Report

A randomized, double-blind, placebo-controlled study of clobetasol propionate 0.05% foam in the treatment of nonscalp psoriasis

Mark Lebwohl, MD, FACP, Daniel Sherer, MD, Ken Washenik, MD, PhD, Gerald G. Krueger, MD, Alan Menter, MD, John Koo, MD, and Steven R. Feldman, MD, PhD

From the Departments of Dermatology, Mount Sinai Medical Center, New York; New York University, New York; University of Utah, Utah; Baylor Psoriasis Center, Dallas, Texas; University of California, San Francisco, California; and Wake Forest University School of Medicine, Winston-Salem, North Carolina

Correspondence
Mark Lebwohl, MD, FACP
Mount Sinai Medical Center
One Gustave L. Levy Place
New York, NY 10029-6574
E-mail: sinaiderom@aol.com

Abstract

Background Topical corticosteroids are the primary treatment for mild to moderate psoriasis. Foam preparations of corticosteroids offer potential cosmetic and pharmacodynamic advantages over cream and ointment vehicles. A clobetasol propionate foam product is as effective as clobetasol propionate solution in the treatment of scalp psoriasis.

Aim To evaluate the safety and efficacy of clobetasol propionate foam in the treatment of psoriasis involving sites other than the scalp.

Methods Eighty-one subjects with mild to moderate psoriasis were randomized in a 3 : 1 ratio to receive clobetasol propionate foam vs. placebo foam treatment in this double-blind study of psoriasis involving nonscalp sites. The investigator's and subject's global assessment of the response at week 2 (or at the end of treatment) and at week 4 (follow-up) and the severity of erythema, scaling, and plaque thickness were assessed. Safety was assessed from reported adverse events.

Results After 2 weeks of treatment, there was significantly greater improvement with clobetasol propionate foam compared with placebo foam in both investigator's and subject's global assessment of the response ($P < 0.0005$). The improvement with clobetasol propionate foam was still present at the 4-week follow-up visit. Adverse effects were generally limited to mild to moderate application site reactions. No subjects withdrew because of adverse events.

Conclusions Clobetasol propionate foam is more effective than placebo in the treatment of nonscalp psoriasis. Twice-daily applications are well tolerated, compliance exceeds 90%, cosmetic characteristics are acceptable, and the medication may eliminate the need for separate scalp and body prescriptions.

Introduction

Psoriasis is a common, chronic disorder, estimated to affect 2–3% of the US population.[1] It usually appears first between the ages of 15 and 30 years and may occur anywhere on the skin, including the scalp.

Psoriasis has considerable impact on a patient's quality of life.[1–3] Patients report that one of the most bothersome aspects of the disease is the messiness of the topical agents used to treat it.[4] Topical corticosteroids of different strengths are the primary treatment for localized psoriasis in the US.[5] Typically, ointment-based vehicles are considered to be optimal for use in psoriasis, although these formulations are among the least cosmetically appealing. In addition to direct negative effects on the quality of life, the bothersome aspects of the vehicle probably reduce patient compliance, reducing the effectiveness of the medication in clinical practice (as opposed to clinical research) settings.[6]

A foam delivery system has certain cosmetic advantages over traditional creams, ointments, and solutions.[7–9] The foam is a nongreasy, low-residue vehicle that holds its shape before application. When applied to the skin, body heat causes the foam structure to break down and deposit the active ingredient directly on the lesion. This aspect is particularly advantageous when used on hairy regions.

Betamethasone valerate is available in a low-residue, thermolabile foam vehicle (0.12%, Luxiq™, Connetics Corporation, Palo Alto, CA, USA). The efficacy of the betamethasone valerate foam is greater than betamethasone valerate lotion, and the skin penetration of betamethasone valerate in foam was more than twice that observed for the lotion.[7] The betamethasone valerate foam is approved by the US Food and Drug Administration (FDA) for the treatment of

Table 1 Subject demographics by treatment group

	Clobetasol propionate foam	Placebo foam
Subjects		
Number of subjects	61	20
Subjects who discontinued	3 (5%)	2 (10%)
Age		
Mean age	48.3	45.9
Aged 18–59 years	46	16
Aged 60 years and older	15	4
Sex		
Male	46	11
Female	15	9
Baseline severity		
Mean psoriasis severity	6.0	5.2
Mean pruritus score	1.9	2.3
Scalp psoriasis (% of subjects)	49	50

None of the differences were statistically significant at the $P = 0.5$ level (using Fisher's exact test for the categorical values and a *t*-test for the continuous variables).

corticosteroid-responsive dermatoses of the scalp. It has also been tested for use in nonscalp sites.[10] While effective in reducing the redness, scaliness, and thickness of nonscalp lesions, only 15% of psoriasis patients treated with betamethasone valerate foam for 12 weeks achieved 90% or greater improvement.

Psoriasis is a relatively corticosteroid-resistant condition.[11] The most commonly used topical corticosteroid for the treatment of psoriasis in the US is clobetasol propionate, an ultrahigh potency topical corticosteroid,[12] being considerably more potent than betamethasone valerate. A foam dosage form of 0.05% clobetasol propionate is as effective as clobetasol propionate solution in the treatment of moderate to severe scalp psoriasis.[13] The modest improvement in nonscalp lesions following the twice-daily application of betamethasone valerate foam was the impetus for evaluating the efficacy of clobetasol propionate foam for the treatment of psoriatic lesions at sites other than the scalp. If clobetasol propionate foam proved to be effective at these sites, physicians would need to prescribe only a single corticosteroid preparation for both scalp and nonscalp psoriasis. In addition, the ease of application and cosmetic elegance of the foam would probably increase compliance, which, for psoriasis, has been reported as 40% with conventional vehicles.[6]

Methods

Study design

The study was a randomized, double-blind, placebo-controlled investigation of subjects with mild to moderate plaque-type psoriasis. Subjects were randomized to one of two treatment groups in a 3 : 1 clobetasol propionate foam vs. placebo foam ratio.

Subject pulation

The study population consisted of 81 adult male and female subjects aged 18 years or older with mild to moderate plaque-type psoriasis (Table 1). A minimum severity score of 1 for erythema, scaling, and plaque thickness (using a 0–4 scale) was required. Subjects had target lesions (greater than 1 cm^2) in one or more of the following five anatomical regions: trunk, upper extremities, lower extremities, elbows/knees, and palms/soles. Total body surface area involvement did not exceed 20%. All subjects signed witnessed informed consent, and the appropriate institutional review boards approved the protocol.

Exclusion criteria

Patients who had received investigational medication within the 4 weeks before the study were excluded. Those who had received topical or systemic antipsoriatic therapy were withdrawn from their medication for 2 or 4 weeks, respectively. Sunbathing and exposure to ultraviolet radiation were prohibited during the study, as was the introduction of any medication known to adversely affect psoriasis. The continued use of medications to treat other diseases was allowed. Other exclusion criteria included: pregnant women, women who were breast feeding, or women of child-bearing potential who were not practicing an acceptable method of birth control; men wishing to father children during the study; and current drug or alcohol abusers.

Protocol

Subjects were assigned to a treatment group upon randomization. There was a 2-week treatment phase with visits at baseline, week 1, week 2, and a follow-up visit at week 4. During each patient's first visit, investigators obtained a medical history, reviewed the body systems, graded the extent of psoriatic skin involvement (Table 1), and gave a pregnancy test to women of child-bearing

potential. Investigators also graded the severities of erythema, scaling, plaque thickness, and pruritus on a scale of 0–4. Participants were shown how, when, and where to apply the foams and instructed to return in 1, 2 and 4 weeks for an investigator evaluation of the severity of the target lesions, extent of disease, amount of medication used, use of other medications, and adverse events. Participants were instructed to apply the smallest amount of foam necessary to cover all the lesions. Concomitant use of other topical medications to lesional sites was prohibited, except for bland emollients and low-potency corticosteroids applied to the face or groin. At each visit, investigators weighed the foam containers to determine the amount of product used to correlate the consumption of medication with the extent of body surface area involved and the time required to clear the lesions.

At each visit, the psoriasis severity was assessed separately for five anatomical regions: trunk, upper extremities, lower extremities, elbows/knees, and palms/soles. The erythema, scaling, and plaque thickness were assessed at target lesions in each anatomical region at each visit. Pruritus was also scored. The investigators and subjects recorded the global assessment of the response to treatment, visually integrating the results at all sites, at week 2 (or at the end of treatment) and week 4 (follow-up).

Study drug and dosing

The active treatment was clobetasol propionate foam containing 0.05% clobetasol propionate in cetyl alcohol, stearyl alcohol, polysorbate 60, ethanol, purified water, propylene glycol, citric acid anhydrous, potassium citrate and a butane/propane propellant in an aluminum epoxy phenolic-lined can. Placebo foam was identical to that given above for clobetasol foam, but without the active ingredient clobetasol propionate.

All treatments were administered twice daily (morning and evening) for 2 weeks. Subjects were instructed to not exceed 50 g of study medication per week. Subjects dispensed foam into the cap of the container and applied small amounts of foam to the target lesions on their body. One cap of foam weighs 3.5 g, the maximum amount that the subject applied at each application. All psoriatic lesions in the five anatomical regions were treated, with the exception of those located on the face and intertriginous sites. Subjects were told to treat their identified target lesions prior to treating other psoriatic lesions.

Data analysis

An intention-to-treat analysis was performed. The primary endpoints of the analysis were the investigator's and subject's global assessment of the response, visually integrating the results at all sites, at week 2 (or at the end of treatment) and at week 4 (follow-up). Low values indicated a positive response and high values indicated a minimal or negative response.

Secondary endpoints were the change from baseline to week 2 (or the end of treatment) in pruritus and in the composite score of the signs of psoriasis (erythema, scaling, plaque thickness) for target lesions at each of the five regions of the body (trunk, upper extremities, lower extremities, elbows/knees, palms/soles). The change from baseline in the composite score was calculated as follows.

First, the difference (Δ) between baseline and week 2 was calculated for each individual sign at each anatomical region (region). Then, the Δ values for the signs were summed up for each region, as shown below:

$$\text{Composite Placebo}_{(\text{region})} = \Delta E_{(\text{region})}{}^{pt} + \Delta S_{(\text{region})}{}^{pt} + \Delta P_{(\text{region})}{}^{pt}$$

$$\text{Composite Active}_{(\text{region})} = \Delta E_{(\text{region})}{}^{at} + \Delta S_{(\text{region})}{}^{at} + \Delta P_{(\text{region})}{}^{at}$$

where E = erythema, S = scaling, P = plaque thickness, pt = placebo treatment, and at = active treatment.

The changes were analyzed by the nonparametric Wilcoxon rank sum test and by comparing the means and standard deviations of each treatment group.

Safety was assessed from reported adverse events.

Results

Demographics

Eighty-one subjects were randomized, 61 to clobetasol propionate foam and 20 to placebo foam (Table 1). Three subjects in the clobetasol propionate foam group (one for protocol violation and two for noncompliance) and two subjects in the placebo group (both for protocol violation) did not complete the study. There were no discontinuations due to adverse events. During the 2 weeks of active treatment, subjects applied a mean of 53 ± 4 g (14 ± 1 g per per cent of body surface area affected) of the clobetasol propionate foam and 69 ± 6 g (22 ± 4 g per per cent body surface area affected) of the placebo foam.

Primary outcomes

After 2 weeks of treatment, there was significantly greater improvement with clobetasol propionate foam compared with placebo foam in the primary outcome, investigator's global assessment of response (Table 2). Of the clobetasol propionate foam-treated subjects, 16 (27%) achieved marked or better improvement, compared with one (5%) in the placebo foam group. The greater improvement with clobetasol propionate foam was still present at the 4-week follow-up visit: 15 subjects (26%) treated with clobetasol propionate foam maintained marked or better improvement at the follow-up visit. Similar results were obtained for the subject's global assessment of response. After 2 weeks of treatment, there was significantly greater improvement with clobetasol propionate foam compared with placebo foam (Table 3). The greater improvement with clobetasol propionate foam was again still present at the 4-week follow-up visit.

Secondary outcomes

Pruritus improved quickly with clobetasol propionate foam treatment (Table 4). At the end of treatment (2 weeks), 31 subjects (50%) treated with clobetasol propionate foam

Table 2 Investigator's global assessment of response

	Clobetasol propionate foam	Placebo foam
Week 2 (end of treatment)		
Completely clear	3	0
Almost clear	7	1
Marked improvement	6	0
Moderate improvement	19	2
Slight improvement	14	5
No change	9	9
Worse	2	2
Mean score	3.2*	4.4
Week 4 (follow-up visit)		
Completely clear	3	0
Almost clear	4	1
Marked improvement	8	0
Moderate improvement	7	1
Slight improvement	13	4
No change	17	7
Worse	6	5
Mean score	3.7†	4.7

*P = 0.0005, †P = 0.015; P values compared to placebo from the Wilcoxon rank sum test.

Table 3 Subjects' global assessment of response

	Clobetasol propionate foam	Placebo foam
Week 2 (end of treatment)		
Completely clear	3	0
Almost clear	5	1
Marked improvement	15	1
Moderate improvement	17	1
Slight improvement	12	6
No change	6	8
Worse	2	2
Mean score	2.9*	4.3
Week 4 (follow up visit)		
Completely clear	5	0
Almost clear	5	1
Marked improvement	13	0
Moderate improvement	7	1
Slight improvement	9	4
No change	12	8
Worse	7	4
Mean score	3.3†	4.7

*P = 0.0002, †P = 0.005; P values compared to placebo from the Wilcoxon rank sum test.

Table 4 Pruritus improves rapidly with clobetasol propionate foam treatment

	Clobetasol propionate foam	Placebo foam
Baseline pruritus	1.92 ± 0.15	2.30 ± 0.31
Week 1	0.93 ± 0.13*	1.80 ± 0.31
Week 2 (end of treatment)	0.79 ± 0.12	1.50 ± 0.26
Week 4 (follow-up)	1.14 ± 0.15	1.89 ± 0.36

*P < 0.05; P value from the Wilcoxon rank sum test for pairwise treatment comparisons.

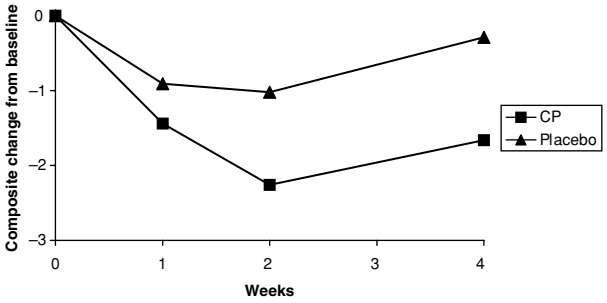

Figure 1 Improvement in the mean composite psoriasis severity score for all treatment sites combined. The composite score of the signs of psoriasis (erythema, scaling, plaque thickness) for target lesions was measured at each of the five regions of the body (trunk, upper extremities, lower extremities, elbows/knees, palms/soles), and the change from baseline in the composite score was calculated. Mean data for all sites combined are shown. Differences between clobetasol propionate foam (CP, filled squares) and placebo foam (filled triangles) were statistically significant at 1, 2 and 4 weeks ($P < 0.05$, P value from the Wilcoxon rank sum test for pairwise treatment comparisons).

had no pruritus compared with four subjects (20%) treated with placebo foam ($P < 0.02$). The composite score of the signs of psoriasis (erythema, scaling, plaque thickness) for target lesions at four regions of the body (trunk, upper extremities, lower extremities, elbows/knees) showed greater improvement with clobetasol propionate foam compared with placebo foam at 1, 2, and 4 weeks (Fig. 1). Palm/sole target lesions showed greater improvement with clobetasol propionate foam compared with placebo foam at 1 and 2 weeks, but there was no statistical difference at the 4-week end-of-treatment visit (however, there were only four subjects with palm/sole target lesions in the clobetasol propionate group and one in the placebo group).

Safety/adverse reactions

Overall, 27 subjects (44%) reported adverse events in the clobetasol propionate group and 10 subjects (50%) in the placebo group. Adverse events in the clobetasol propionate group included application site reactions (17), infection (four), headache (two), dry skin (two), cellulitis, viral infection, dry mouth, coagulation disorder, arthritis, insomnia, contact dermatitis, and fungal dermatitis (one each). In the placebo group, there were application site reactions (six), infection, dry skin, allergic reaction, cyst, flu syndrome, and sinusitis (one each). Only one patient reported an adverse event rated as severe, an application site reaction in the clobetasol propionate foam treatment group.

There were 24 adverse events judged as being possibly, probably, or definitely related to the drug: 18 (30%) in the clobetasol propionate group and six (30%) in the placebo group. In the clobetasol propionate group, these included 17 subjects reporting application site reactions, one with contact dermatitis, and one with dry skin. In the placebo group, six reported application site reactions and one reported dry skin.

Discussion

Numerous topical corticosteroids and other topical products are effective in the treatment of localized psoriasis. Several factors contribute to successful psoriasis treatment. Patient education is one component.[14] Another is to set appropriate expectations.[5] Third, the use of combinations of different treatments improves efficacy and can reduce side-effects.[15,16] Treatment regimens that are too complex or too messy may result in reduced compliance and a less than successful outcome.

Of the many topical corticosteroids available, clobetasol propionate is that most widely used to treat psoriasis.[12] In clinical trials, clobetasol propionate solution and foam exhibited considerable efficacy in treating scalp psoriasis, a notoriously difficult area to treat.[13,17,18] The presence of clobetasol propionate also appears to be responsible for the efficacy of a zinc pyrithione product ("Skin Cap") that caused considerable excitement for the treatment of psoriasis before the presence of clobetasol propionate was identified.[19,20] Clobetasol propionate in a foam vehicle may offer similar potential for increased efficacy through effective delivery of the drug and compliance with therapy.

The safety of clobetasol propionate is important to consider. Local (cutaneous atrophy and striae) and systemic (adrenal suppression and pustular flares) side-effects can occur. ("Skin Cap" was also associated with such reactions.[20,21]) While these reactions were not observed in this short-term study, such reactions might be seen with exposure of a larger number of patients or with more prolonged use; clobetasol propionate foam should be used with caution. Future studies should evaluate safety issues in greater detail. In addition, studies should be performed to compare compliance between clobetasol propionate foam and cream.

Clobetasol propionate foam may be a good choice for many patients. In only 2 weeks, considerable improvement was seen. In this time period, clearing to near-clearing was seen in 17% of subjects, a much more rapid response than was seen with betamethasone valerate foam, where it took 12 weeks to reach this level of improvement. While this was much better than that seen with placebo foam, for many patients it would not be sufficient. Clinical response may be better in patient care settings because of increased duration of use tailored to the severity of the lesions. In addition, the use of the product in combination with other psoriasis treatments may be helpful, but these are as yet undefined.

Acknowledgments

Connetics Corporation provided financial support.

All of the authors have served as funded investigators for Connetics Corporation. Dr Feldman has served as a consultant and Dr Lebwohl as an advisor for Connetic Corporation.

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