Azelaic Acid Foam 15% in the Treatment of Papulopustular Rosacea: A Randomized, Double-blind, Vehicle-Controlled Study

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Rosacea is a common chronic inflammatory skin disease that primarily affects facial skin. Its etiology is unknown, and currently there is no cure. Rosacea can be associated with severe symptoms, including transient erythema (flushing), nontransient erythema, papules, pustules, and telangiectases, leading to substantial discomfort and an unattractive appearance. This randomized, double-blind, vehicle-controlled, multicenter, parallel-group study conducted over 12 weeks with a 4-week follow-up period evaluated the efficacy and safety of a new formulation of azelaic acid (AzA) foam in a 15% concentration compared to vehicle alone in patients with papulopustular rosacea (PPR). Primary efficacy variables assessed were investigator global assessment (IGA) dichotomized into success and failure, and nominal change in inflammatory lesion count from baseline to end of treatment. Results indicated that the new foam formulation of AzA is effective and well-tolerated in a population of patients with PPR. Although no single formulation is appropriate for all patients, the development of a new foam formulation in addition to other available vehicles provides patients with options and allows health care providers to match the needs as well as preferences of individual patients and skin types with appropriate delivery modalities.

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Rosacea is a common chronic inflammatory skin disease affecting approximately 16 million Americans alone[1] and is responsible for 0.5% to 3% of all cases seen in dermatology clinics.[2-6] Notably, a rosacea prevalence of 10% was reported in a nonselected population of office employees in Sweden (N=809).[7] Rosacea primarily affects individuals aged 30 to 50 years who are of Northern European descent. Up to one-third of rosacea patients have a family history of the disease.[2]

Rosacea primarily affects the convex surfaces of the central face and is characterized by a range of heterogeneous symptoms, including transient erythema (flushing), nontransient erythema, papules, pustules, and telangiectases. Patients may report burning and stinging sensations, skin irritation, scaling, and edema on the face. Many symptoms

of rosacea (eg, flushing) can be exacerbated by external factors such as exercise, emotional stress, alcohol consumption, and extreme weather conditions.[2] Although rosacea is not life threatening, there currently is no cure. Furthermore, rosacea can have a negative impact on a patient's quality of life (QOL), often causing substantial physical and emotional discomfort.

The pathogenesis of rosacea is believed to be multifactorial. Dysregulation of the innate immune system is thought to play a primary role in the disease.[2] The symptoms of rosacea also may be elicited or exacerbated by the presence of reactive oxygen species in the skin.[8] Microorganisms, particularly *Bacillus oleronius* (carried by the common human skin mites *Demodex folliculorum* and *Demodex brevis*) have been implicated in the pathogenesis of rosacea.[9] In some patients, disordered keratinization also may play a role. Nevertheless, the etiology of rosacea remains unknown.

Rosacea is classified into 4 subtypes and 1 variant based on morphology,[10,11] including erythematotelangiectatic rosacea (subtype 1), papulopustular rosacea (PPR)(subtype 2), phymatous rosacea (subtype 3), ocular rosacea (subtype 4), and granulomatous rosacea (variant). Papulopustular rosacea, the focus of this study, is characterized by persistent central facial erythema with transient papules and/or pustules in a centrofacial distribution.[11] The PPR subtype resembles acne vulgaris, except for the absence of comedones and presence of persistent erythema. Patients with PPR may report burning and stinging sensations; however, irritation from external stimuli is not a consistent feature.

Azelaic acid (AzA)(1,7-heptanedicarboxylic acid or nonanedioic acid) is a straight, medium-chain, saturated dicarboxylic acid produced naturally by a yeast *Malassezia furfur* that lives on the skin of many animals, including humans; it also is found in plants such as wheat, rye, and barley. Low levels of AzA have been identified in healthy individuals and higher levels have been noted in patients with ketosis as well as those with a congenital or acquired inability to oxidize monocarboxylic acids.[12,13] Data show that AzA lacks acute or chronic toxicity; in addition, it is nonteratogenic and nonmutagenic.[13] Azelaic acid has multiple, potentially additive or synergistic mechanisms of action in the treatment of dermatologic conditions (eg, rosacea), including substantial anti-inflammatory,[14] antioxidant,[15] and antimicrobial[16-21] properties, as well as mild antikeratinizing properties.[22,23] Azelaic acid also may reduce inappropriate melanization of the skin through its antityrosinase activity.[24] In clinical settings, AzA has demonstrated efficacy and safety in the initial treatment of and long-term maintenance therapy for PPR,[25-32] and a 15% gel formulation has been approved by the US Food and Drug Administration for the treatment of inflammatory papules and pustules of mild to moderate rosacea.[33] Currently, AzA is only approved for treatment of rosacea in a gel formulation; however, clinical studies are being conducted to evaluate the efficacy and safety of a new AzA 15% foam formulation.

Azelaic acid foam 15% is an oil-in-water emulsion prepared using standard processes and excipients, with active AzA dispersed in a micronized form. Foam has become an increasingly popular vehicle in the treatment of skin conditions because of its ability to deliver drugs to the affected area while maintaining characteristics preferred by patients over other vehicles.

This randomized, double-blind, vehicle-controlled, multicenter, parallel-group study evaluated the efficacy and safety of AzA foam 15% versus vehicle in the treatment of PPR. Participants from each group applied AzA or vehicle twice daily for 12 weeks, and maintenance effects and recurrence of disease were evaluated during a 4-week follow-up period. Results indicated that a foam formulation of AzA would be a useful addition to the armamentarium of topical products that currently are available for treatment of PPR.

Methods

Study Design—A randomized, double-blind, vehicle-controlled, parallel-group study was conducted in 20 study centers across the United States. Before initiation of the study, the institutional review board at each institution where the trial was conducted approved the protocol. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Guideline for Good Clinical Practice, and other applicable regulatory requirements. All patients provided written informed consent. Only investigators qualified by dermatology training and experience and approved by the sponsor were selected as appropriate experts.

The study participants included men and women aged 19 years and older who had been diagnosed with PPR (investigator global assessment [IGA] score of moderate or severe) and presented with a minimum of 12 but no more than 50 inflammatory lesions as well as persistent erythema with or without telangiectasia. Major exclusion criteria included known unresponsiveness to AzA; presence of dermatoses that might interfere with rosacea diagnosis and/or evaluation; presence of ocular or phymatous rosacea; laser surgery on the face for

treatment of telangiectasia or other conditions within 6 weeks of the study; use of any topical prescription or nonprescription medications to treat rosacea within 6 weeks of or during the study; systemic use of any prescription or nonprescription medications to treat rosacea (ie, retinoids within 6 months of or during the study; tetracycline [eg, doxycycline, minocycline] within 2 months of or during the study; corticosteroids, erythromycin, and/or azithromycin within 4 weeks of or during the study); and expected initiation or change in dose in the last 90 days of treatment with beta-blockers, vasodilators, vasoconstrictors, nonsteroidal anti-inflammatory drugs, hormone therapy, and/or other drugs known to cause acneform eruptions.

Participants were randomly assigned in a 1:1 ratio to 1 of 2 treatment groups: AzA foam or vehicle (excipients alone). Both treatments were administered twice daily. The computer-generated randomization procedure used blocks. Whole randomization blocks were allocated to the study centers, ensuring that the comparison groups maintained the planned allocation ratio for the treatment groups overall and within each center. For each application, 0.5 g of foam was dispensed in the palm of the hand, dispersed with the fingers, administered to facial skin (ie, cheeks, chin, forehead, nose), and rubbed in gently until fully absorbed twice daily in the morning and evening during the entire 12-week treatment period. Compliance with treatment was assessed from participant diaries; in addition, the foam dispensers were weighed to calculate the total amount of product used. After completing the 12-week treatment period, all participants underwent a 4-week follow-up period.

Efficacy Evaluations—There were 2 primary efficacy variables. The first primary end point was therapeutic success rate, which was classified as either success (defined as at least a 2-point improvement from baseline, with resulting IGA scores of clear or minimal) or failure (defined as IGA scores of mild, moderate, or severe) at end of treatment (Table 1). The second primary end point was the nominal change in inflammatory lesion count from baseline to end of treatment. Change in inflammatory lesion count was calculated by subtracting the sum of the inflammatory lesions (papules and pustules) at baseline from the number of lesions at the end of treatment.

Secondary efficacy variables included the percent change in inflammatory lesion count as well as treatment response rate, which was determined by dichotomizing the IGA as responders (clear, minimal, or mild IGA) and nonresponders (moderate or severe IGA).

For success rate and response rate analyses, participants who withdrew from treatment due to lack of efficacy were considered nonresponders.

Additional variables included ratings of erythema, telangiectasia, and facial skin color (Tables 2–4), as well

Table 1.

Investigator Global Assessment

Score	Description
Clear	Virtually no rosacea, no papules or pustules, no erythema
Minimal	Rare papules and/or pustules, residual to mild erythema
Mild	Few papules and/or pustules, mild erythema
Moderate	Pronounced number of papules and/or pustules, moderate erythema
Severe	Numerous papules and/or pustules, occasionally with confluent areas of inflamed lesions; moderate to severe erythema

Table 2.

Erythema Assessment

Score	Description
Clear or almost clear	No visible erythema or minimal erythema
Mild	Slight erythema, either centrofacial or generalized to whole face
Moderate	Pronounced erythema, either centrofacial or generalized to whole face
Severe	Severe erythema, red to purple hue, either centrofacial or generalized to whole face

as subjective reports on QOL, treatment response, cosmetic acceptability, and local tolerability.

Quality of life was measured using the RosaQoL, a 21-item rosacea-specific QOL instrument.[34] At the end of treatment, participants were asked to rate their treatment response as excellent, good, fair, no improvement, or worse. They also were asked to rate cosmetic acceptability as very good, good, satisfactory, poor, or no opinion. Local tolerability also was rated as excellent, good, acceptable despite minor irritation, less acceptable due to continuous irritation, not acceptable, or no opinion.

Safety—Adverse events (AEs) were recorded throughout the study and were classified using the MedDRA (Medical Dictionary for Regulatory Activities)(version 12.1).

Statistical Analysis—This study was considered exploratory and the planned number of participants (N=400) was considered to be sufficient in achieving insight into the efficacy and safety of AzA foam 15%. Therapeutic success and change in inflammatory lesion count from baseline to end of treatment were analyzed using the full analysis set (FAS)(ie, all participants who were randomized and had the study drug dispensed) using a last observation carried forward (LOCF) methodology. The IGA score at the end of treatment was categorized as success or failure (also called the therapeutic success rate). Success rates were summarized across visits by counts and percentages. At the end of treatment, the therapeutic success rate was analyzed for differences between the 2 treatment groups using Cochran-Mantel-Haenszel statistics controlling for center. The homogeneity of the odds ratio across centers was tested using the Breslow-Day test at 10% level of significance. The difference between the 2 treatment groups in change in inflammatory lesion count was analyzed at the end of treatment using the analysis of covariance model with treatment and study center as the fixed effects and number of lesions at baseline as the covariate.

The secondary end points were analyzed using a Cochran-Mantel-Haenszel test stratified by pooled center for the IGA response rate and the analysis of covariance model for percent change in inflammatory lesion count.

Rating of grouped change (improved/no change/worsened) at the end of treatment in erythema and telangiectasia were analyzed using a van Elteren test stratified by pooled center. The components of the QOL instrument and overall QOL were analyzed based on nominal values, and the change from baseline in the component scores (ie, emotion, symptom, function) was analyzed using a *t* test.

The end-of-treatment analyses of the primary and secondary end points were assessed at week 12 to assess the robustness of the analyses. Differences between treatment groups during the course of treatment and during the follow-up were analyzed by applying χ^2 tests or *t* tests for efficacy end points at each visit.

Table 3.

Telangiectasia Assessment

Score	Description
Clear	No telangiectasia
Mild	Only few fine vessels discernible, involves <10% of facial area
Moderate	Multiple fine vessels and/or few large vessels discernible, involves 10%–30% of facial area
Severe	Many fine vessels and/or large vessels discernible, involves >30% of facial area

Table 4.

Facial Skin Color Assessment

Score	Description
1	Normal skin color compared to untreated skin
2	Barely visible skin lightening compared to untreated skin
3	Mild skin lightening compared to untreated skin
4	Moderate skin lightening compared to untreated skin
5	Severe skin lightening compared to untreated skin

All data summary and statistical analyses were performed using SAS (version 9.1.3). Significance was taken at the 2-sided 5% level ($P<.05$).

Results

Study Participants—Of the 486 total patients screened (age range, 19–83 years), 401 were enrolled and randomly allocated to either the AzA foam (n=198) or vehicle (n=203) treatment groups (Figure 1). These participants comprised the FAS. Forty-one participants did not complete the treatment (21 participants in the AzA foam group; 20 participants in the vehicle group). The most common reasons for discontinuation were lost to follow-up (5 participants in the AzA foam group; 7 participants in the vehicle group) and withdrawal of consent (5 participants in the AzA foam group; 6 participants in the vehicle group). Four participants from the AzA foam group discontinued treatment due to AEs versus 1 from the vehicle group. The per-protocol (PP) population excluded a total of 71 patients who discontinued treatment prematurely or had major protocol deviations, resulting in a PP population of 162 (81.8%) participants in the AzA foam group and 168 (82.8%) in the vehicle group.

Treatment compliance was equivalent among the AzA foam group (97.7%) and the vehicle group (98.0%). The average amount of product used also was roughly equivalent among the AzA foam and vehicle treatment groups (1.3 g/d vs 1.5 g/d).

Both treatment groups were well balanced in terms of demographics and baseline characteristics, with no statistically significant differences between the groups (Table 5). The mean age of study participants was 48.5 years, with 91.5% of participants younger than 65 years. The majority of participants were female (74.3%) and white (96.5%); 27.7% of participants were identified as Hispanic or Latino. At baseline, all participants had moderate or severe rosacea. There was a slight, albeit statistically significant imbalance between the groups in IGA at baseline ($P=.038$) that was not considered clinically relevant.

Efficacy—Participants were considered a success if the IGA score improved to clear or minimal (equivalent to a 2-point improvement). In the FAS with LOCF population, the success rate increased gradually starting at week 4, with the AzA foam showing a nominal advantage over the vehicle (6.1% vs 5.4% success); the groups continued to diverge through treatment (Figure 2). At the end of

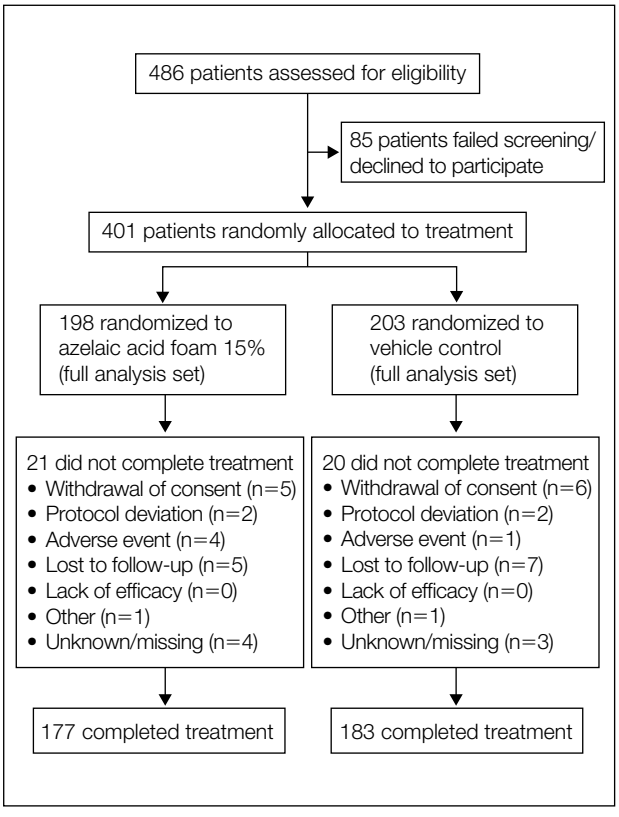

Figure 1. Study disposition.

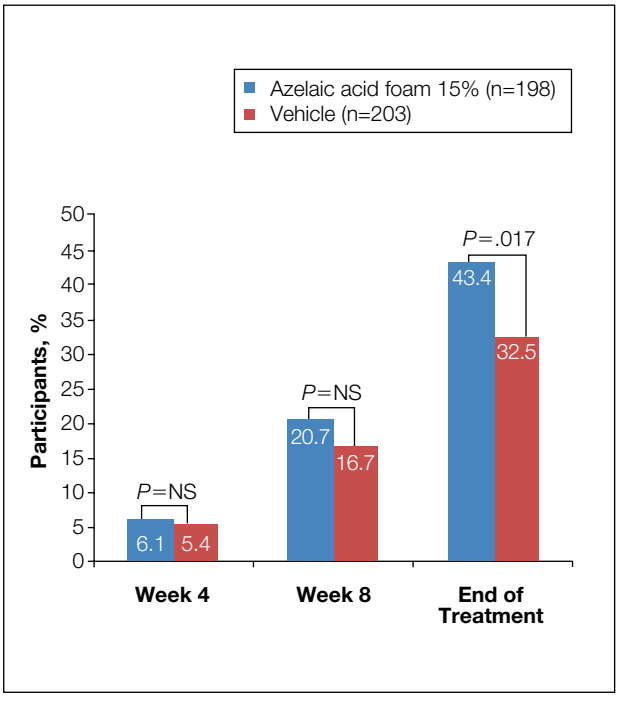

Figure 2. Number of participants who had successful treatment outcomes based on investigator global assessment scores (clear or minimal) at weeks 4 and 8 and at the end of treatment in the full analysis set (last observation carried forward). NS indicates not significant.

Table 5.

Demographics and Baseline Characteristics of Study Participants

	Azelaic Acid Foam 15% (n=198)	Vehicle (n=203)	Total (N=401)
Age, y			
Mean (range)	48.1 (19–78)	48.9 (20–83)	48.5 (19–83)
Median	48.5	49.0	49.0
<65, n (%)	180 (90.9)	187 (92.1)	367 (91.5)
Sex, n (%)			
Female	155 (78.3)	143 (70.4)	298 (74.3)
Male	43 (21.7)	60 (29.6)	103 (25.7)
Race, n (%)[a]			
White	190 (96.0)	197 (97.0)	387 (96.5)
Other	8 (4.0)	7 (3.0)	15 (3.5)
Ethnicity, n (%)			
Not Hispanic or Latino	140 (70.7)	150 (73.9)	290 (72.3)
Hispanic or Latino	58 (29.3)	53 (26.1)	111 (27.7)
Prior rosacea duration, mo			
Mean (range)	121.4 (1–672)	126.3 (6–528)	123.8 (1–672)
Median	84.0	96.0	96.0
Rosacea severity, n (%)[b]			
Moderate	172 (86.9)	189 (93.1)	361 (90.0)
Severe	26 (13.1)	14 (6.9)	40 (10.0)

[a]Participants may be counted in multiple categories. One participant in the vehicle group was counted as both white and American Indian or Alaskan Native.

[b]According to the investigator global assessment scale.

treatment, the therapeutic success rate was 43.4% in the AzA foam group and 32.5% in the vehicle group (P=.017). Similar results were seen in the PP population. Subanalyses based on inflammatory lesion count at baseline, gender, and age did not reveal any statistically significant differences in efficacy. At the end of the study (4 weeks after discontinuation of treatment), treatment success was maintained in 35.4% of the AzA foam group and 32.0% of the vehicle group.

Treatment response rate also was evaluated as a secondary end point. Participants were classified as responders (clear, minimal, or mild) and nonresponders (moderate or severe) based on IGA at the end of treatment. The response rate was higher in the AzA foam group versus the vehicle group at week 4 (43.4% vs 33.5%; *P*=.041), week 8 (66.7% vs 54.7%; *P*=.014), and end of treatment (69.2% vs 57.6%; *P*=.012). After 4-week follow-up (end of study), the response rate was slightly lower (vs end of treatment) for both groups (67.2% vs 56.2%), but the difference remained statistically significant (*P*=.023). In the PP population, treatment differences were statistically significant at the end of treatment (*P*=.04) but not at other study visits.

The mean (standard deviation [SD]) inflammatory lesion count at baseline was 21.6 (9.91) in the AzA foam group and 20.4 (8.83) in the vehicle group; at the end of treatment, the mean (SD) inflammatory lesion count was 8.2 (8.86) versus 10.8 (10.28)(Figure 3). The mean (SD) reduction from baseline at the end of treatment was −13.4 (10.4) in the AzA foam group and −9.5 (9.73) in the vehicle group (*P*<.001)(Figure 4). Treatment differences at both weeks 4 and 8 reached statistical significance in favor of AzA foam (*P*=.003 and *P*=.001, respectively)(Figure 4). Similar results were seen in the PP population. Subanalyses based on inflammatory lesion count at baseline, gender, and age did not reveal any statistically significant differences in efficacy. After 4-week follow-up, the difference was smaller for the AzA group (vs end of treatment)(−12.1 [11.02] vs −9.9 [10.68]) but remained statistically significant (*P*=.041).

When assessed by percent change in inflammatory lesion count, the mean reduction in lesion count was substantially greater in the AzA foam group versus the vehicle group at week 4 (−39.8% vs −31.4%; *P*=.008), week 8 (−57.9% vs −47.1%; *P*=.002), and end of treatment (−65.4% vs −51.0%; *P*<.001).

The primary end points also were analyzed for the PP population and the FAS without LOCF. There were no relevant differences between the FAS LOCF and the PP population/FAS observed case analyses.

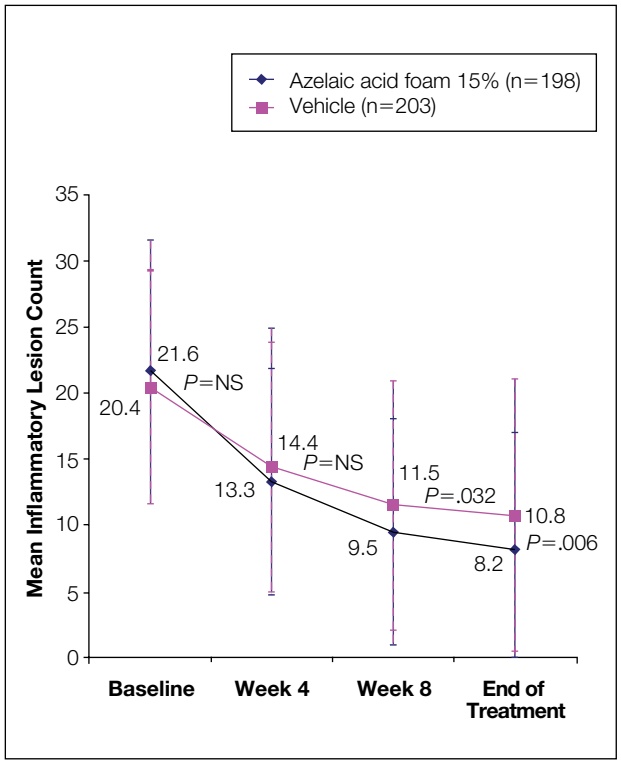

Figure 3. Mean inflammatory lesion count at each visit in the full analysis set (last observation carried forward). Error bars indicate standard deviation. NS indicates not significant.

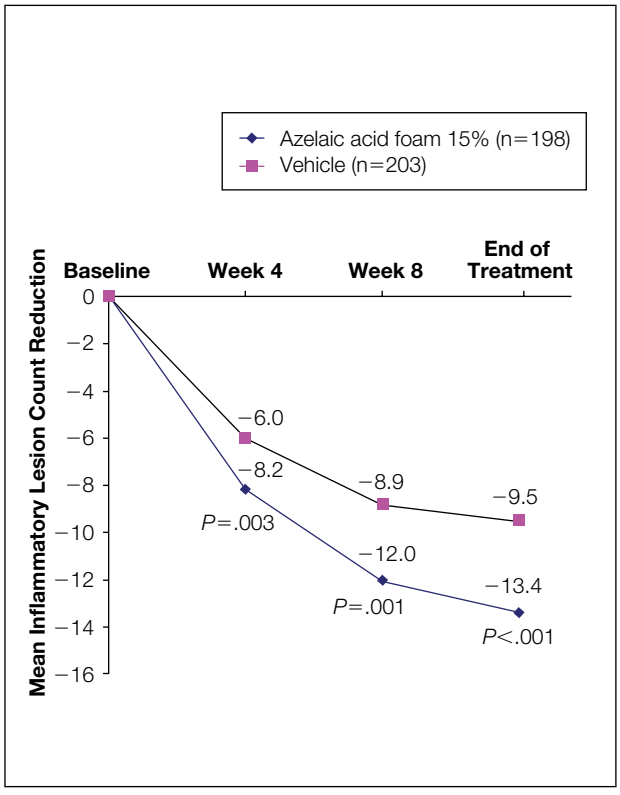

Figure 4. Mean reduction in inflammatory lesion count from baseline in the full analysis set (last observation carried forward).

A number of additional outcomes were examined in exploratory analyses. There were no statistically significant differences between the 2 groups in end-of-treatment or end-of-study erythema, telangiectasia, or QOL scores. Importantly, there were no apparent differences in facial skin color at the end of treatment, as assessed by the mean skin lightening score (assessed on a scale of 1 [normal skin color vs untreated skin] to 5 [severe skin lightening vs untreated skin]).

Subjective global assessments included treatment response, cosmetic acceptability, and local tolerability. According to the summary of the participants' global assessment of treatment response at the end of treatment, 62.2% of participants in the AzA foam group reported excellent or good improvement versus 45.5% in the vehicle group. At the end of treatment, a greater proportion of participants in the AzA foam group (66.5%) assessed cosmetic acceptability as very good or good versus the vehicle group (60.8%). According to the participants' ratings of local tolerability at the end of treatment, 70.2% of participants in the AzA foam group reported excellent or good local tolerability compared to 78.3% of the vehicle group. Among the AzA foam group, 21.3% of participants reported that local tolerability was acceptable despite minor irritation versus 13.2% of participants in the vehicle group. A similar number of participants found local tolerability to be less acceptable due to continuous irritation or not acceptable in the AzA foam group versus the vehicle group (5.9% vs 5.3%).

Safety—Azelaic acid foam generally was safe and well-tolerated in participants with rosacea. Drug-related AEs were mostly cutaneous in nature and were reported more frequently in the AzA foam group (10.6%) than in the vehicle group (3.9%) (Table 6). The most commonly reported drug-related AEs (ie, >2% of participants in either treatment group) were application-site pain, reported in 4.5% of AzA foam participants and 1.5% of vehicle group participants, and pain, reported in 2.5% and 0% of participants, respectively; application-site pruritus, burning sensation, and pruritus, were each reported in 1.5% and 0% of participants, respectively. All other drug-related AEs were reported for less than 3 participants in either treatment group. There was only 1 report of a severe drug-related reaction (erythema), which occurred in 1 (0.5%) participant from the vehicle group; all other AEs in both groups were mild or moderate in severity. Most (>70%) drug-related cutaneous AEs were considered transient (ie, subsided within ≤60 minutes of onset) in both treatment groups. Persistent (ie, subsiding >60 minutes after onset) drug-related AEs included burning sensation, erythema, rosacea, skin lesion, sunburn, tenderness, and urticaria in the AzA foam group, and application-site dryness and dry skin in the vehicle group.

The prevalence of drug-related AEs decreased over the treatment course, with a greater decline between the end-of-treatment and end-of-study visits. The percentage of participants with AEs leading to withdrawal from the study was similar in both groups (2.0% in the AzA foam group and 1.5% in the vehicle group).

Comment

This study demonstrated the efficacy and safety of a new AzA foam in the treatment of patients with PPR when applied twice daily for 12 weeks. Azelaic acid demonstrated a statistically significant advantage over the vehicle in both primary measures of efficacy: therapeutic success rate (based on IGA) ($P=.017$) and the nominal change in inflammatory lesion count from baseline to end of treatment ($P<.001$). Moreover, AzA foam demonstrated significant efficacy for the secondary end points of treatment response ($P=.012$) and rate of change in inflammatory lesion counts ($P=.023$). Both the study drug and the vehicle were safe and well-tolerated. Drug-related AEs were predominantly local, cutaneous, and of mild intensity, and the prevalence of AEs decreased over the treatment period.

These results are not unexpected, as the approved 15% gel formulation of AzA has shown significant ($P<.02$) efficacy in the treatment of patients with mild to moderate PPR. Consistent with the results in the current study, no serious treatment-related AEs associated with AzA gel have been reported; however, among patients treated with the gel formulation, a total of 38% of patients in one active treatment group experienced burning, stinging, or itching.[28] In contrast, local, drug-related, cutaneous AEs were observed in only 10.6% of participants treated with AzA foam in the current study, though a head-to-head comparison is lacking and this trend needs to be confirmed by more data from larger studies. Data from this study suggest overall efficacy with substantial improvement in tolerability.

It is likely that the efficacy of AzA in the treatment of rosacea is attributable to multiple factors. Several investigations indicate that the drug's inhibitory effect on cellular oxidoreductase, oxyradical activities, and nuclear DNA acid synthesis may be of importance.[35-37] Furthermore, it has been demonstrated that AzA has the ability to modify the activation of nuclear factor κB in vitro and lowers the expression of kallikrein-5 and cathelicidin in epidermal keratinocytes. Azelaic acid exerts

Table 6.

Drug-Related Cutaneous Adverse Events[a]

	Azelaic Acid Foam 15% (n=198)		Vehicle (n=203)	
Adverse Event	**No. of Events**	**Participants, n (%)**	**No. of Events**	**Participants, n (%)**
Any event	34	21 (10.6)	11	8 (3.9)
Application-site pain	9	9 (4.5)	4	3 (1.5)
Pain (stinging on the face)	5	5 (2.5)	0	0 (0)
Application-site pruritus	3	3 (1.5)	0	0 (0)
Burning sensation	3	3 (1.5)	0	0 (0)
Pruritus	3	3 (1.5)	0	0 (0)
Application-site paresthesia	2	2 (1.0)	1	1 (0.5)
Tenderness	2	1 (0.5)	0	0 (0)
Urticaria	2	1 (0.5)	0	0 (0)
Erythema	1	1 (0.5)	1	1 (0.5)
Paresthesia	1	1 (0.5)	0	0 (0)
Rosacea	1	1 (0.5)	0	0 (0)
Skin lesion	1	1 (0.5)	0	0 (0)
Sunburn	1	1 (0.5)	0	0 (0)

[a]Events reported in >1 participant in either treatment group.

anticomedonic activities and antimicrobial effects against *Propionibacterium acnes* and *Staphylococcus epidermidis*, contributing to its observed efficacy in treating acne,[20,21] and also may exert an indirect anti-inflammatory effect by inhibiting the production of inflammatory mediators by follicular bacteria. It has been suggested that efficacy of AzA in the treatment of hyperpigmentation disorders might be based on its antityrosinase activity.[38] Azelaic acid has anti-inflammatory, antimicrobial, antimycotic, and antikeratinizing properties at least partially due to the inhibition of neutrophil-mediated reactive oxygen species.[36,39]

Foam products have become an increasingly popular vehicle for treatment of a variety of skin conditions because of their ability to deliver drugs to the affected area while maintaining characteristics preferred by patients over other vehicles. Although topical treatments of rosacea are common, foam formulations of AzA are not yet available, and no head-to-head comparisons with other vehicles have been conducted. Nevertheless, this study suggests that foam formulations of AzA are likely to be at least as effective at providing a therapeutic benefit as more conventional AzA gels and creams.[26-28,40,41] Different delivery vehicles may prove effective as

is reported for other topical agents. For example, steroid foams have been shown to be more efficacious treatment vehicles because of their more rapid penetration and greater total absorption compared with creams and lotions.[42] Studies also demonstrate comparable efficacy with foams of other dermatologic topical medications as delivery vehicle.[43-49] Consistent with these findings, we saw remarkable improvement similar to rosacea patients who were treated with topical medications including AzA (in formulations other than gels), highlighting the likely comparable therapeutic benefit of an AzA foam to other topical agents.[50-52] The treatment success demonstrated in the current study also is likely due in part to the inherent characteristics of foams (eg, ease of application and spread, more rapid drying time, reduced density), which often are preferred by patients over other vehicles such as gels or creams. Certainly, greater patient preference for a particular formulation is associated with increased treatment adherence and improved treatment outcomes, an option particularly critical for patients with rosacea whose adherence to medication regimens typically is suboptimal.[53] Tolerability also has an impact on treatment adherence. Patients are more likely to adhere to treatment regimens that have a good tolerability profile. Patients with PPR treated with gels commonly experience mild to moderate burning, stinging, and/or itching.[26] In the current study, the foam formulation showed good tolerability, which is always a concern in patients with rosacea who often have heightened skin sensitivity.[52] No serious AEs were associated with the AzA foam; only 10.6% of patients experienced cutaneous local AEs, which gradually decreased over the course of the study to levels reported by patients treated with the vehicle. In addition, foam formulations offer cosmetic advantages over other topical vehicles (eg, ointments, creams), which are more likely to leave a persistent residue and/or odor at the application site. Accordingly, a foam formulation of AzA would likely be a beneficial addition to the currently available armamentarium of topical agents used for the treatment of PPR.

Conclusion

This study demonstrated the efficacy and tolerability of a new AzA foam formulation in the treatment of patients with moderate to severe PPR. Although no single formulation is appropriate for all patients, the availability of a foam formulation in addition to other vehicles provides patients with options and allows health care providers to match the needs as well as preferences of individual patients and skin types with appropriate delivery modalities.

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