Desoximetasone 0.25% and Tacrolimus 0.1% Ointments Versus Tacrolimus Alone in the Treatment of Atopic Dermatitis

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Long-term in vitro compatibility of desoximetasone and tacrolimus ointments prompted the current trial in humans. We aimed to evaluate the efficacy of twice-daily simultaneous application of desoximetasone and tacrolimus in the treatment of atopic dermatitis versus tacrolimus monotherapy. Eighty-two subjects were treated in this multicenter, single-group, double-blinded, paired, 3-week follow-up clinical study of desoximetasone 0.25% and tacrolimus 0.1% ointments versus tacrolimus 0.1% ointment and vehicle. Subjects were treated twice daily for 21 days or until clearing. Safety and efficacy were assessed at days 3, 7, 14, and 21. The combination of desoximetasone and tacrolimus ointment was superior to tacrolimus alone (P=.0002) in treating atopic dermatitis as measured by the summary of the scores for erythema, lichenification, pruritus, scaling/dryness, and oozing/crusting. Of note, pruritus at the application site was diminished in subjects treated with desoximetasone and tacrolimus together compared with tacrolimus alone (P=.04). Combination treatment with desoximetasone and tacrolimus offered increased efficacy and tolerability over tacrolimus alone in patients with atopic dermatitis.

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Combination therapy is a mainstay of topical dermatologic therapeutics. Classically, this strategy has been employed to treat psoriasis.[1-3] Often, physicians take for granted that 2 ointments, when simultaneously applied, will be compatible and that one will not degrade in the presence of the other. However, topical drug incompatibilities do exist. For example, calcipotriene ointment 0.005% degrades in the presence of salicylic acid ointment 6% or hydrocortisone-17-valerate ointment 0.2%,[4] as does tazarotene gel 0.05% (partially) in the presence of betamethasone dipropionate or clobetasol propionate gel 0.05%.[5] Understanding in vitro compatibility provides a guide for which topicals can be simultaneously used without compromising efficacy.

Flares of atopic dermatitis often require therapy stronger than a single topical agent yet may not warrant systemic medication (prednisone or cyclosporin) or UV light therapy. Combination therapy is not new to atopic dermatitis,[6] and several investigators have experience with combination regimens of tacrolimus and steroids.[7,8] Definitive long-term compatibility of desoximetasone and tacrolimus ointments recently was demonstrated,[9] verifying the stability of both agents in combination for up to

28 days. The present study was performed to validate predictions of enhanced efficacy with simultaneous combination therapy of desoximetasone and tacrolimus ointments versus tacrolimus alone. Given the reported 20% incidence of skin burning, 14% incidence of pruritus, and 8% incidence of erythema with tacrolimus ointment,[10] the adverse event profile of the combination also was examined.

Methods

Subject Selection—To be included, subjects had to be aged 18 years or older, of any race, with a clinical diagnosis of atopic dermatitis of at least 2 months' duration. All subjects signed written informed consent to participate in the study. The severity of the disease at baseline was assessed by totaling the numeric rating for erythema, lichenification, pruritus, scaling/dryness, and oozing/crusting; the total had to be at least 8 out of a possible 15 (for each sign/symptom: 0=none, 1=mild, 2=moderate, 3=severe). Subjects needed 2 bilateral symmetrical target lesions for evaluation at each visit. Pertinent exclusion criteria included superinfected eczema, pregnancy, psoriasis, and use of any confounding topical or systemic medication, especially use of systemic corticosteroids within 28 days of entering the study or topical corticosteroids within one week of entering the study.

Study Design—This was a multicenter, single-group, double-blinded, paired, 3-week follow-up clinical study in which double-active (tacrolimus ointment 0.1% on top of desoximetasone ointment 0.25%) and single-active (tacrolimus ointment 0.1% on top of inert desoximetasone vehicle) sides were compared within individual subjects. One half of the subjects were randomized to apply double-active treatment to affected areas on the left side of the body and single-active treatment to affected areas on the right side, whereas the other subjects were randomized to apply double-active treatment on the right side and single-active treatment on the left side.

Randomization was done individually using a random number table generated independently from the assigning investigator. Assignment was done at the baseline visit. Tubes were labeled and packaged to conceal the identity of the active versus vehicle form of desoximetasone from both investigator and study subject. Both treatments had virtually identical appearance, texture, and odor. The randomization schedule was held by a data management coordinator and with the clinical packaging records. After the database of trial results was locked, the data management coordinator made the randomization code available to the biostatistician. There was no evidence of unmasking by either study subject or investigator.

Subjects were treated twice daily for 21 days or until clearing. Safety and efficacy were assessed at days 3, 7, 14, and 21. Each subject served as his/her own control.

The trial was conducted with the approval of the institutional review boards of the 4 respective study centers (Miami, Florida; Houston, Texas; San Francisco, California; and Louisville, Kentucky).

Clinical Efficacy and Safety Assessments—Representative target lesions of each side of the body were graded for erythema, lichenification, pruritus, scaling/dryness, and oozing/crusting at each visit on a scale of 0 (none) to 3 (severe), allowing for half values (eg, 2.5). The maximum total symptom score was 15, and a score of at least 8 was required for the study. Examinations for signs of skin atrophy and telangiectasia (graded on a scale from 0–3, with half values) of the target lesions also were conducted at each visit. A visit-to-visit global evaluation of change in disease status was made on a 1 (clear) to 6 (flare) scale. Subject self-assessment at each visit was graded from 0 (complete disease control) to 3 (uncontrolled disease). Subject pruritus and burning severity assessments, graded on the same scale as symptom scores (ie, 0–3, with half values), were made at the first 3 visits (baseline, day 3, and day 7). For this measurement, medication was applied under the supervision of an investigator, and burning and itching were assessed by the subject 20 to 30 minutes following the application.

Study Outcomes—Three different outcome types were evaluated in this study: mean change from baseline to day 21 for individual and summary symptom scores, physician global assessment at day 21, and subject perception of pruritus severity from baseline to day 7. All study outcomes were compared within subjects between the double-active and single-active sides.

Statistical Analysis—The statistical procedures employed in this study reflected the fact that the subjects served as their own controls. Statistical analyses were carried out on an intent-to-treat basis (ie, last observation carried forward [LOCF]). The Student 2-tailed paired *t* test, accompanied by 95% confidence limits, was used to compare double-active and single-active sides for individual and total symptom scores and physician global assessment. Any differences were considered statistically significant if their 95% confidence limits excluded the value of zero. For the subject's perception of pruritus severity, rank order distributions for the double-active and single-active sides were compared using the 2-tailed Wilcoxon signed rank test.[11] All statistical procedures were carried out using the SAS® version 8.02 software package.[12] With a sample size of 82, a patient dropout

Table 1.

Demographics of the Study Population (N=82)

Age±SD, y	45.9±18.0
Sex, n (%)	
Male	33 (40)
Female	49 (60)
Race, n (%)	
White	48 (59)
Black	20 (24)
Asian	6 (7)
Hispanic	5 (6)
Other	3 (4%)

allowance of 5%, an α level of 5% (2-tailed), and a standard deviation of 0.6, we had greater than 80% power to detect a difference in the main outcome, physician global assessment score, of 0.2 or greater between the 2 treatment sides.[11]

Results

Demographic Data—Eighty-two subjects who met all inclusion and exclusion requirements were enrolled in the study. Demographic breakdowns of the study group are summarized in Table 1. The study subjects ranged in age from 18 to 85 years, with a mean±SD of 45.9±18.0 years. Men (n=33) comprised 40% of the study group. Forty-eight subjects (59%) were white, 20 subjects (24%) were black, 6 subjects (7%) were Asian, 5 subjects (6%) were Hispanic, and 3 subjects (4%) were other.

Individual Symptom Scores—Seventy-seven of 82 enrolled study subjects had physician-recorded symptom data for both the baseline and day 21 visits (or LOCF). For the 5 subjects who failed to complete the study (because of noncompliance, protocol violation, or withdrawal due to an adverse event), there were no significant differences in baseline symptom scores as compared with the 77 completed subjects. For erythema, pruritus, scaling/dryness, and oozing/crusting, the mean reductions in severity score from baseline were significantly greater for the double-active sides than for the single-active sides ($P<.05$)(Figure 1), with double-active versus single-active differentials ranging from 0.1 to 0.3 (SD,±0.5–0.8). Although lichenification trended toward a greater reduction in the double-active group than in the single-active group, this result failed to reach statistical significance.

Summary Symptom Scores—Mean summary symptom scores for both the double-active and single-active sides were 9.7±1.6 at baseline for the 77 subjects who completed the study. The values for the full study group at baseline were 9.8±1.5. After 21 days of follow-up or LOCF, the mean score for the double-active sides was reduced by 8.1 (95% confidence limits: 7.7, 8.6). The reduction on the single-active sides was 7.3 (6.8, 7.9). When comparing the reduction in summary symptom scores from baseline to day 21 or LOCF on double-active and single-active sides, there was a 0.8 (0.4, 1.2) greater reduction on the double-active side ($P=.0002$).

Physician Global Assessment—The physician global assessment was performed on 77 of 82 study subjects at the day 21 visit or LOCF. The mean score for the double-active sides was 1.9 versus 2.2 for the single-active sides. The difference, 0.3 (0.1, 0.5), between the double-active and single-active sides was statistically significant ($P=.004$). Figure 2 illustrates a typical before and after clinical result for both treatment arms, with some subjects demonstrating a particularly good response to the combination (Figure 3).

Subject Perception of Pruritus Severity—Pruritus related to the application of study medication was assessed at the first 3 visits (baseline, day 3, and day 7). Table 2 shows the distribution of pruritus scores at baseline and day 3 for 69 double-active and single-active sides, with data at both baseline and day 3. The proportions of subjects with pruritus of any degree were quite similar in both groups at baseline (double active, 42%; single active, 39%), and the distributions were not significantly different ($P=.73$, 2-tailed Wilcoxon signed rank test).

At day 3, both the double-active and single-active sides showed improvement from baseline. The maximum scores on the double-active and single-active sides did not exceed 1.5 and 2.0, respectively. The proportions of subjects with any degree of pruritus also decreased but more so on the double-active than the single-active side (16% vs 29%, respectively), and the distributions were significantly different ($P=.04$, 2-tailed Wilcoxon signed rank test).

Comment

Atopic dermatitis can be a frustratingly difficult disease to treat. Effective therapy requires a multifactorial approach, including elimination of superimposed infection, skin hydration, liberal use of emollients,

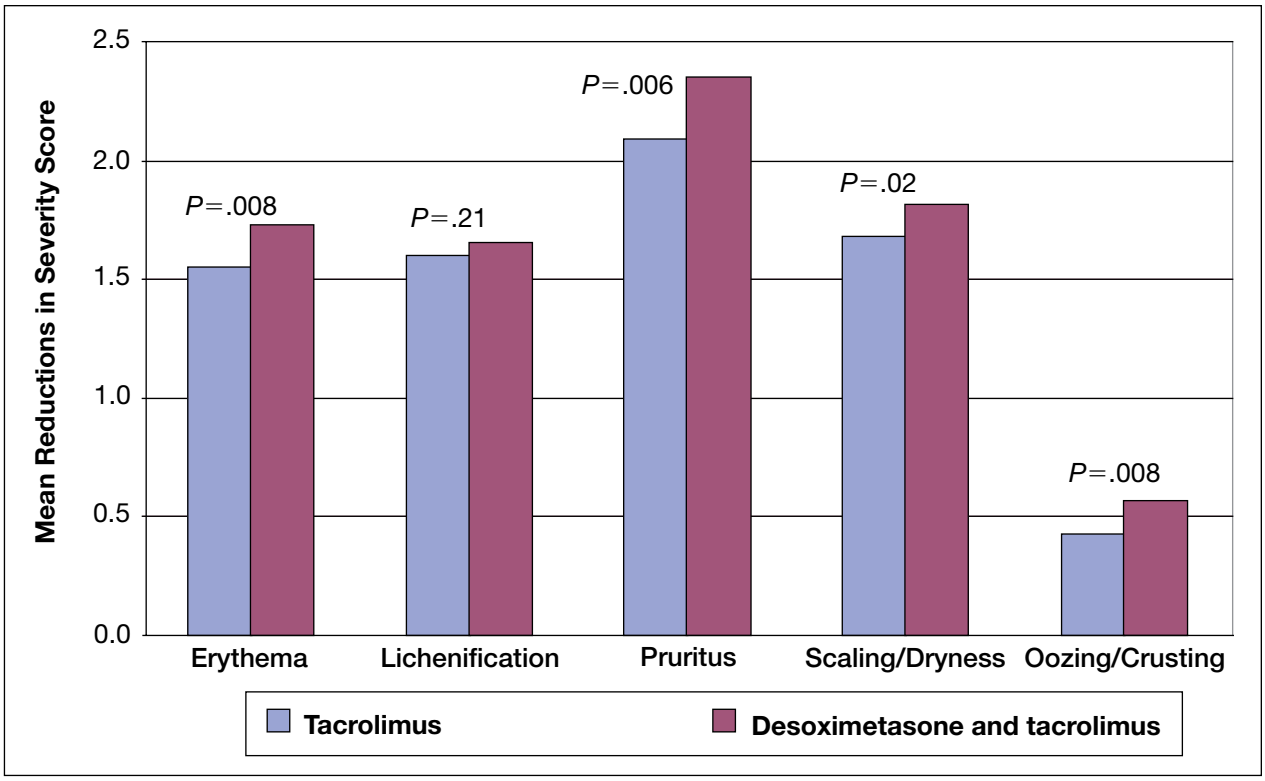

Figure 1. Mean reduction in severity score from baseline to day 21 by symptom. Scores were measured on the following scale: 0=none, 1=mild, 2=moderate, and 3=severe. The differences between placebo and treatment with desoximetasone 0.25% and tacrolimus 0.1% ointments were statistically significant ($P<.05$), barring lichenification.

avoidance of harsh soaps, and medical therapy. Medical therapies range from those with a favorable safety profile to those considered more dangerous. Topical therapies, such as steroids and nonsteroidal immunomodulators, when used appropriately, are considered safe. Risks of topical steroids include skin atrophy, hypopigmentation, and telangiectasia.[13] UVB phototherapy generally is safe, though inconvenient; UVA (although, perhaps not UVA-1) therapy carries a future risk of squamous cell carcinoma. Oral and parenteral steroids, though used frequently for severe flares, have the attendant risk of rebound and dependence, with resulting long-term issues of hypertension, hyperglycemia, osteoporosis, aseptic necrosis of the femoral and humeral heads, cushingoid features, immunosuppression, and adrenal suppression. Other oral immunosuppressants, such as cyclosporin and azathioprine, carry risks of nephrotoxicity, bone marrow suppression, and lymphoma.[13]

The present study demonstrates that the combination of desoximetasone and tacrolimus simultaneously applied twice daily improves atopic dermatitis more than tacrolimus monotherapy. Except lichenification, all signs and symptoms that were examined improved in the combination group more than in the tacrolimus monotherapy group. The relatively short duration of the study might account for the lack of difference in lichenification between the 2 groups. Lichenification takes some time to develop; likewise, it takes time to resolve. The incidence of pruritus is less in the first days of therapy with the combination, which bodes well for increased compliance with therapy using this strategy.

This trial did not compare an arm of desoximetasone monotherapy. It is entirely possible that similar clinical results would have occurred in the absence of tacrolimus in the double-active arm. Because the subjects served as their own controls, the potential for bias in this study was greatly reduced. However, it was still possible that some of the study subjects could have applied the assigned treatments to the wrong side. Because the rules of intent-to-treat dictated that subjects be analyzed according to their randomly assigned treatment, any observed differences could have appeared lower than their actual values. However, in a study with a positive finding, such as ours, a bias to the null was not an issue. The study population had a mix of both sexes, multiple races, and was performed over a varied geographic distribution. For these reasons, the results can be generalized.

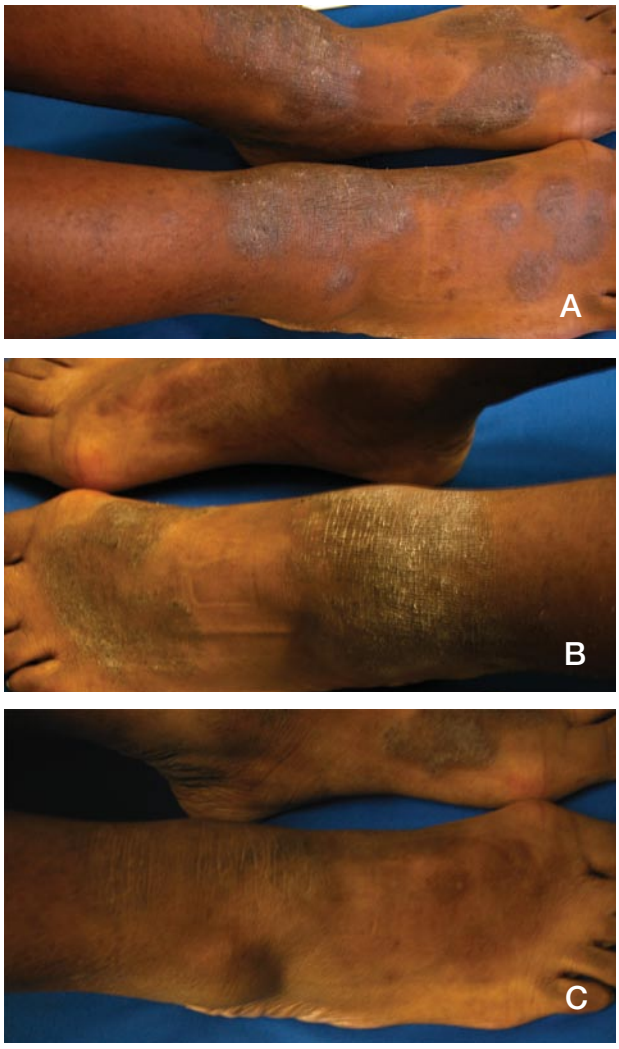

Figure 2. Subject at baseline (A), day 21 after treatment with tacrolimus plus vehicle (B), and day 21 after treatment with desoximetasone plus tacrolimus (C).

The anti-inflammatory effects of topical steroids and the drug's rapid restoration of skin barrier function likely account for the increased tolerability of tacrolimus in the initial stages of a flare when local adverse effects of tacrolimus are known to occur. In fact, an additive, if not synergistic, effect is predicted because of the different mechanisms of action of the 2 agents. Steroids are thought to act through a number of mechanisms, resulting from binding to intranuclear steroid receptors and inhibiting nuclear factor-κB, which is otherwise responsible for chronic inflammation.[14] Tacrolimus is known to inhibit calcineurin, which ultimately prevents entry of nuclear factor of activated T cells from entering the nucleus, thereby avoiding the production of proinflammatory mediators.[15] The enhanced effect observed in the study can likely be accounted for by blocking 2 separate pathways of inflammatory mediator production.

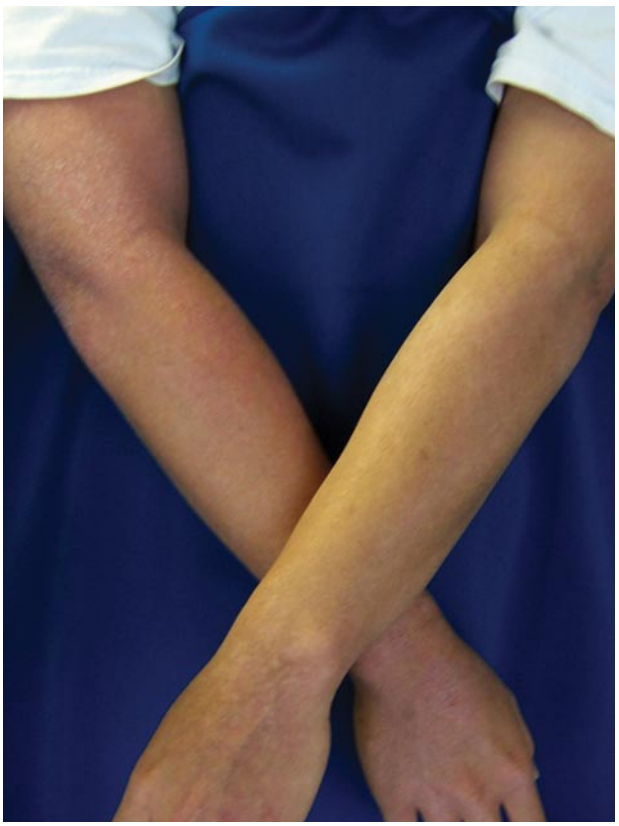

Figure 3. Subject with particularly good outcome with desoximetasone plus tacrolimus (subject's left arm) relative to tacrolimus plus vehicle (subject's right arm) at day 21.

One paradigm to atopic dermatitis therapy envisions a staged approach, akin to that of psoriasis therapy.[16,17] The first stage calls for a quick fix, and the second stage calls for a transition period toward the ultimate goal of the third stage, maintenance. If we apply this paradigm to topical therapy, the quick fix could be combination therapy with desoximetasone and tacrolimus simultaneously applied twice daily. The transition step might be desoximetasone on weekends only with continuous tacrolimus use. The maintenance step could be tacrolimus ointment alone. Furthermore, if systemic agents are used, there is no reason to exclude the addition of an effective topical regimen. Insofar as the present study constitutes the quick fix portion of atopic dermatitis, we anecdotally noticed on poststudy follow-up that the use of the combination on weekends to suppress flares appeared effective when combined with a standard atopic skin care regimen. Indeed, given the current regulatory environment for topical immunomodulators and the standard of care of avoiding continuous long-term application of topical steroids, the combination weekend-only approach leading to maintenance may be worth exploring.

Table 2.

Subject Perception of Pruritus Severity (n=69)*

	Baseline				Day 3			
	Single Active		Double Active		Single Active		Double Active	
Score	n	%	n	%	n	%	n	%
0.0	42†	61	40†	58	49‡	71	58‡	84
0.5	6	9	4	6	8	12	4	6
1.0	8	12	12	17	9	13	5	7
1.5	3	4	4	6	2	3	2	3
2.0	5	7	6	9	1	1	0	0
2.5	3	4	3	4	0	0	0	0
3.0	2	3	0	0	0	0	0	0
Total	69	100	69	100	69	100	69	100

*No data collected for 13 subjects due to missed visits.
†*P*=.73 (2-tailed Wilcoxon signed rank test).
‡*P*=.04 (2-tailed Wilcoxon signed rank test).

Conclusion

The present study demonstrates the existence of novel treatment options for atopic dermatitis based on combination therapy. The enhanced efficacy of twice-daily simultaneous application of desoximetasone and tacrolimus yields an intermediate step between topical monotherapy and more risk-prone systemic therapy. Some advocate the use of a steroid in the morning and tacrolimus at night; however, tacrolimus is indicated for twice-daily application, as are many topical steroids. Although alternate morning/evening application avoids the problem of potential incompatibility, it may not be maximizing efficacy. The significance of this study is that, in the context of rigorous in vitro compatibility data,[9] it provides the largest in vivo data set supporting the simultaneous combination of a steroid, here desoximetasone, and tacrolimus.

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