New Insights Into Azelaic Acid

As we learn more about this agent, we also discover new ways of understanding and approaching rosacea, acne, and hyperpigmentation.

BY JOSHUA ZEICHNER, MD

This month marks the 10th year since azelaic acid has been commercially available under the brand name of Finacea Gel (Bayer). Indicated for mild to moderate papulopustular rosacea, Finacea was FDA approved in December 2002, and released in March 2003.[1] Over the past decade, research has elucidated the pathways through which it works, and several new applications have been reported in the literature. The following will review recent advances, the latest data, and uses for this unique agent.

BACKGROUND

Azelaic acid is a naturally occurring dicarboxylic acid derived from rye, wheat, and barley. A single mechanism of action has not been identified to explain the effects of azelaic acid on the skin. It helps scavenge reactive oxygen species, reduces expression of kallikrein-5 (KLK-5) and pro-inflammatory cathelicidins such as LL-37, as well as inhibits toll-like receptor 2 (TLR-2).[2,3] In addition, it inhibits the pigment producing enzyme tyrosinase, has comedolytic properties, and may reduce epidermal hyperkeratinization.[3] While the 15% gel formulation is FDA approved for the treatment of rosacea, a separate 20% cream formulation (Azelex, Allergan) is indicated for the treatment of acne.[4] Both formulations carry a pregnancy category B rating.

AZELAIC ACID FOR ROSACEA

The 15% gel formulation of azelaic acid is FDA approved to treat the papules and pustules of mild to moderate rosacea. While the 15% gel has a lower concentration of azelaic acid compared to the 20% cream, advances in formulation technology give the gel greater cutaneous biovailability.[3,5] While the indication is for use of azelaic acid 15% gel twice daily[1], a study subsequent to its approval demonstrated equivalent efficacy of once compared to twice daily application.[6]

Recent data suggest abnormal over-activity of the innate immune system as a major contributor to the pathophysiology of rosacea. Excess skin antimicrobial peptides (e.g., cathelicidins) and stimulation of TLR-2 both play significant roles.[7] Cathelicidins are processed by serine proteases (e.g., KLK-5) into pro-inflammatory peptides, such as LL-37. Overactivity of KLK-5 leads to a high level of cathelicidin processing into peptides with greater pro-inflammatory properties than antibacterial properties. This imbalance promotes angiogenesis and chronic skin inflammation. Topical application of azelaic acid 15% gel has been demonstrated to reduce skin serine protease activity and help reverse these changes.[8]

AZELAIC ACID FOR ACNE

TLR-2 over-activity plays a role in the pathogenesis of acne. *Propionibacterium acnes* itself has been shown to stimulate TLR-2 activity, resulting in skin inflammation and comedogenesis.[9,10] Topical retinoids are a staple in treating acne not only because of their ability to normalize follicular hyperkeratinization but also due to their anti-inflammatory properties.[9,11] Similar to its mechanism of action in treating rosacea, azelaic acid's ability to inhibit TLR-2 activity helps explain its efficacy in treating acne vulgaris.[9,12] The use of azelaic acid 15% gel is considered off label for the treatment of acne vulgaris. Many practitioners may use it off-label for acne as part of a combination therapy for patients who cannot tolerate topical retinoids, those who also suffer from hyperpigmentation, and for women who are pregnant or breastfeeding (as it is pregnancy category B).

AZELAIC ACID FOR HYPERPIGMENTATION

Post-inflammatory pigmentation clinically manifests as dark spots in areas of skin that previously were inflamed, be it from acne or another inflammatory dermatosis. While not

improved for this indication, azelaic acid is commonly used off-label to treat pigmentation. One clinical trial demonstrated 15% azelaic acid gel to be both efficacious and safe in treating hyperpigmentation associated with acne for 16 weeks.[13] This effect may be explained by two properties of the drug. First, azelaic acid is known to inhibit the enzyme tyrosinase, which is needed for the production of melanin.[3] Second, its role as an anti-inflammatory may be beneficial as well. When active acne lesions (e.g., papules and pustules) resolve, evidence shows that the skin in these areas still possess subclinical inflammation.[14] While this has been demonstrated in acne scars, the same may also be true in cases of persistent erythema and pigmentation. More research is needed to substantiate this theory, however.

CONCLUSION

Having a drug that effectively treats a condition helps us better understand that condition, as we discover the mechanism by which the drug works. Just as biologics have shed light on the pathogenesis of psoriasis, research into the mechanism of action of azelaic acid has greatly improved our knowledge about the pathogenesis of rosacea, specifically the role of an over-active innate immune system. A greater understanding of the disease translates to improved treatment algorithms and patient outcomes, and ultimately this helps influence the future of drug development. ■

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