. Whereas these agents provide broad immunosuppression and are very effective,^{1,2} their use is limited by local adverse effects (skin atrophy, telangiectasias, and striae) and systemic effects (glaucoma, cataracts, hypothalamic-pituitary-adrenal axis suppression, and growth retardation).³

Tacrolimus (FK506) ointment and pimecrolimus (ASM 981) cream are the first topical immunosuppressants that are not cortisone derivatives. Tacrolimus and pimecrolimus are topical inhibitors of calcineurin and have been approved in the United States for the treatment

of atopic dermatitis in both adults and children.^{4,5} Both agents modulate immune function through the inhibition of the dephosphorylation of nuclear factor of activated T cells (NFAT) by calcineurin in T lymphocytes. NFAT has been shown to be a critical switch for numerous cytokines, including interleukin (IL)-2, IL-3, IL-4, IL-5, interferon- γ , tumor necrosis factor- α , and granulocyte-macrophage colony-stimulating factor.^{2,6} Leukotriene, histamine, and serotonin release from mast cells are also reduced.² This inhibition effectively suppresses the immune response.^{2,4} Studies have shown that tacrolimus and pimecrolimus also target human epidermal Langerhans' cells and may lead to a greatly impaired stimulatory activity by inhibiting the expression of the co-stimulatory molecules CD40 and CD80.⁷ Both pimecrolimus and tacrolimus have been shown to inhibit the elicitation phase of allergic contact dermatitis in a mouse model.⁸ Tacrolimus has been shown to suppress the sensitization phase of allergic contact dermatitis in humans⁹ and guinea pigs¹ whereas pimecrolimus does not.⁸ When used topically, the principal

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adverse effects for both agents are local application site reactions.^{4,10}

The primary objective of this double-blind randomized controlled study was to obtain pilot data regarding the relative efficacies of pimecrolimus 1% cream, tacrolimus 0.1% ointment, clobetasol propionate 0.05% ointment, and triamcinolone acetonide 0.1% ointment, as compared to control preparations (Vanicream [Pharmaceutical Specialties, Rochester, MN] and petrolatum), for the treatment of experimentally induced nickel contact dermatitis. A study comparing these immunomodulating agents with each other as well as with midpotent (group III) and superpotent (group I) topical steroids could provide valuable data regarding the potential use of these newer agents in clinical practice as well as their relative impact on the treatment of allergic contact dermatitis.

Methods

This double-blind randomized placebo-controlled pilot evaluation of the relative efficacies of pimecrolimus 1% cream (Elidel, Novartis, East Hanover, NJ), tacrolimus 0.1% ointment (Protopic, Fujisawa Healthcare, Deerfield, IL), triamcinolone acetonide 0.1% ointment, and clobetasol propionate 0.05% ointment as compared to Vanicream emollient and petrolatum in the treatment of allergic contact dermatitis from nickel was approved by the Human Studies Subcommittee of the Minneapolis Veterans Affairs (VA) Medical Center.

Inclusion criteria included (1) history of a reaction to nickel; (2) adequate space on the forearms or upper lateral arms for the experimental induction of six sites of allergic contact dermatitis (ACD) from nickel (three sites per arm); (3) the ability to express 0.05 mL of a topical agent with a tuberculin syringe; (4) the ability to reach test sites on the arms (eg, no debilitating arthritis or physical limitation); and (5) an age of 18 years or greater. Exclusion criteria included (1) pregnancy or lactation; (2) use of systemic therapy (corticosteroids, immunosuppressive agents, cytostatics, pentoxifylline, leukotriene antagonists,

or other medications known or suspected to have an effect on ACD) within 2 weeks prior to participation; (3) use of intramuscular steroids in the previous month; (4) use of topical steroids, tar, or topical immunomodulating agents on the forearms or lateral upper arms within the previous 3 days; (5) phototherapy (psoralen plus ultraviolet A or ultraviolet B) within 2 weeks prior to participation; (6) other significant immunodeficiency; and (7) any other significant dermatologic or general medical condition that could interfere with clinical evaluations.

The study protocol was designed to allow the evaluation of each agent in a controlled manner while remaining feasible for both study participants and investigators. The upper outer arms were chosen as the preferential site for testing. Patch tests with nickel sulfate 5% in petrolatum (Chemotechnique Diagnostics, Malmö, Sweden) were freshly prepared on the day of patch testing (day -3). Six patches were prepared in six alternating 8 mm aluminum Finn Chambers (Allerderm, Petaluma, CA) by expression of 0.05 mL aliquots, measured with 1.0 mL tuberculin syringes, onto each Finn Chamber as previously described.¹¹ Alternating Finn Chambers were used, with a distance of 3 cm between patches. Three patches were applied to each arm and secured with Scanpor tape (Norgesplaster A/S, Vennessla, Norway). Patients were provided with standard instructions regarding the care of the patches.

The second visit (day -1) took place 48 hours after placement of the patches. At this time, the patches were removed and the skin was examined. Reactions were graded on days -1, 0, 3, 7, 10, and 14, according to standard guidelines of the North American Contact Dermatitis Group (NACDG) scoring system: 1 (erythema, infiltration, possible papules), 2 (erythema, infiltration, papules, vesicles), 3 (intense erythema, infiltration, coalescing vesicles, bullous, spreading), 4 (doubtful), 5 (irritant), or 6 (negative). In addition to this global assessment of each site, the individual parameters (erythema, vesiculation, and induration) of each reaction were separately recorded as shown in Table 1. The greatest diameter of each reaction was also recorded.

Table 1. Grading of Individual Parameters*

Parameter	Score			
	0	1	2	3
Erythema	None	Faint to pink	Red	Bright Red
Induration	None	Mild	Moderate	Severe
Papules/vesicles	None	Few	Moderate	Many

*Total score = erythema + induration + papules/vesicles.

At the third visit (day 0, 72 hours after the first visit), the reactions were graded by one of the authors (S.B. or E.W.) according to the NACDG scoring system. This assessment served as the baseline score. At the same visit (day 0), patients were given two capped 1 mL syringes (without attached needle) containing each of the following topical agents: Elidel (pimecrolimus 1%) cream, Protopic (tacrolimus 0.1%) ointment, triamcinolone acetonide 0.1% ointment, clobetasol propionate 0.05% ointment, Vanicream (control cream), and petrolatum (control ointment). Important, each of these agents was randomly assigned a letter (“A” to “F”) according to a computerized randomization schedule. Thus, the syringe labeled “A” for patient 1 to apply to site A contained a different formulation from the syringe labeled “A” for patient 2 to apply to site A. Only the research pharmacist had access to the randomization log. This assured that neither investigator nor patient had knowledge of the syringe’s contents beyond that of its being ointment or cream. Patients were instructed to apply 0.05 mL of each agent with a separate cotton-tipped applicator to an assigned site (study medication “A” to patch-test site A and study medication “B” to patch-test site B, etc) twice daily as previously described.¹¹ The first application for each patient was done in the presence of an investigator to ensure the highest level of understanding and to facilitate instruction. Detailed written instructions and a map of sites were also provided. After assessments were completed and data were entered for all subjects, the study blind was broken.

The primary outcome measure of this trial was an evaluation of the efficacy of each topical immunomodulating agent, as compared to topical corticosteroids and placebo, for the treatment of experimentally induced ACD. Analyses used an intent-to-treat approach and were performed with SAS (Statistical Analysis System, SAS Institute Inc., Cary, NC). For the primary efficacy variable (the proportion of reactions in each treatment group that were resolved or almost resolved [NACDG score of 6 or 4] on day 14 and those that were resolved, almost resolved, or mild [NACDG score of 6, 4, or 1] on day 7), the Fisher exact test (two-tail) was used to compare treatment groups; statistical significance was defined as $p < .05$.

In addition, change from baseline analyses were performed in a stepwise fashion (univariate by visit, generalized by visit, generalized linear model, repeated measurement model, random effect model, and longitudinal effects model). Most steps were repeated twice, first with continuous endpoints and then with categorical data. After this process, a rather simple model was chosen.

In this simple model, medication, visit, and medication by visit interaction were covariates. Site was not included as it was not statistically associated with outcome. Subject was random effect; medication and visit were fixed effects. Visit was also the repeated factor. Sensitivity analyses were performed to fill missing intermediate data points, using data as evaluable, last observation carried forward (LOCF), imputed as group minimum, imputed as group mean, and imputed as group maximum.

Results

Of 33 volunteers who met the inclusion criteria, 21 were enrolled (Fig 1). Figure 2 depicts a typical set of reactions at day 0.

The proportions of reactions in each treatment group that were resolved, almost resolved, or mild on day 7 and were resolved or almost resolved on day 14 are presented in Tables 2, 3, and 4. The results of pairwise Fisher exact tests for these values were not statistically significant (p values $> .0931$).

No statistically significant differences were found for pairwise comparisons of treatment and control groups with evaluable data or imputing data as group minimum for erythema, induration, papules and vesicles, or global or total scores. Statistically significant differences found with LOCF, group mean, and group maximum methods are

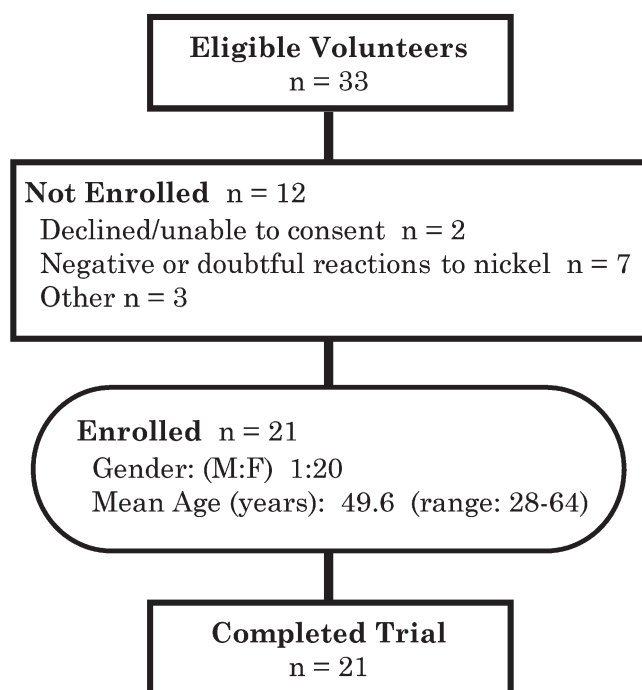


Figure 1. Randomization and patient demographics.



Figure 2. Typical reactions at day 0.

shown in Table 5. Significant differences in mean diameter were noted for pairwise comparisons of clobetasol with petrolatum, pimecrolimus and tacrolimus.

Discussion

Most of the ACD reactions to nickel were resolved or almost resolved by day 14 post baseline, regardless of treatment. Although most pairwise comparisons were not

Table 2. Patients with Reaction Scores of 1, 4, or 6 at 7 Days after Baseline

Agent	No. of Patients
Tacrolimus	17/21
Pimecrolimus	15/21
Triamcinolone	16/21
Clobetasol	20/21
Vanicream	15/21
Petrolatum	19/21

p Values > .0931.

Table 3. Patients with Reaction Scores of 4 or 6 at 7 Days after Baseline

Agent	No. of Patients
Tacrolimus	2/21
Pimecrolimus	3/21
Triamcinolone	5/21
Clobetasol	5/21
Vanicream	3/21
Petrolatum	2/21

p values > .4099.

Table 4. Patients with Reaction Scores of 4 or 6 at 14 Days after Baseline

Agent	No. of Patients
Tacrolimus	14/21
Pimecrolimus	12/21
Triamcinolone	15/21
Clobetasol	15/21
Vanicream	11/21
Petrolatum	16/21

p Values > .1971.

statistically significant, a clear trend was observed for sites treated with active drug to do better than control sites.

The results of our study differ from those of several studies that have indicated a difference among topical immunomodulators, topical steroids, and vehicles. Weissenbacher and colleagues recently demonstrated that pretreatment with 1% pimecrolimus cream suppressed reactions to house dust mite patch tests and skin prick tests in atopic individuals.¹² Meingassner and Stutz demonstrated the ability of topical tacrolimus to profoundly inhibit inflammatory skin reactions of hypersensitivity to dinitrofluorobenzene in a pig model. This study used both dexamethasone and clobetasol propionate as reference compounds and concluded that the treatment response of topical FK506 at concentrations of 0.04 to 0.4% was clearly superior to that of dexamethasone and similar to that of a 0.13% formulation of clobetasol-17-propionate.¹³ A large randomized vehicle-controlled study by Reitamo and colleagues demonstrated that tacrolimus 0.1% ointment was not significantly different from hydrocortisone butyrate 0.1% when used in the treatment of atopic dermatitis.¹⁴ In 2003, Saripalli and colleagues induced two sites of nickel allergy contact dermatitis, one on each of the inner upper arms of 19 patients, and evaluated the efficacy of tacrolimus as compared to vehicle.¹⁵ Tacrolimus was added after the reactions had become active, and the investigators repeated the nickel insults to each site during the study.¹⁵ Tacrolimus was statistically significantly more effective than vehicle in ameliorating the reactions to nickel as measured by an investigator's global assessment ($p = .0001$ at day 7 and $p = .0003$ at day 14).¹⁵

Alomar and colleagues in Spain conducted a randomized ointment-controlled double-blind study to evaluate the ability of topical tacrolimus 0.1% and mometasone furoate 0.1% to suppress nickel-elicited contact dermatitis when used under occlusion for 48 hours.¹⁶ Three nickel patch tests were placed on the back of their subjects (day 0). After removal at 48 hours (day 2), the investigators

Table 5. Change from Baseline Analyses: Statistically Significant Differences Found with Different Methods Used

Method	Endpoint	Label	Estimate	SE	p Value
LOCF	Diameter	Immunomodulating vs corticosteroids	−0.07	0.03	.016
Mean	Diameter	Immunomodulating vs corticosteroids	−0.07	0.026	.009
LOCF	Diameter	Petrolatum vs clobetasol	−0.12	0.043	.006
Mean	Diameter	Petrolatum vs clobetasol	−0.09	0.037	.016
Mean	Diameter	Pimecrolimus vs clobetasol	−0.09	0.037	.019
LOCF	Diameter	Tacrolimus vs clobetasol	−0.14	0.043	.001
Max	Diameter	Tacrolimus vs clobetasol	−0.14	0.06	.02
Mean	Diameter	Tacrolimus vs clobetasol	−0.12	0.037	.001
LOCF	Diameter	Vanicaream vs tacrolimus	0.09	0.043	.042
Mean	Diameter	Vanicaream vs tacrolimus	0.08	0.037	.028
Mean	Induration	Tacrolimus vs clobetasol	−0.13	0.062	.037
LOCF	Induration	Triamcinolone vs clobetasol	−0.2	0.093	.033
Mean	Induration	Vanicaream vs tacrolimus	0.13	0.062	.031
LOCF	Induration	Vanicaream vs triamcinolone	0.18	0.092	.047
LOCF	Total	Vanicaream vs triamcinolone	0.44	0.212	.04

LOCF = last observation carried forward; Max = data imputed as group maximum; Mean = data imputed as group mean; SE = standard error.

applied tacrolimus, mometasone furoate, and petrolatum in Finn Chambers randomly to each site, where they were left for 48 hours (day 4).¹⁶ Alomar and colleagues concluded that at days 4 and 7, mean visual scores of reaction sites treated with petrolatum were statistically significantly higher than those of reaction sites treated with tacrolimus or mometasone furoate.¹⁶

In 1998, ASM 981 0.1% was shown to be as effective as clobetasol-17-propionate 0.05% in a pig model of ACD.^{4,17} In 2000, Queille-Roussel and colleagues published the first report of the use of pimecrolimus to successfully treat nickel-induced ACD in humans.¹⁸ Dermatitis was induced on the backs of 66 volunteers, who were then treated with ASM 981 twice daily for up to 12 days.¹⁸ Both 0.2% and 0.6% cream formulations were found to be superior to vehicle and equal to betamethasone valerate 0.1% in regard to time until partial clearing (erythema, induration, and vesiculation).¹⁸ However, in 2003, Amrol and colleagues reported on a double-blind randomized vehicle-controlled study of 12 patients with *Toxicodendron*-induced ACD. This study found no statistically significant difference between topical pimecrolimus and vehicle.¹⁹

The inability of our study to detect a significant difference in efficacy among the six topical preparations when a true difference could exist may be due to at least four possibilities. The first and most likely explanation is that the induced nickel contact dermatitis reactions were placed too close to one another, allowing diffusion of the medications and cross-contamination between sites. The study design allowed for a 3 cm space between patches.

Sixteen patients had at least two reactions with an NACDG score of 3 and a diameter ranging from 1.4 to 2.5 cm. Because of the intense and spreading nature of these reactions, the distance from one lesion's margin to the next was small (see Fig 2). In a study by Parneix-Spake and colleagues, a minimum distance of 20 cm was used between experimentally induced nickel contact dermatitis sites on the patients' backs.²⁰ Furthermore, participants may have had difficulty restricting the application surface of topical medications when the lesions were so close to one another. We studied the assessments of those patients who had two control substances (Vanicaream and petrolatum) and one active medication on the same arm. We pooled the reaction scores from each arm and compared the assessments of the reactions to which each of the four active drugs had been applied and found differences in the global and total scores among the medications. At day 3 post baseline, the global and total scores of reactions to which clobetasol had been applied were lower (most improved), followed by those of triamcinolone, tacrolimus, and (least improved) pimecrolimus (data not shown). Although the sample size of patients with drug placement that allowed such comparison was very small, the data provide some indication that cross-contamination between sites occurred owing to their close proximity.

A second possible explanation for our findings is the lack of repeated applications of nickel antigen. The study by Saripalli and colleagues, which demonstrated the effectiveness of topical tacrolimus for the treatment of nickel ACD, used a study design that incorporated

repeated nickel insults to a single patch on each inner upper arm.¹⁵ In the study done by Parneix-Spake and colleagues, however, a single insult to induce nickel allergy sufficed for carrying out their 7-day post-nickel ACD study.²⁰

Third, our findings may also be explained by the timing of study visits. In the study conducted by Alomar and colleagues,¹⁶ the visual scores of the reactions to petrolatum started to decrease between 4 and 7 days after the induction of ACD by a nickel patch. Our first assessment after randomization was performed 6 days after the induction of nickel ACD, which may have been too late to detect a difference.

Fourth, our findings may also be explained by the scale used to grade the reactions. With a positive grading scale of 1 to 3 (the NACDG scoring system), the difference between observations may have been too coarse. In a similar study of patch-testing experimentally induced poison ivy and poison oak ACD, Marks and colleagues²¹ used a positive scale of 1 to 7 to grade their reactions. An expanded scale with finer gradations might have been more accurate.

Finally, the size of the sample and the amount of intermediate data points may have been inadequate to detect differences. Future trials involving more patients and an improved study design are needed for comparing the effects of topical steroids and immunomodulating medications on the treatment of ACD.

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