

Dermatology



Dermatology Rosacea

Real-World Efficacy of Azelaic Acid 15% Gel for the Reduction of Inflammatory Lesions of Rosacea

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Conflicts of Interest:

PJW has no conflicts to disclose. MHB has no conflicts to disclose. NS has been a principal investigator and received research grant from Bayer, and has acted as consultant and/or received honoraria from Allergan, Celgene, Cutera, Cynosure, Eclipse, Endo, EndyMed, Galderma, Nutraceutical Wellness, Venus Concept.

ABSTRACT

Approximately 16 million Americans have rosacea, an inflammatory cutaneous disorder with central facial erythema, papules, pustules, telangiectasia, flushing, and swelling being among the more commonly recognized features. Overexpression of cathelicidin peptide LL-37 has been implicated in the pathophysiology of rosacea. Azelaic acid has been found to inhibit the pathologic expression of cathelicidin, as well as the hyperactive protease activity that cleaves cathelicidin into LL-37. Given these findings, a small prospective, open-label, interventional trial was undertaken to assess the effects of azelaic acid 15% gel on inflammatory lesions of papulopustular rosacea in a real-world setting. Use of azelaic acid was associated with a significant reduction in inflammatory lesions, which persisted beyond the active treatment phase. Overall, azelaic acid 15% gel is an appropriate initial topical therapy for the treatment of moderate facial rosacea.

Key Words:

Introduction

Rosacea is a common chronic cutaneous disorder that is estimated to affect close to 10% of Americans in the community setting.¹ It is characterized by central facial erythema, papules, pustules, telangiectasia, flushing, and swelling. The precise pathogenesis of rosacea remains unclear. Dysregulation of the innate immune system, overgrowth of commensal skin organisms, and aberrant neurovascular signaling have been implicated in the pathophysiology of rosacea.²

The facial skin of rosacea patients has been documented to exhibit increased baseline expression of cathelicidin antimicrobial peptide, LL-37 (the active form of cathelicidin), and kallikrein 5 (KLK5), the protease responsible for cleaving cathelicidin into LL-37.³ In rosacea skin, KLK5 also cleaves cathelicidin into other abnormal peptide fragments. These forms of LL-37 are pro-inflammatory and stimulate angiogenesis, contributing to the clinical manifestations of rosacea. In addition, increased expression of toll-like receptor 2 (TLR2), a pattern recognition receptor, has been identified.⁴ This may contribute to the enhanced inflammatory responses to exogenous trigger factors seen in rosacea.

Azelaic acid, a naturally occurring, saturated, straight-chained, 9-carbon atom dicarboxylic acid, is used topically for the treatment of papulopustular rosacea (PPR). Azelaic acid has been shown to have anti-inflammatory activity through reduction of the cathelicidin pathway that is upregulated in facial skin of patients with rosacea. In vitro studies performed using murine or human skin showed that azelaic acid directly inhibits KLK5 in cultured keratinocytes, KLK5 gene expression, TLR2 expression, and cathelicidin and LL-37 formation.^{5,6} An in vivo study conducted in patients with PPR showed reduction in cathelicidin and KLK5 activity after treatment with azelaic acid 15% gel applied twice daily.⁵ Azelaic acid also has known antimicrobial, antioxidant, and anti-keratinization effects.⁷

Clinical trials have shown that azelaic acid 15% gel is an effective and safe first-line topical monotherapy for patients with PPR.⁸ Exposure to azelaic acid 15% gel has been associated with statistically significant reductions in inflammatory lesions of rosacea.⁹ However, there is a lack of data in the literature on the use of azelaic acid 15% gel outside a clinical trial setting, in real-world clinical practice. The objective of this study was, therefore, to assess the effectiveness of azelaic acid 15% gel when used as monotherapy for the treatment of mild to moderate PPR in a real-world setting.

Methods

This prospective, open-label, interventional study enrolled 20 subjects with PPR. Individuals aged 18 years or older with mild to moderate facial rosacea (as classified by Investigator Global Assessment [IGA]) and who had between 2 and 50 inflammatory facial lesions (papules or pustules) were eligible for participation. Patients with moderate or severe rhinophyma, ocular rosacea requiring topical or systemic antibiotics, or a history of hypersensitivity to any component of the gel were excluded. To prevent any carry-over effects of other medications, patients underwent an adequate washout according to drug type. Concomitant use of any treatments with effects in rosacea was prohibited for the duration of the study.

Subjects were instructed to apply azelaic acid 15% gel (Finacea Gel®) topically to the face twice daily for 12 weeks. They were also advised to avoid known rosacea triggers as much as possible. Clinical evaluations were made at baseline, weeks 4 and 12, and at 4 weeks after completion of active treatment (week 16). Effectiveness endpoints included inflammatory lesion counts, the IGA of rosacea severity, and participant's subjective evaluation of rosacea improvement. Adverse events were also monitored.

Findings

Treatment with azelaic acid 15% gel was associated with a statistically significant reduction in all lesions types, and the reduction in lesions persisted beyond the treatment period. There was a significant decrease in mean total inflammatory lesion count at all study visits compared to baseline. The greatest decrease was observed at week 12, the conclusion of active treatment, with a difference of -3.4 from baseline ($P<0.05$). The difference in mean lesion count between week 16 and baseline was -2.4. This reduction in lesions 4 weeks after treatment discontinuation remained significant relative to baseline ($P<0.05$) (Figure 1).

Most subjects perceived a change in their facial skin over the course of azelaic acid treatment. At week 12, 47% of patients self-reported a moderate to significant improvement while 31% reported a mild improvement (Figure 2).

At the baseline visit, the IGA of rosacea was documented as “moderate” or “mild” for the majority of patients. IGA scores improved at each visit, with all visits showing a significant improvement when compared to the IGA at baseline ($P<0.05$). By week 16, the majority of IGA scores had become ratings of “almost clear” or “mild” (Figure 3).

Overall, azelaic acid 15% gel was safe and well-tolerated. Adverse events were limited to mild itching and stinging that did not require a disruption of treatment or any additional intervention. No subjects discontinued participation in the study for any reason.

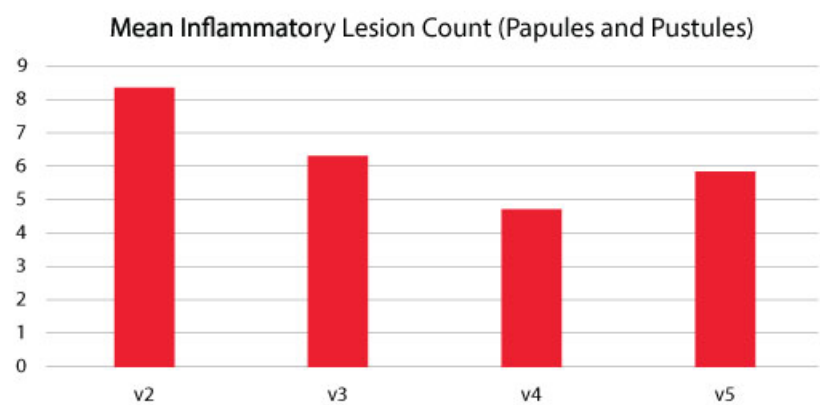


Figure 1. Mean inflammatory lesion counts at baseline (v2), week 4 (v3), week 12 (v4), and week 16 (v5).



Figure 2. Both – Left: Patient at baseline, Right: Patient after 12 weeks of azelaic acid treatment

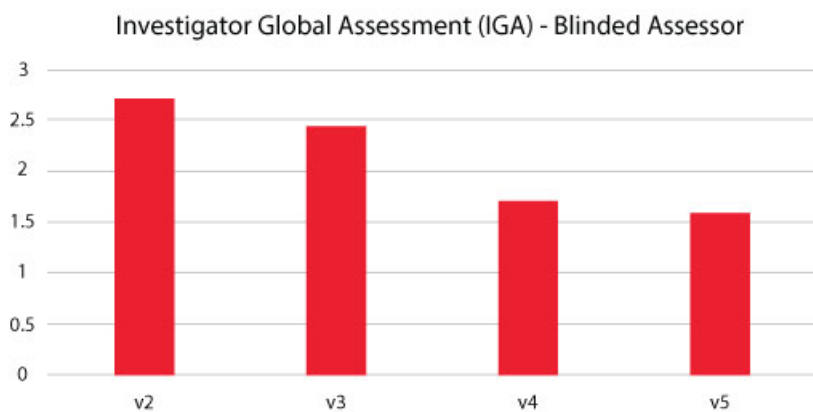


Figure 3. Mean Investigator Global Assessment (IGA) of rosacea severity at baseline (v2), week 4 (v3), week 12 (v4), and week 16 (v5). The assessor was blinded to time-points.

Discussion

Data regarding the effectiveness of therapeutics is typically derived from rigorously administered, randomized, controlled phase 3 trials for FDA approval. While these studies are essential to document the efficacy of topical drugs, it is not always possible to predict the therapeutic benefits of a topical treatment used in the real-world setting.

Azelaic acid 15% gel resulted in a significant reduction in inflammatory lesion counts after 4 weeks of treatment in this study, and IGA scores showed clear improvement in the majority of patients. The effectiveness of azelaic acid 15% gel increases as treatment duration increases. Most patients reported that they had experienced improvement, with none reporting worsening of their condition since the start of the study.

The main limitations of this study were the small sample size, the short study duration, and a single center trial.

Further investigations will be needed to observe the long-term efficacy and safety of azelaic acid 15% gel. Additional work is needed to determine patient preference and changes in quality of life associated with use of azelaic acid 15% gel. Future directions may also include real-world effectiveness of azelaic acid 15% gel applied once daily and when used in combination with other agents such as metronidazole.

Conclusion

This study confirms the benefits of azelaic acid 15% gel for the management of mild to moderate PPR in a real-world setting. Treatment with azelaic acid 15% gel applied twice daily to the face was associated with a significant reduction in inflammatory lesions and elicited an effect that persisted beyond the active treatment phase.

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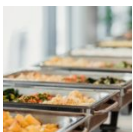
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