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Efficacy and Safety of Azelaic Acid (AzA) Gel 15% in the Treatment of Post-Inflammatory Hyperpigmentation and Acne: A 16-Week, Baseline-Controlled Study

Leon H. Kircik, MD
Indiana University School of Medicine, Indianapolis, IN

ABSTRACT

Although there are few differences in the incidence and pathophysiology of acne across various races and ethnicities, there is some evidence that black patients may have larger sebaceous glands and increased sebum production. Of greater clinical relevance, patients with darker skin types are at increased risk for the development of post-inflammatory hyperpigmentation (PIH), which some find as or more troubling than acne itself. This common and bothersome sequelum of acne can be difficult to manage in this population. Topical azelaic acid gel is recognized to have anti-tyrosinase activity, suggesting it may be a suitable treatment option for mild-to-moderate acne with associated moderate-to-severe PIH. This pilot study demonstrates the efficacy of topical AzA gel 15% when applied twice daily for the reduction of both acne and PIH.

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INTRODUCTION

Acne vulgaris affects people of all ethnicities and races in the United States with little difference in pathophysiology.[1] One report in the United Kingdom showed that acne vulgaris is the most common dermatologic diagnosis among adult black patients.[2] Another study from 1965 revealed that nine percent of black patients had acne versus 18 percent of white patients.[3] Halder and his group reported that acne was the most common diagnosis in both black and white patient populations: 29.5 percent of white patients compared to 27.7 percent of black patients.[4] The fact that patients with skin of color may seek treatment at lower rates than white patients may affect these results. Therefore, efforts to identify differences in the frequency of acne in skin of color have failed to provide conclusive evidence.[5] While the pathophysiology of acne is invariable across all skin types, there is some evidence to suggest that black patients may have larger sebaceous glands[6] and increased sebum production compared to whites.[5,7] Nonetheless, the experience of acne among patients with darker skin (Fitzpatrick skin types IV to VI) may differ because these individuals are more susceptible to post-inflammatory hyperpigmentation (PIH), a common and troubling antecedent of acne.[1,5]

Treatments for PIH are available, but their efficacy and suitability are not optimal. For example, topical tretinoin, a first-line treatment for mild-to-moderate acne has been shown to reduce the appearance of post-inflammatory hyperpigmentation, but it was also shown to lighten normal skin.[8] Additionally, topical retinoids are known to contribute to PIH by causing irritation. Azelaic acid (AzA), a naturally occurring dicarboxylic acid with anti-inflammatory, antimicrobial, antikeratinizing, antioxidant and antityrosinase mechanisms of action[9,10] may be ideal for both the management of acne and treatment of PIH associated with it. AzA's anti-inflammatory, antimicrobial and antikeratinizing effects have been shown to be beneficial in the topical treatment for acne.[11] Thought to inhibit the synthesis and release of melanin,[10,12] AzA has direct anti-tyrosinase activity that has demonstrated efficacy in the management of PIH.[13] An AzA cream 20% formulation has been approved for acne vulgaris, while AzA gel 15% has been approved for papulopustular rosacea. While AzA has been used clinically for the management of acne and associated PIH, this study is the first to assess the effects of AzA gel 15% on both acne and PIH in patients with skin of color.

METHODS AND STUDY DESIGN

This single-center, open-label, IRB-approved pilot study was conducted over 16 weeks. Adults (n=20) with mild-to-moderate acne and moderate-to-severe PIH and Fitzpatrick skin type IV

TABLE 1.

PIH IGA Scores, 6-Point Scale						
0	**1**	**2**	**3**	**4**	**5**	**6**
None	Slight	Mild	Moderate	Moderately Severe	Severe	Very Severe

TABLE 2.

PIH IGA Scores, PIH Distribution, 7-Point Scale						
0	**1**	**2**	**3**	**4**	**5**	**6**
No PIH	PIH on 1%-10% of face	11%-20%	21%-30%	31%-40%	41%-50%	>50%

TABLE 3.

Subject Demographics (n=20)			
Sex	**Race**	**Age**	**Fitzpatrick Skin type**
Male, 25%, n=5 Female, 75%, n=15	Black, 100%	Mean: 24 years	V=20%, n=4 VI=80%, n=16

to VI were recruited for this trial. Inclusion criteria were: 15–60 inflammatory lesions with no more than 2 nodules and 20–100 non-inflammatory lesions and moderate-to-severe PIH.

At the baseline visit (week 0), patients were given AzA gel 15% (Finacea, Intendis, Inc. Morristown, NJ) and were instructed to apply the gel twice daily after facial cleansing. Patients returned for four follow-up visits at weeks 4, 8, 12 and 16. Assessments at each visit (baseline and each follow-up) included Investigator's Global Assessment (IGA) of acne, assessed on a 6-point scale (0=clear, 5=very severe) and total (papules, pustules, nodules, open/closed comedones), inflammatory (papules, pustules and nodules) and non-inflammatory lesion (open and closed comedones) counts were also conducted.

IGA for PIH, assessed on a 7-point scale (0=clear, 6=very severe, Table 1), was made at each visit. Distribution of PIH, assessed on a 7-point scale (Table 2), was also assessed at each visit. Tolerability, as indicated by the presence and degree of peeling, erythema, dryness, oiliness, burning and pruritus, was assessed at each follow-up visit.

A total of 20 adult subjects were enrolled. Mean age of subjects was 24 years. The majority of subjects (75%) were female; 25 percent were male. Eighty percent of subjects had Fitzpatrick skin type VI and 20 percent had Fitzpatrick skin type V (Table 3).

RESULTS

Acne

At baseline, acne was rated by IGA as mild in 65 percent and moderate in 35 percent of subjects.

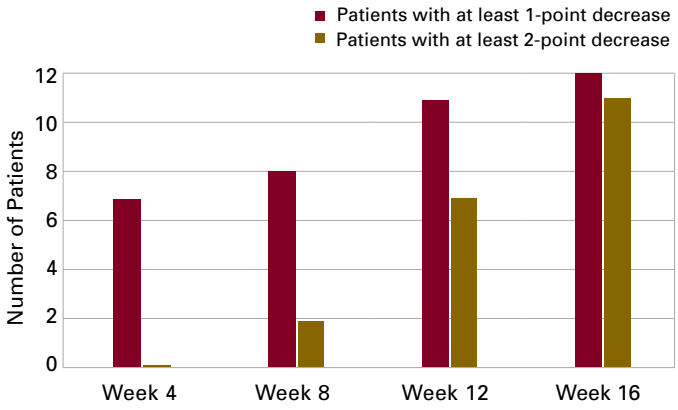
At week 4, 47 percent of subjects had at least a one-point improvement in IGA for acne (Table 4). Absolute mean reduction in IGA at week 4 was statistically significant (P=0.0156). Statistical significance continued throughout the study (week 16, P=0.0005). At week 16, a significant proportion of subjects (92%) had at least a one-point improvement in IGA for acne. The percentage of subjects achieving at least a 2-point improvement in their IGA for acne was 85 percent. Of note, at week 16, 69 percent of all subjects were rated as clear based on IGA.

There was a statistically significant reduction in total acne lesion counts at week 4, at which time a 48 percent median reduction in total lesion count was seen (P<0.0001, Table 5). Reduction in total lesions remained statistically significant within the group throughout the study period. At week 16, the mean reduction in total lesions was 98 percent.

> While AzA has been used clinically for the management of acne and associated PIH, this study is the first to assess the effects of AzA gel 15% on both acne and PIH in patients with skin of color.

In terms of inflammatory lesions, specifically, the reduction in inflammatory lesions was statistically significant throughout the trial period, starting at week 4. Median reduction in lesion

TABLE 4. Acne Severity Grading Scores. Number of Patients with 1-Point or 2-Point Decrease at Each Visit (by IGA*)



* IGA = Investigator Global Assessment

TABLE 5. Median Percent (%) Lesion Reduction at Each Visit

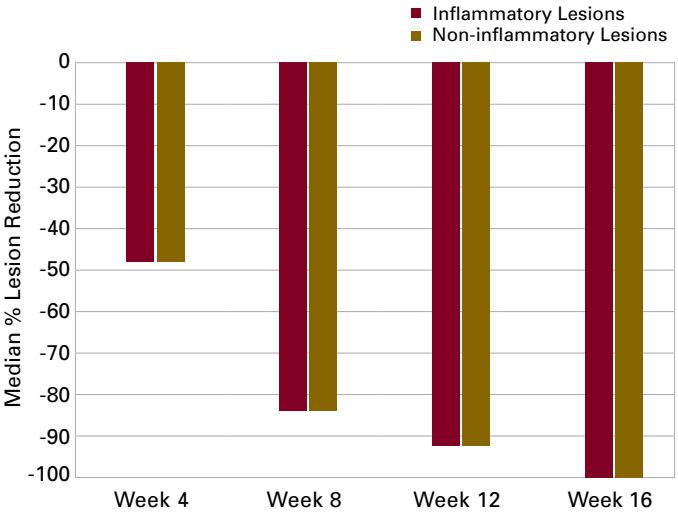
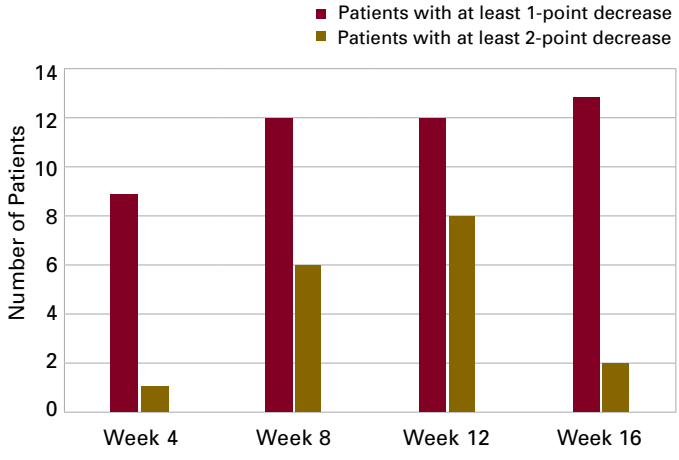
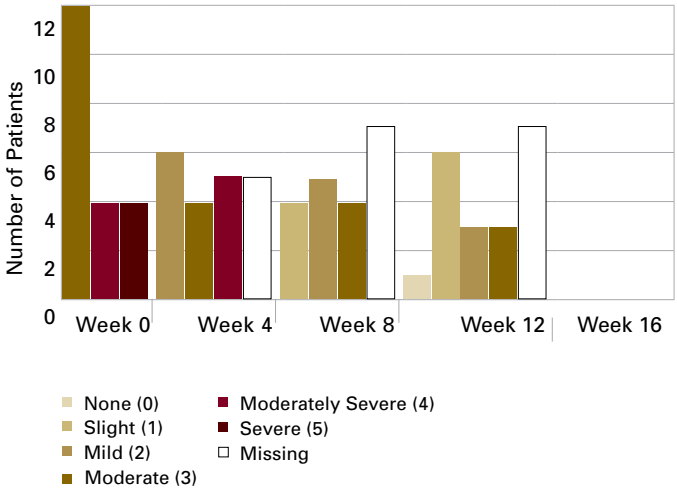


TABLE 6. Post-inflammatory Hyperpigmentation (PIH) Severity Grading Scores. Number of Patients with 1-Point or 2-Point Decrease at Each Visit (by IGA*)



* IGA = Investigator Global Assessment

TABLE 7. Post-inflammatory Hyperpigmentation (PIH) Severity Grades. Patient Rating by Investigator Global Assessment (IGA) at Each Visit



count was 46 percent at week 4 ($P<0.0001$) and 100 percent at week 16 ($P=0.0002$).

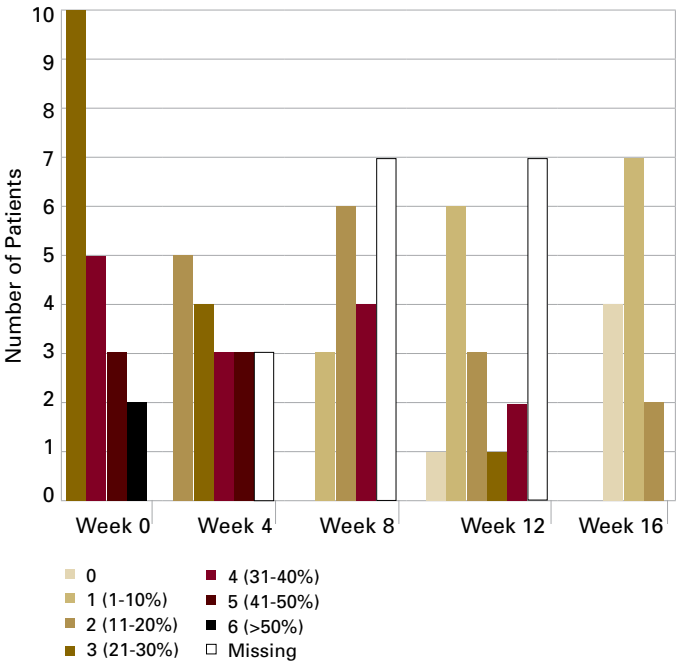
Similarly, there was a 45.5 percent median reduction in non-inflammatory lesion counts at week 4 ($P<0.0001$) and a 100 percent median reduction at week 16 ($P=0.0002$).

Post-Inflammatory Hyperpigmentation

PIH Severity

At baseline, 60 percent of subjects were rated as having moderate PIH based on IGA, 20 percent had moderately severe

TABLE 8. Extent of Post-inflammatory Hyperpigmentation (PIH) Grading of Facial Distribution by Investigator at Each Visit



PIH and 20 percent had severe PIH. At week 4, 67 percent of subjects had achieved at least a one-point improvement in IGA scores (Table 6). At the conclusion of the trial (week 16), 100 percent of subjects had at least a 2-point improvement in IGA scores. Of note, 31 percent of subjects had no PIH at all at week 16, 54 percent of subjects had only slight PIH at week 16 and 15 percent of subjects had just mild PIH at week 16. No patients had moderate or severe PIH at week 16 (Table 7).

PIH Distribution

At week 4, there was a statistically significant 1-point median improvement in distribution scores (P=0.0039). The majority (60%) of subjects had at least a one-grade improvement in distribution scores and 6.7 percent had at least a two-grade improvement. At week 16, 100 percent of subjects had at least a one-grade improvement and 92 percent of subjects had at least a 2-grade improvement in distribution scores. Complete clearance of PIH was noted in 31 percent of subjects at week 16; 54 percent of subjects had only 1–10 percent distribution of PIH (Table 8).

Improvements in PIH severity and distribution were all statistically significant starting at week 4.

Tolerability

Tolerability of AzA gel was good throughout the trial period, with no serious adverse events reported. Erythema at baseline was absent in 55 percent of subjects, trace in 30 percent and mild in 15 percent. At week 4, 86.7 percent of subjects had no erythema, 6.7 percent of the subjects had mild erythema and 6.7 percent had only trace erythema. By week 12, no subject had erythema.

At week 4, 20 percent of the subjects reported trace dryness and 6.7 percent had moderate dryness. Reported rates of dryness remained low until week 16, at which point no subjects reported dryness. Peeling, which was reported as trace in 6.7 percent of subjects and mild in 13.3 percent of subjects at week 4 was not reported by any subjects at week 12 or 16.

DISCUSSION

The development of PIH secondary to acne is a significant clinical concern for many patients, especially those with darker skin types. In our clinical practice, patients present every day complaining of PIH, which they sometimes report is more disturbing than acne itself. To be able to treat acne and PIH simultaneously is a logical approach to care that may provide enhanced convenience and better outcomes for patients. The use of topical AzA gel 15% for the management of acne in patients with PIH has been demonstrated to be well tolerated and effective. Therefore, AzA gel may be considered for patients at risk for this troubling sequelum of acne.

The limitation of this study is that it was an open-label study with a small number of patients. However, positive findings of this pilot study will hopefully encourage larger, randomized controlled trials of AzA gel 15% for acne and post-inflammatory hyperpigmentation, which is a significant unmet need.

CONCLUSION

Twice-daily topical application of AzA gel 15% improved all aspects of acne severity and PIH severity measured during this 16-week study. This study revealed early onset of action in both acne and PIH improvement starting at week 4.

In acne, improvement in total, inflammatory and non-inflammatory lesion counts were seen throughout the study, with an impressive 98 percent median reduction in total acne lesions at week 16. IGA scores for acne showed statistically significant improvement by week 4 that continued throughout the trial period. Furthermore, both the severity and distribution of PIH improved throughout the trial period. By the end of the study period, nearly two-thirds of subjects had no PIH, and more than half had only 1–10 percent involvement. AzA Gel 15% was also well tolerated with minimal dryness and erythema. This open label pilot study demonstrated that AzA Gel 15% is a safe and effective treatment for PIH in skin of color patients with acne.

DISCLOSURES

Dr. Leon H. Kircik has served as an investigator, speaker, consultant or advisory board member for Allergan, Amgen, Astellas Pharma US, Colbar, CollaGenex, Connetics Corporation, Ferndale Laboratories, Galderma, Genentech, Intendis, Johnson & Johnson, Leo Pharma, 3M, Nano Bio, Vovartis AG, Onset Therapeutics, OrthoNeutrogena, Promius, PharmaDerm, SkinMedica, Stiefel, Valeant, Warner-Chilcott; a speaker for Abbott Laboratories, Dermik, Embil, Innovail, Merck Serono and Triax; an investigator for Acambis, Asubio, Bayer HealthCare, Biolife, Biopelle, Breckinridge Pharma, Centocor, Combinatrix, Coria, Dow Pharmaceutical Sciences, Dusa, GSK, Health Point, Medicis, Nucryst, Obagi, QLT, Pfizer, QuatrixTolerRx and UCB; and as a consultant for Laboratory Skin Care, Medical International Technologies and ZAGE.

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ADDRESS FOR CORRESPONDENCE

Leon H. Kircik, MD
Physicians Skin Care
1169 Eastern Parkway, Suite 2310
Louisville, KY 40217
Phone:…….…..... (502) 456-2783
Fax:…….…..... (502) 456-2728