

The Efficacy and Safety of Azelaic Acid 15% Foam in the Treatment of Facial Acne Vulgaris

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ABSTRACT

Background: Azelaic acid demonstrates anti-inflammatory, anti-oxidative, anti-comedogenic, and anti-microbial effects. Azelaic acid 20% cream is currently approved for the treatment of acne vulgaris, and azelaic acid 15% foam has recently been approved for rosacea. Given the favorable tolerability profile of foam preparations, it is reasonable to assume that azelaic acid 15% foam could serve as a viable treatment option for facial acne.

Objective: To examine the efficacy and safety of azelaic acid 15% foam in the treatment of moderate-to-severe facial acne

Methods: Twenty subjects with moderate-to-severe facial acne vulgaris were enrolled in this two-center, open-label pilot study. All study subjects were treated with azelaic acid 15% foam for 16 weeks. Efficacy analyses were based on the change in facial investigator global assessment (FIGA) and changes in total, inflammatory, non-inflammatory lesion counts between baseline and week 16.

Results: There was a significant reduction in FIGA scores from baseline to week 16 ($p = .0004$), with 84% of subjects experiencing at least a 1 grade improvement, and 63% of subjects achieving a final grade of Clear or Almost Clear. All subjects experienced reductions in inflammatory and total lesion counts by week 16, and 89% of subjects experienced reductions in non-inflammatory lesions. Azelaic acid 15% foam was well tolerated, with almost all instances of erythema, dryness, peeling, oiliness, pruritus, and burning being of mild or trace degree, and most adverse effects resolving by the end of the study.

Conclusion: Azelaic acid 15% foam is effective and safe in the treatment of facial acne vulgaris. Given the convenience of foam vehicles, azelaic acid 15% foam should be considered as a viable treatment option for this condition.

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INTRODUCTION

Acne vulgaris is a common chronic inflammatory skin disorder with a global prevalence reaching as high as 60-80% in individuals 12-25 years of age.[1] Although acne is traditionally perceived as a disease affecting adolescents, there is an increasing prevalence of late-onset, recurrent, or persistent acne in post-adolescent females over the age of 25.[2,3] The pathogenesis of acne is multifactorial, including abnormal follicular hyperkeratinization, androgen-related sebum overproduction, proliferation of *Propionibacterium acnes* in pilosebaceous follicles, and subsequent perifollicular inflammation.[3,4] Conventional first-line therapies, such as topical retinoids, anti-bacterials, and anti-inflammatory agents, are used to address each major factor in acne formation.

Azelaic acid is a naturally occurring, saturated, dicarboxylic acid that targets the major factors implicated in the pathogenesis of acne through its anti-inflammatory, anti-bacterial, and anti-keratinizing actions.[5,6] Azelaic acid 20% cream is currently approved for the topical treatment of mild-to-moderate inflammatory acne and has been shown to provide statistically significant reductions in both inflammatory and non-inflammatory lesions in phase III clinical trials.[7-10] It provides an especially useful topical treatment for women who are pregnant or breastfeeding (classified as pregnancy risk category B).

Although the foam formulation of azelaic acid 15% is currently only approved for the topical treatment of papulopustular rosacea, it is commonly used off-label in the treatment of acne.[11] The foam formulation is highly efficacious due to its enhanced drug release and bioavailability.[12,13] Importantly, the favorable cosmetic acceptability and tolerability profile of the foam vehicle may enhance treatment compliance and outcomes.[10,12] This pilot study aimed to evaluate the efficacy, safety, and tolerability of azelaic acid 15% foam in the treatment of moderate-to-severe facial acne.

METHODS

Study Design and Subjects

This 16-week, two-center, open-label study was conducted in patients with moderate-to-severe facial acne. Male and female subjects of any race, 18 years of age or older, were eligible for inclusion in the study if they exhibited moderate-to-severe

facial acne as defined by a Facial Investigator Global Assessment (FIGA) score of 3 or 4 (Table 1). Subjects were required to be able to understand the requirements of the study and be capable of providing informed consent. Pregnant women, breastfeeding mothers, and females of childbearing potential who were not practicing a reliable method of contraception were excluded from study participation. Females of childbearing potential were required to have a negative urine pregnancy test at baseline and at every study visit, in addition to practicing a reliable method of contraception for the duration of the study. The following exclusionary criteria were also applied: allergy or sensitivity to any component of the test medication, medical conditions that contraindicated participation, skin diseases/disorders that interfered with the diagnosis or evaluation of acne vulgaris, evidence of recent alcohol or drug abuse, history of poor cooperation, non-compliance with medical treatment, or unreliability.

Subjects were required to complete the following washout periods: 1 week for over-the-counter acne medications or bleaching agents; 2 weeks for topical therapy with retinoids, antibiotics, benzoyl peroxide, dapsone, bleaching agents, cryotherapy, chemical peels, or microdermabrasion; 4 weeks for oral antibiotics or other investigational drugs; 24 weeks for oral retinoids or laser resurfacing and dermabrasion.

The study was performed in accordance with Good Clinical Practices, including guidelines outlined by the International Conference on Harmonisation. Institutional review board approval was obtained from each participating center. Informed consent was obtained from all study participants prior to enrollment.

Treatment

All subjects received azelaic acid 15% foam, a white to off-white hydrophilic emulsion supplied in a 50 g aluminum can pressurized with propellants. Azelaic acid 15% foam contains 15 mg/g of azelaic acid in a vehicle consisting of benzoic acid, cetostearyl alcohol, dimethyl isosorbide, medium-chain triglycerides, methylcellulose, mono- and di-glycerides, polyoxyl 40 stearate, polysorbate 80, propylene glycol, purified water, sodium hydroxide, and xanthan gum.[11]

Subjects were instructed to apply azelaic acid 15% foam sparingly to the entire facial area (cheeks, chin, forehead, and nose) twice daily (morning and evening) and to massage gently into the skin until the foam vanished.

Efficacy Assessments

All subjects were evaluated at baseline before drug administration and at follow-up visits at week 4, week 8, week 12, and week 16. Static assessments of facial acne severity were completed at each visit using the 6-point FIGA, ranging from 0 (clear) to 5 (very severe) (Table 1). The primary efficacy endpoint of this study was the percent of subjects who achieved Clear or Almost Clear FIGA scores at week 16. Secondary endpoints included the percent reduction of total, inflammatory, and non-inflammatory lesion counts at week 16 as compared to baseline.

TABLE 1.

Facial Investigator Global Assessment Scale (FIGA)		
Score	**Severity**	**Description**
0	Clear	No inflammatory or non-inflammatory lesions
1	Almost Clear	Rare non-inflammatory lesions with no more than one small inflammatory lesion
2	Mild	Greater than Grade 1; some non-inflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
3	Moderate	Greater than Grade 2; some to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4	Severe	Greater than Grade 3; some to many non-inflammatory and inflammatory lesions, but no more than a few nodular lesions
5	Very Severe	Greater than Grade 4; many non-inflammatory and/or inflammatory lesions with some or many nodular lesions

At the final visit at week 16, subjects were additionally given a "Patient Preference Questionnaire". This questionnaire asked subjects to rank different treatment vehicles that they had used in the past (gel, lotion, cream, ointment, and spray) from "liked the least" to "liked the best". Subjects were also asked to compare the study medication against medications that they had used in the past based on ease of use, ability to continue daily activities directly after application, feeling of skin after application, ability to apply to large body surface areas, and absorption. Finally, subjects were asked to rate the study foam on the following qualities: moisturizing, lack of residue, grease, absorption, ease of application, lack of fragrance, spreadability.

Safety and Tolerability

Tolerability was evaluated at baseline before drug administration and at all visits. Investigator assessments of erythema, dryness, peeling, and oiliness severity were rated on a 5-point scale (absent, trace, mild, moderate, severe) (Table 2). Subject assessments of pruritus and burning/stinging severity were rated on a 6-point scale (absent, trace, mild, moderate, marked, severe) (Table 3).

Adverse events and concomitant medications or treatments were monitored throughout the study. For each adverse event, including cutaneous and systemic events and any reported subjective skin symptoms, the investigator assessed the duration,

TABLE 2.

Investigator Assessments of Erythema, Dryness, Peeling, and Oiliness Severity					
Score	**Severity**	**Erythema**	**Dryness**	**Peeling**	**Oiliness**
0	Absent	No redness	None	Smooth	Normal
1	Trace	Faint red or pink coloration, barely perceptible	Barely perceptible dryness by palpation with no accentuation of skin markings, skin desquamation (flakes) or fissure formation	Fine peeling, barely perceptible	Mild and localized
2	Mild	Light red or pink coloration	Easily perceptible dryness by palpation with accentuation of skin markings but no skin desquamation (flakes) or fissure formation	Slight peeling	Mild and diffuse
3	Moderate	Medium red coloration	Easily noted dryness with accentuation of skin markings and skin desquamation (small flakes) but no fissure formation	Definitely noticeable peeling	Moderate and diffuse
4	Severe	Beet red coloration	Easily noted dryness with accentuation of skin markings, skin desquamation (large flakes) and/or fissure formation	Extensive peeling	Prominent and dense

severity, seriousness, causal relationship to the study medication, and the course of action taken.

Statistical Analyses

Analyses of efficacy endpoints were based on data from subjects who completed the study. All statistical tests were two-sided and interpreted at a 5% significance level. Changes in FIGA as well as total, inflammatory, and non-inflammatory lesion count were evaluated using the Wilcoxon signed-rank test. The incidence and severity of all adverse and/or unexpected events was tabulated and classified by intensity and relationship to the study medication.

RESULTS

Subjects

Twenty subjects with moderate-to-severe facial acne vulgaris were enrolled (Table 4). The average age was 26 years, with ages ranging from 18 to 39 years. All subjects were female, of which 75% were white, 20% were black, and 5% were of mixed race. All study subjects were treated with azelaic acid 15% foam for 16 weeks. All subjects completed the 16-week study period, with the exception of 1 subject who was lost to follow-up (moved away) after week 8.

TABLE 3.

Subject Assessments of Pruritus and Burning/Stinging		
Score	**Severity**	**Description**
0	Absent	Normal, no discomfort
1	Trace	An awareness, but no discomfort and no intervention required
2	Mild	Noticeable discomfort causing intermittent awareness
3	Moderate	Noticeable discomfort causing continuous awareness
4	Marked	Definite discomfort causing continuous awareness interfering occasionally with normal daily activities
5	Severe	Definite, continuous discomfort interfering with normal daily activities

Efficacy

Facial Investigator Global Assessment (FIGA)

There was a significant reduction in FIGA scores from baseline to week 16 ($p = 0.0004$). At baseline, 18 subjects had a FIGA score of 3 (moderate), and 1 subject had a FIGA score of 4 (severe). 12 subjects (63%) were Clear or Almost Clear by week 16. 16 subjects (84%) experienced at least a 1-grade improvement, and 12 subjects (63%) experienced at least a 2-grade improvement by week 16.

TABLE 4.

Subject Demographic and Baseline Characteristics	
Age, years	Subject Characteristics (n=20)
Mean (SD)	26 (7)
Range	18-39
Sex, % female	100
Ethnicity	
White (%)	15 (75)
Black (%)	4 (20)
Mixed Race (%)	1 (5)
Mean scores at baseline	
Total lesion count (SD)	38 (17)
Inflammatory lesion count (SD)	16 (5)
Non-Inflammatory lesion count (SD)	23 (18)

TABLE 5.

Summary of FIGA Scores by Study week. Values are count (%)

Visit	Facial IGA					Clear or Almost Clear	1-Grade Improvement	2-Grade Improvement
	Clear	Almost Clear	Mild	Moderate	Severe			
Baseline	-	-	-	18 (95%)	1 (5%)	-	-	-
Week 4	-	-	5 (26%)	14 (74%)	-	-	6 (32%)	0 (0%)
Week 10	-	3 (16%)	7 (37%)	9 (47%)	-	3 (16%)	11 (58%)	3 (16%)
Week 12	1 (5%)	5 (26%)	6 (32%)	7 (37%)	-	6 (32%)	13 (68%)	6 (32%)
Week 16	2 (10%)	10 (53%)	4 (21%)	3 (16%)	-	12 (63%)	16 (84%)	12 (63%)

Lesion Counts

Significant reductions in mean and median lesion counts occurred within the first 4 weeks of treatment and were sustained or improved throughout the remainder of the study (Figure 1; Table 6). All subjects experienced reductions in inflammatory and total lesion counts by week 16, and 17 of 19 experienced reductions in non-inflammatory lesion counts.

Questionnaire

When questioned regarding preferences in treatment vehicle, subjects indicated that lotions and creams were generally preferred over gels, ointments, and sprays. Subjects generally preferred the study medication over previously used medications, and most commonly rated its qualities as "good" or "excellent".

Safety and Tolerability

Azelaic acid 15% foam was well tolerated. There were 14 reports of erythema, 3 reports of dryness, 4 reports of peeling, 4 reports of oiliness, 12 reports of pruritus, and 7 reports of burning. There was 1 instance of moderate erythema, 2 instances of moderate pruritus, and 1 instance of moderate burning. All other instances were mild or trace readings, and most instances involved only trace readings that resolved by the end of study.

Nine subjects experienced a total of 12 adverse events. Non-serious adverse events that were determined by investigators to be related to the study medication were mild in nature, cutaneous, and occurred at the application site. These included: itching on an eyebrow after drug application (resolved), itching at the application site for 25 minutes (resolved), burning at the application site (unresolved), and a tingling sensation at the application site (resolved). One subject experienced swelling and peeling in the treatment area of moderate severity that was determined to be unlikely to be related to study medication. Study drug application was interrupted for 4 days, and the event resolved with no residual effects. Other non-serious adverse events were mild and determined to be definitely unrelated to study medication included: sunburn, sinus infection, hyperthyroidism, streptococcal pharyngitis, tonsillitis, and

FIGURE 1. Reduction in inflammatory, non-inflammatory, and total lesion count at each study visit (mean and SEM).

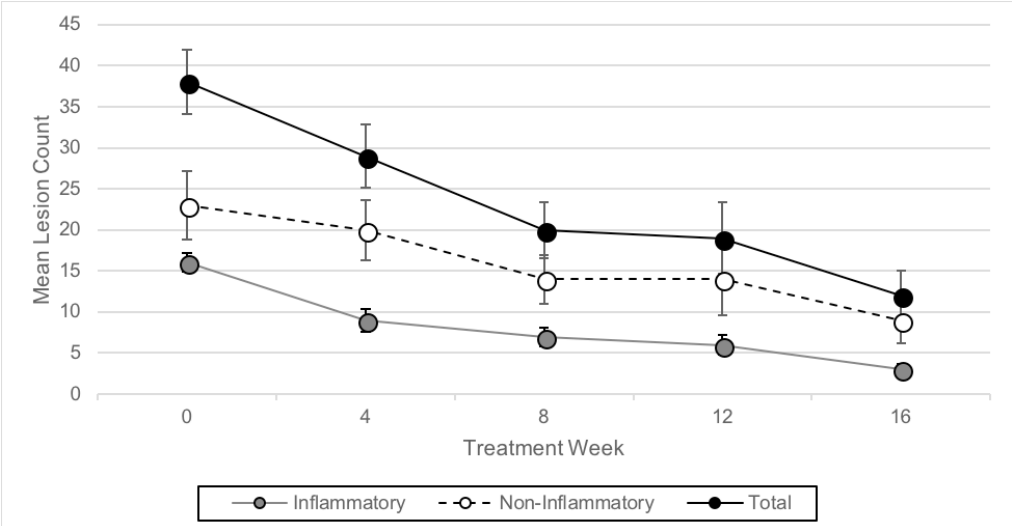

TABLE 6.

Percent Reduction in Inflammatory, Non-inflammatory, and Total Lesion Count at Each Study Visit

Week	Inflammatory		Non-Inflammatory		Total	
	% Reduction from Baseline (SD)	*P*-Value	% Reduction from Baseline (SD)	*P*-Value	% Reduction from Baseline (SD)	*P*-Value
4	45 (28)	0.0002	4 (54)	0.39	26 (27)	0.002
8	57 (23)	0.0001	42 (44)	0.004	50 (21)	0.0002
12	64 (24)	0.0002	46 (41)	0.002	55 (27)	<0.0001
16	77 (23)	0.0001	64 (33)	0.0003	73 (17)	<0.0001

sinus infection. One serious adverse event of bronchitis, moderate severity, was reported and determined to be unrelated to study medication. No therapy was initiated, and the event resolved with no residual effects.

DISCUSSION

Over a 16-week period, treatment with azelaic acid 15% foam led to decreases in the number of total, inflammatory, and non-inflammatory lesions in subjects with moderate-to-severe facial acne. Subjects showed an average 77% reduction in inflammatory lesion counts, 64% reduction in non-inflammatory lesion counts, and 73% reduction in total lesion counts. Reductions in lesion counts were supported by static physician assessments of facial severity, with a majority of subjects rated as "clear" or "almost clear" by the conclusion of the study. Azelaic acid 15% foam was well-tolerated on the facial area, and questionnaire results indicated that subjects viewed the foam vehicle as easily applicable and cosmetically appealing.

Future research should expand upon this work in larger sample sizes and with vehicle control as well as active comparators. This study establishes azelaic acid 15% foam as a promising, safe, and efficacious therapy option for patients with moderate-to-severe facial acne.

DISCLOSURES

Dr. Hashim and Tinley Chen have no conflicts of interest to disclose. Dr. Harper is a consultant, researcher, and speaker for Bayer HealthCare Pharmaceuticals Inc. Dr. Kircik has served as an advisor, investigator, consultant, and speaker for Allergan, Bayer, Galderma, Promius Pharma, Sun Pharma, Stiefel/GSK, LeoPharma, Taro, Valeant, and Warner-Chilcott. This study was funded by Bayer as an investigator-initiated study.

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