An Open Label Study of Clobetasol Propionate 0.05% and Betamethasone Valerate 0.12% Foams in the Treatment of Mild to Moderate Acne Keloidalis

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Acne keloidalis (AK) is a disease affecting primarily African American men. Topical steroids are a widely accepted treatment of AK; however, no studies have been published investigating their effectiveness. The purpose of this open-label study was to assess the efficacy and tolerability of clobetasol propionate 0.05% and betamethasone valerate 0.12% foams in the treatment of AK in 20 African American patients. These patients were treated for 8 to 12 weeks using a pulsed-dose regimen. We found topical clobetasol propionate foam to be effective in improving AK, and our patients found the foam vehicle to be cosmetically acceptable.

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Acne keloidalis (AK) was first described as dermatitis papillaris capillitii by Kaposi in 1869.[1] It was later coined *acne keloidalis* by Bazin in 1872 and *folliculitis keloidalis* by Fox in 1942.[2,3] It is predominantly a condition of African American men[4]; however, it also occurs in African American women[5] and other ethnic groups. The true incidence of AK is varied, and studies suggest a range of 0.45% to 13.7% in blacks.[6-8] Studies performed by Halder et al[9] and Kenny[10] did not find AK to be in the 12 most common diagnoses in African Americans.

AK begins as papules and pustules on the occipital scalp and posterior neck that may develop into nodules or coalesce into plaques. In some cases, other areas of the scalp may be involved, including the vertex. Initially, hair shafts can be seen exiting the affected areas of the scalp; however, continued inflammation leads to the eventual rupture of the hair follicle, follicular scarring, and failure of the hair to regrow, resulting in patchy scarring alopecia. Additionally, abscesses and sinuses may be present. Although AK can be asymptomatic, many patients experience burning, pruritus, or pain in the affected areas, and AK can be cosmetically disfiguring.[1,4,5]

The etiology of AK remains unclear, though infection,[1] chronic irritation from shirt collars[1] or football helmets,[11] drugs such as antiepileptics,[12] autoimmune reactions,[2] and trauma from improperly shaving curved hairs[13] all have been implicated.

Histologically, lesions of AK consist of perifollicular/follicular infiltrates of neutrophils, lymphocytes, and plasma cells. This chronic perifollicular inflammation is most intense at the level of the isthmus and lower infundibulum.[14] Other common histologic findings include lamellar fibroplasia,

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most marked at the level of the isthmus; complete absence of sebaceous glands associated with inflamed follicles; thinning of the follicular epithelium, especially at the level of the isthmus; and polytrichia and total epithelial destruction with residual hair fragments.[14] Epithelial destruction results in a follicular scar, and hypertrophic scarring may occur.

Treatment of early AK focuses on arrest of the inflammatory cycle. Topical steroids have been the primary method of treatment. Yet intralesional corticosteroids, antibiotics, and retinoids also have been used successfully. Delivering topical corticosteroids to hair-bearing areas is somewhat problematic, particularly for cream and ointment preparations. Clobetasol propionate and betamethasone valerate are available in foam vehicles. These foams have been used to successfully treat scalp dermatoses; additionally, they have been found to have greater bioavailability and efficacy than comparable lotion or liquid products.

The purpose of this study was to assess the efficacy of clobetasol propionate 0.05% and betamethasone valerate 0.12% foams in the treatment of AK. No studies to date have shown efficacy of monotherapy with topical steroids in the treatment of AK. We also assessed the tolerability of the foam vehicle in an African American population with AK.

Methods

The study was conducted as an open-label evaluation of 20 African American men and women with a clinical diagnosis of AK of the scalp. All patients were older than 18 years and in good health. Patients were classified as having mild, moderate, or severe disease. Mild disease was defined as less than 25 papules/pustules, moderate as 25 to 50 papules/pustules, and severe as more than 50 papules/pustules. Patients with severe disease were excluded from the study. Evaluations were performed in a private dermatology practice. Patient histories were taken regarding acne, keloids, and pseudofolliculitis barbae. Clinical photographs were taken at baseline and at weeks 4, 8, and 12.

In the first phase of the study, after obtaining informed consent, each patient was treated with a pulsed dose of clobetasol propionate foam (twice-daily therapy for 2 weeks alternated with no therapy for 2 weeks) for 8 weeks. Patients were evaluated every 2 weeks with a papule/pustule count and were again classified as having mild, moderate, or severe disease. Additionally, symptoms of burning, pruritus, and pain were reported using a symptom assessment scale. Global assessments of disease severity also were completed by both the physician and patients at each visit.

At the end of 8 weeks, patients who continued to have persistent disease were given a second phase of treatment using betamethasone valerate foam twice daily for an additional 4 weeks. These patients were evaluated using the papule/pustule count and symptom and global assessments at the end of the 4 weeks (week 12 of the evaluation). At the conclusion of the study, patients were asked to complete a questionnaire regarding the cosmetic acceptance of the foams in addition to a global assessment of efficacy.

Statistical Analysis—Trends in the total count of papules/pustules were statistically analyzed first by fitting a Poisson regression model (accounting for overdispersion) using the generalized estimating equation method to take into account subject clustering and second by including age, gender, and time as predictors. Trends in the global assessment score were tested for significance by using Cochran-Mantel-Haenszel statistics and a weighted least squares approach and by fitting a proportional odds model using the generalized estimating equation method. Trends relating to severity, burning, pruritus, or pain were analyzed using the same techniques, where appropriate. In the evaluation of mild to moderate disease severity data, Poisson models were fit to the data with total counts at a particular time point as the outcome and with severity and counts at the previous time point as predictors. Estimated differences between total counts of disease severity groups controlling for counts at a previous time point could then be assessed to compare the rate of change between both groups.

Results

The study enrolled 20 African American patients (17 men, 3 women). The mean age was 34.8 years (range, 31–46 years). Two patients discontinued the study after the initial visit for unknown reasons. Eighteen patients completed the initial 8 weeks of the study. In addition, 11 patients (61%) continued on to phase 2 of the study and were treated for a total of 12 weeks.

The mean papule/pustule count improved over the course of the study, decreasing from approximately 25 to 10. The mean total papule/pustule count at baseline was significantly greater than at all other time points (adjusted P value, $<.0015$). The mean papule/pustule count also was significantly greater at week 2 compared with weeks 6 and 12 ($P<.05$). There was a slight increase in the mean papule/pustule count from week 2 to week 4 during a time when the patients did not use clobetasol propionate, though this increase was not statistically significant. The mean count

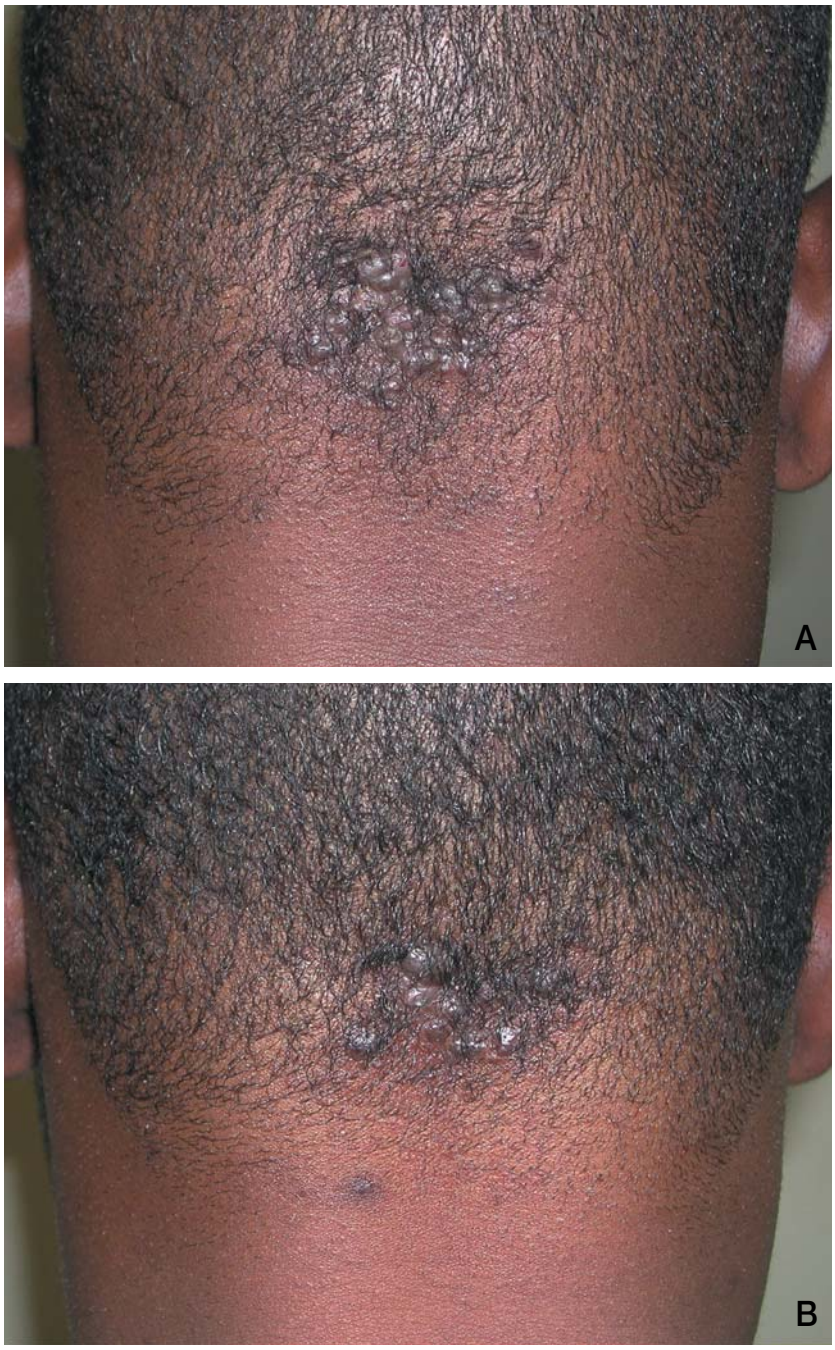

Figure 1. Patient at baseline (A) and after 8 weeks of treatment with clobetasol propionate 0.05% foam and 4 weeks of treatment with betamethasone valerate 0.12% foam (B).

significantly decreased again at the 6-week period after treatment was restarted ($P<.0015$). At the 8-week time point, the total papule/pustule count remained significantly lower than the baseline count and the 4-week count ($P<.05$), despite the second 2-week break from the medication.

Global severity assessments were based on the papule/pustule counts. At baseline, 10 patients were classified as having mild disease and 10 as having moderate disease. At week 8, 16 patients were classified as having mild disease, and only 2 were classified as having moderate disease. Examples of clinical improvement during the 12-week study period are shown in Figures 1 and 2.

Pruritus was the most severe symptom reported by patients. The mean pruritus score decreased significantly from baseline to week 2 ($P<.05$) and increased again from week 2 to week 4 when treatment was withheld. Pruritus severity declined again at week 6 and remained low at week 8. Mean symptom assessment scores for burning and pain were initially very low, limiting our ability to detect a significant change; however, these scores showed a decreasing trend from baseline during the study.

In the second phase of the study, 11 patients were treated for an additional 4 weeks with betamethasone valerate foam twice daily. Paired comparisons involving the differences from week 8 to week 12 for the total papule/pustule count showed no statistically detectable change at $\alpha=.05$. Global assessments by investigators and patients also failed to show a statistically significant improvement/decrement for this 4-week treatment period.

To assess the tolerability of the foams, the patients completed an optional questionnaire. Seventeen questionnaires were partially completed and 12 were fully completed. Seven of 8 respondents (88%) ranked foam as their first preference in vehicle (vs ointment, cream, or gel) for treatment of their AK. When asked to assess the vehicle's impact on their quality of life, 9 of 10 respondents believed that foam was "superior" or "significantly superior" to their previous treatments regarding ease of use, interference in daily tasks, and feeling free from medications. All respondents rated the foam vehicle as "good" or "excellent" in not

leaving a residue and in being stain free, being easy to apply, and not irritating the skin. When asked their dislikes of the new vehicle, 2 patients complained of the medication staying wet/failing to dry, 1 complained of dripping, and 2 complained of the medication drying too fast. Lastly, the questionnaire assessed whether the patients thought the vehicle would impact their adherence to treatment. Twelve of 12 patients believed they would use the medication at least 75% of the time compared with only 4 patients for ointment, 4 for cream, and 2 for gel.

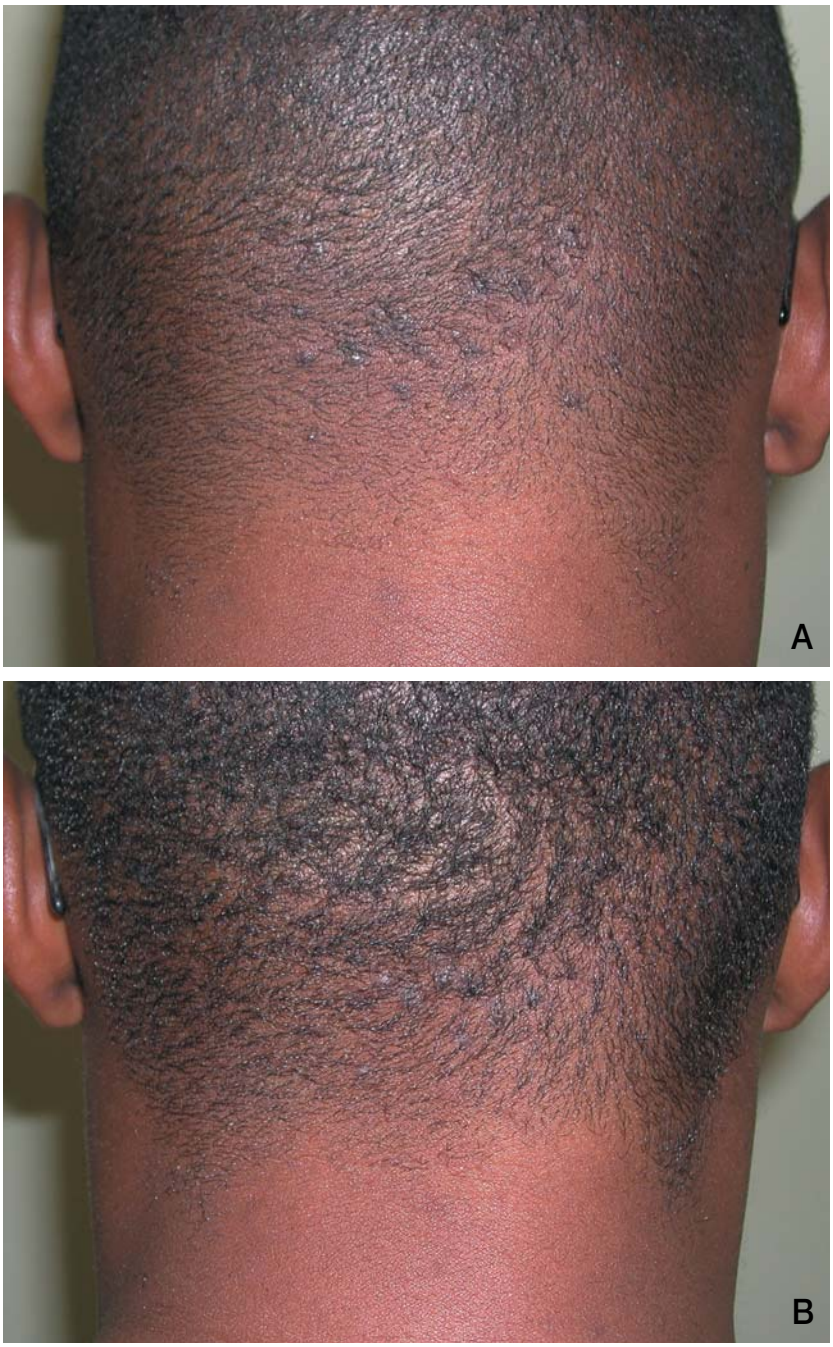

Figure 2. Patient at baseline (A) and after 8 weeks of treatment with clobetasol propionate 0.05% foam (B).

Comment

AK can be a disfiguring disease. It is possible that with early treatment, permanent scarring can be minimized and the need for surgery prevented. Topical corticosteroids have been used as a primary treatment for early AK. In this study, the efficacy of clobetasol propionate foam applied twice daily was confirmed both by objective assessment (number of papules/pustules) and by physician and patient global assessments.

Using a 2-week on/2-week off pulsed-dose regimen, there was initial improvement that was generally maintained throughout the 8-week study. There was some increase in severity after the first 2-week treatment-free period, but this was not seen after the subsequent pulsed-dose regimen. The treatment also reduced the patients' symptoms of burning, pruritus, or pain. The mean pruritus severity score was greatly decreased from baseline at all time points with the clobetasol propionate treatment.

Most published reports on AK treatment focus on management of extensive disease. Intralesional triamcinolone acetonide,[15,16] surgical excision with both primary[17] and secondary[18] intention closure, cryosurgery,[16] and carbon dioxide laser[18] all have been reported to be effective in treating large keloidal lesions of AK. Although topical corticosteroids are widely regarded as an effective treatment of AK,[4,5,19,20] an extensive search of the literature revealed no published data supporting their use. Our study may therefore be the first to demonstrate the effectiveness of topical corticosteroids as monotherapy in the treatment of mild to moderate AK. Our study focuses mainly on the use of intermittent dosing with superpotent topical corticosteroids. Perhaps a randomized

control trial using different topical steroids with alternative dosing regimens would help elucidate the optimal steroid preparation and dosing schedule for treating AK.

Patients reported satisfaction with the foam vehicle. The cosmetic acceptability of the foam may have a role in improving patient adherence to a therapeutic regimen. The location of AK in most patients is the occipital area and posterior neck, which is in close contact with shirt collars; therefore, vehicle selection is an important factor in treatment because most ointment-based preparations have the potential to stain shirt collars, which may decrease patient compliance.

A limitation of this and previous studies that analyzed patients' preferences for a foam vehicle is that they do not directly assess adherence to therapy. Analysis of adherence using a validated measure would add considerably to our understanding of the impact of vehicle on adherence and treatment outcomes.

The small size of this study is not a major limitation as the study was sufficiently powered to detect improvement in disease severity. However, a significant limitation of this study is its open design. A placebo-controlled trial may be warranted, but in defense of the open design, one would not expect significant improvement in AK with placebo alone. Moreover, all parameters of the condition improved. Finally, we consider the office-based setting of this study to be a major strength. The efficacy of clobetasol propionate was observed in actual patients in a private practice setting, and this patient population may be more representative of clinical practice than participants in a research clinic setting.

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