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# Rosacea Management Strategies: Azelaic Acid 15% Gel in Clinical Practice

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## INTRODUCTION

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*Leon H. Kircik MD*

## ORIGINAL ARTICLE

s101 **Update on the Management of Rosacea: A Status Report on the Current Role and New Horizons With Topical Azelaic Acid**
*James Q. Del Rosso DO FAOCD and Leon H. Kircik MD*

 

# Challenges and Advances in Rosacea Management

Leon H. Kircik MD

For the roughly 16 million Americans with rosacea, the condition can be quite troubling. Research from the National Rosacea Society (NRS) highlights the psychosocial and physical effects of rosacea. In surveys, 90% of those affected by rosacea have said that its effect on their personal appearance has lowered their self-esteem and self-confidence, and almost as many as 88% have said they have suffered embarrassment due to the condition. Perhaps surprisingly to many clinicians, the vast majority of surveyed rosacea patients, almost 93%, have reported experiencing physical discomfort such as burning, itching, and stinging associated with the condition.[1]

Over the past several decades, dermatologists have made important strides in the diagnosis and treatment of rosacea. Of course, the recognition of rosacea as having a distinct etiology rather than being a variant of acne vulgaris led to the development of specifically targeted therapies for this common condition. In recent years we have learned much about the inflammatory mediators that drive the disease, and more clearly elucidated its molecular basis.[2,3] As such, we now better understand how existing therapies provide benefits, and have identified potential new treatments.

For example, the fact that we now have studies demonstrating the targeting of cathelicidin and toll-like receptor 2 activity by azelaic acid confirms our clinical practice.[3] Discovering that topical molecules such as brimonidine and oxymetazoline reduce the persistent facial erythema of type 1 rosacea by acting on alpha adrenergic receptors of subcutaneous vasculature has been a very important addition to our treatment armamentarium. Moreover, the introduction of an anti-inflammatory dose of doxycycline as the first Food and Drug Administration–approved systemic medication for rosacea has empowered us with an appropriately indicated treatment for the condition.

Nonetheless, management of rosacea can still be a clinical challenge. Despite the availability of numerous topical treatment options for rosacea, patients may not be satisfied with their treatment. In NRS surveys, up to 75% of patients reported feeling frustrated by their condition.[1] Therefore, more and more clinicians recognize the need for combination therapeutic strategies to target multiple elements of the pathophysiology of rosacea. These strategies integrate all aspects of management from basic skincare to pharmacologic therapies, including consideration for selection of vehicles in case of topical therapy. Developing tolerable regimens that encourage patient adherence while also providing effective treatment should be our goal.

The pages ahead offer extensive information into drug activity and the influence of vehicle on treatment outcomes in rosacea, providing important insights into patient management.

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# Update on the Management of Rosacea: A Status Report on the Current Role and New Horizons With Topical Azelaic Acid

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## ABSTRACT

Azelaic acid (AzA) 15% gel has been available in the United States for slightly over a decade, approved for treatment of the inflammatory lesions (papules and pustules) of rosacea. Efficacy and safety have been established in multiple studies both as monotherapy and in combination with oral doxycycline. Azelaic acid 15% gel has been shown not to induce epidermal permeability barrier impairment, and proper skin care reduces the likelihood of neurosensory adverse effects of stinging and burning that can affect a subset of patients with rosacea. Azelaic acid 15% gel appears to produce a quicker onset of clinical effect than metronidazole in some patients when either agent is used in combination with subantimicrobial dose doxycycline; however, both topical agents are effective when used in this combination approach for papulopustular rosacea (PPR). Although more information is needed on the modes of action of AzA in the treatment of rosacea, downregulation of the cathelicidin pathway appears to be one operative mode of action based on in vitro and in vivo studies, including data from patients treated with AzA 15% gel for PPR. Azelaic acid 15% foam is currently in the latter stages of development for PPR, with pivotal studies demonstrating efficacy and favorable tolerability, including a very low incidence of stinging, burning, and itching even without the use of designated skin care products.

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## INTRODUCTION

Since the publication of the landmark article by the National Rosacea Society in 2002, which introduced a standard classification system for rosacea, there has been a plethora of basic science and clinical research publications addressing the clinical presentations of rosacea and the underlying pathophysiologic mechanisms that appear to correlate with specific visible manifestations.[1-6] The magnitude of the individual contribution of each of these mechanisms can vary among different patients, thus accounting for the range of differences in the clinical presentations of rosacea.[3,4,7-9]

The 2 main pathophysiologic mechanisms fundamental to rosacea that have been reported based on several studies are neurovascular dysregulation and abnormal immune detection and response, with both signaled by a variety of exogenous triggers.[3-13] A greater understanding of these underlying pathophysiologic pathways has led to improved correlations between the clinical features of rosacea and the integration of specific therapies, although much more research needs to be completed to achieve further understanding because the pathophysiology of rosacea and the natural history of its progression are complex.[3-5,14,15] The current belief is that rosacea, especially in its most common clinical presentations, is an inflammatory facial skin disorder most commonly affecting adults who are affected by rosacea-prone skin.[3-6,10,11,16,17] Essentially, rosacea-prone skin is "wired differently," with the facial skin of those with rosacea exhibiting physiochemical, neurovascular, and microanatomic and ultrastructural differences compared with normal skin.[3-13,15-17] Various triggers that have been noted to incite flares of rosacea (such as ambient heat, ultraviolet light exposure, spicy foods, and *Demodex* mite proliferation) induce the onset of central facial vasodilation and cutaneous inflammation due to the heightened responsiveness of both neurovascular and innate immunologic pathways associated with rosacea-prone skin.[3-12,16,17]

Most of the development of medical therapies for rosacea occurred while the pathophysiology was not well understood.[1,5,13] As a result, researchers were limited by the absence of specific targets against which to direct therapies, which hampered the development of therapeutic agents for rosacea.[5] Prior to 2013, only 3 medical therapies have been submitted to the United States (US) Food and Drug Administration (FDA) for approval for rosacea, with all 3 receiving an approved indication for the inflammatory lesions (papules and pustules) of rosacea, commonly referred to as papulopustular rosacea (PPR). These 3 agents are topical metronidazole (first formulation 0.75% gel, approved in 1988; 0.75% and 1% available subsequently in multiple formulations); azelaic acid (AzA) 15% gel (approved in 2002); and doxycycline 40 mg modified-release capsule once daily (doxy-MR 40 mg QD, approved in 2006).[15,18] Most recently, alpha-adrenergic agonists (brimonidine 0.33% gel, approved in August 2013; oxymetazoline in Phase 3 studies) have been

developed specifically to treat persistent non-transient facial erythema of rosacea through vasoconstriction of chronically enlarged and dilated superficial vasculature of the central face, which is commonly referred to as *background erythema*.[5,13-16]

It is important that clinicians recognize that background erythema is a visible manifestation of rosacea which is both clinically and pathophysiologically distinct from papulopustular lesions and inflammatory erythema induced by pathways of inflammation that are activated during flares of rosacea.[1,5,13,15,16] Topical metronidazole, AzA 15% gel, and doxy-MR 40 mg QD are approved by the FDA for rosacea based on studies completed only in subjects with PPR; studies completed with these agents for cutaneous rosacea subsequent to FDA approval have also been performed only in patients with PPR.[3,5,13-18] The approved indication for all 3 of these agents, as stated in their current product labeling (package inserts), is for treatment of the inflammatory lesions (papules and pustules) of rosacea, with none of these agents evaluated in patients with rosacea who did not have papulopustular lesions. Topical metronidazole (all strengths and formulations), AzA 15% gel, and doxy-MR 40 mg QD are not FDA-approved specifically for facial erythema of rosacea as a "stand alone" indication. However, AzA 15% gel (n=333) demonstrated statistically significantly greater reduction in overall facial erythema scores compared with vehicle gel (n=331) in both Phase 3 pivotal trials (*P*=.0017 study 1; *P*=.0005 study 2) performed in subjects with PPR, compared with topical metronidazole formulations and doxy-MR 40 mg QD, which did not achieve statistically significant reduction in overall facial erythema in all Phase 3 studies in subjects with PPR.[19-21] It is important to recognize that overall facial erythema of rosacea in a patient with a flare PPR is distinct from background erythema, which is persistent, non-transient, and present between rosacea flares.[3-4,14,16]

"A summary of data on azelaic acid 15% gel serves to maintain a clinically relevant perspective of the therapeutic value of this agent in the management of rosacea."

As a result of the statistical consistency of reduction in overall facial erythema in subjects with PPR treated with AzA 15% gel, the approved FDA indication statement is the following: "[AzA 15% gel] is indicated for topical treatment of inflammatory papules and pustules of mild to moderate rosacea. Efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated."[22] This labeling serves to distinguish facial erythema related to the augmented inflammation present in patients with active PPR from the persistent and non-transient background erythema related to fixed dilatation and enlargement of centrofacial superficial cutaneous vasculature.[4,5,11,12,15,16,22,23] However, it is also important to recognize that AzA 15% gel markedly reduced both papulopustular lesions and overall facial erythema in pivotal Phase 3 studies, both of which are clinical signs associated with augmented inflammation present in rosacea patients with centrofacial erythema and papulopustular lesions.[19]

This supplement reviews the treatment of rosacea with emphasis on the track record of data with AzA 15% gel, which has been available in the US marketplace for over a decade. Also included are important considerations related to its formulation and optimal use, newer information on pharmacologic properties of AzA that appear to correlate with possible modes of therapeutic action in rosacea, and new horizons related to formulation development.

## A Panoramic Review of Azelaic Acid 15 % Gel Properties and Study Outcomes

The formulation characteristics, efficacy, skin tolerability, and safety of AzA 15% gel have been thoroughly reviewed elsewhere.[19,24-39] Nevertheless, a summary of data on AzA 15% gel serves to maintain a clinically relevant perspective of the therapeutic value of this agent in the management of rosacea.

### *Azelaic Acid: The Molecule*

Azelaic acid (1,7-heptanedicarboxylic acid) is a naturally occurring dicarboxylic acid, which exists as a white, odorless, large-particulate crystalline powder that is soluble in ethanol and not highly soluble in water.[25,40]

Azelaic acid is a naturally occurring organic compound found in grains such as wheat, barley, and rye. Application of AzA 15% gel does not result in systemic accumulation of AzA, with plasma concentrations not increasing above levels reflective of usual nutritional ingestion and endogenous metabolism (formed from the metabolism of larger chain dicarboxylic acids, ie, oleic acid).[25,40,41]

### *Vehicle Formulation*

Azelaic acid 20% cream was the initial formulation approved by the FDA in 1995 for the topical treatment of inflammatory acne vulgaris.[42] The decision to reformulate AzA in the 15% gel was due to improvements in the cutaneous delivery of AzA.[25]

- The vehicle gel formulation improved the pharmacologic characteristics of AzA through micronization of the AzA crystals to create a uniformly small particle size; incorporation into an aqueous-based gel (70% water) using polyacrylic acid and lecithin to form the gel matrix as dispersers and thickening agents; and using polysorbate 80 as an emulsifier and stabilizer of the aqueous formulation.[25,40,41]

- The percutaneous penetration of AzA was shown to be approximately 8-fold greater after application of AzA 15% gel compared with AzA 20% cream based on results from an in vitro Franz flow-through diffusion cell test in murine skin.[25]

*Skin Barrier Effects*

Sensitive skin is common in rosacea patients, with increased centrofacial transepidermal water loss reported in those with centrofacial erythema both with and without papulopustular lesions.[1,5,13,43]

- Application-site stinging and/or burning, reported in a subset of patients treated with AzA 15% gel, are usually transient in duration, mild to moderate in severity, no longer occurring after the first week to a few weeks of use in many patients, and not commonly resulting in discontinued use of the AzA 15% gel.[19,25,26,28,36,44] These symptoms are not associated with visible skin changes suggestive of contact dermatitis or contact urticaria, but rather are neurosensory and idiosyncratic in nature.[38]

- Regular proper skin care with a gentle cleanser and well-formulated moisturizer has been shown to reduce the likelihood, frequency, and intensity of stinging and burning after application of AzA 15% gel in most rosacea patients who experience these idiosyncratic effects.[15,24,25,44,45]

- An in vitro modified Franz diffusion chamber test performed with human skin showed that applying 1 of 3 studied brand moisturizer lotions (CeraVe® Moisturizing Lotion, Cetaphil® Moisturizing Lotion, Dove® lotions) *before* applying AzA 15% gel did not reduce the percutaneous penetration of AzA, and in some cases resulted in an incremental increase in percutaneous penetration compared with applying the moisturizer *after* applying the AzA 15% gel. The study results suggested that any of the 3 tested moisturizers may be applied either before or after AzA 15% gel without a major change in the percutaneous penetration/absorption profile of AzA.[39]

- In a split-face, investigator-blinded, 12-week study of 40 subjects with PPR, the idiosyncratic neurocutaneous symptoms of stinging and burning that affect a subset of rosacea patients treated with AzA 15% gel were shown not to be related to worsening of the epidermal permeability barrier function by the medication.[46] One side of the face was treated with AzA 15% gel twice daily, and the other side remained untreated. The results were as follows:

    - Decline in skin hydration measured by corneometry was greater on the untreated side. There was an increase in skin hydration at week 1 compared with baseline on the AzA-treated side ($P$=.009).
    - Investigator assessments of parameters such as facial erythema, desquamation, and overall facial appearance were scored using a 6-point ordinal scale (Table 1). Subjects used this same scale to report symptoms.
    - A statistically significant decrease in overall facial erythema was also noted on the treated side at week 2 ($P$=.003) and week 4 ($P$<.001) (Figure 1).
    - Overall facial appearance assessment was statistically superior on the treated side at week 2 ($P$=.005) and week 4 ($P$<.001).
    - A statistically significant decrease in desquamation was noted on the treated side over the untreated side at each time point ($P$<.001) (Figure 2).
    - Longitudinal analysis showed an increase in desquamation on the untreated side at 48 hours, week 1, week 2, and week 4 (Figure 2).
    - There was no increase noted in facial stinging and itching at any time point on the treated side. By week 4, there was a reduction in itching in both groups.

This study supports that AzA 15% gel does not appear to induce impairment of the epidermal permeability barrier, and improves signs and symptoms of rosacea, including skin changes inherent to rosacea-prone facial skin. This supports that the disease state itself is associated with epidermal permeability barrier impairment that is often not visibly evident or may present with visible signs such as fine facial scaling ("rosacea dermatitis").[5,43-46]

**TABLE 1.**

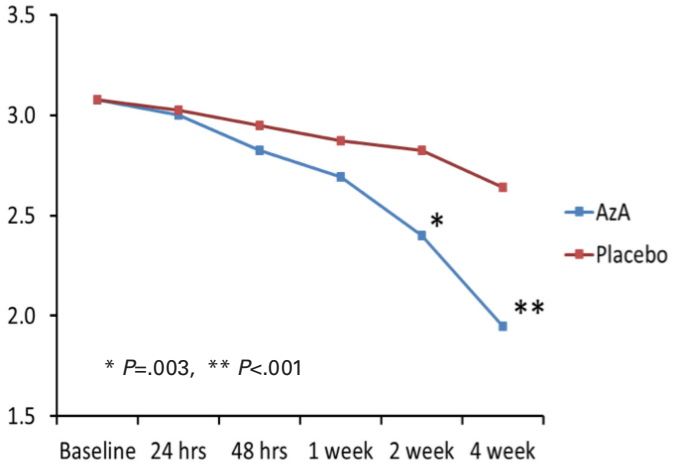
**Assessment Rating Scale: Split-Face Study of Azelaic Acid 15% Gel Twice Daily on Treated Side vs Untreated Side**

| Rating | Assessment |
|---|---|
| 0 | None |
| 1 | Minimal |
| 2 | Mild |
| 3 | Moderate |
| 4 | Moderately Severe |
| 5 | Severe |

*Efficacy and Safety*

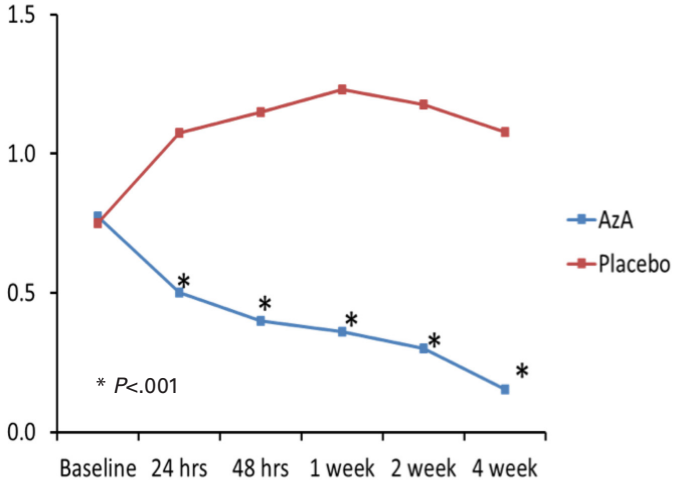
The efficacy and safety of AzA 15% gel for PPR have been demonstrated in multiple studies, both as monotherapy and in combination with oral therapy (ie, doxycycline); no major cutaneous or systemic safety issues have been associated with AzA 15% gel.[19,26-29,31-34,36,37]

**FIGURE 1.** Investigator assessment of overall facial erythema. Split-face study of azelaic acid 15% gel twice daily on treated side vs untreated side.




AzA, azelaic acid 15% gel.

**FIGURE 2.** Investigator assessment of facial desquamation. Split-face study of azelaic acid 15% gel twice daily on treated side vs untreated side.




AzA, azelaic acid 15% gel.

- Use of AzA 15% gel in combination with oral doxycycline expedites clinical improvement of PPR, especially in patients presenting with greater disease severity.[31-34] Once adequate control of a PPR flare was achieved within 1 to 3 months, AzA 15% gel applied twice daily proved to sustain satisfactory control of PPR in 75% of treated subjects over 6 months of follow-up.[32]

- The approved application frequency with AzA 15% gel is twice daily as this was the frequency in the pivotal studies submitted to obtain approval.[19,26,40] However, if patients with PPR end up applying AzA 15% gel once a day, there are published data to support comparable efficacy to twice-daily application.[37]

- In a 12-week study of PPR patients treated with doxy-MR 40 mg once daily in combination with either AzA gel 15% twice daily (n=106) or metronidazole 1% gel (metro 1%) once daily (n=101), efficacy parameters supported that both combination regimens were effective, with a trend toward earlier and greater therapeutic benefit with the AzA-based regimen than with the metronidazole-based regimen. Nominal differences were noted, but most were not statistically significant.[33]

    - Subjects at baseline in both groups had a mean lesion count of approximately 20 papules and pustules, most patients were rated as moderate severity by investigator global assessment (IGA), and all had at least mild overall facial erythema.[33]

    - After 2 weeks of treatment, a 25% reduction of papules and pustules was achieved by almost 85% of subjects in the AzA 15% gel group, with 61.3% and 20.8% of them achieving 50% and 75% reduction in papulopustular lesions, respectively. The percent lesion reductions observed in the metro 1% group were lower for each clearance category at each time point (Figure 3).

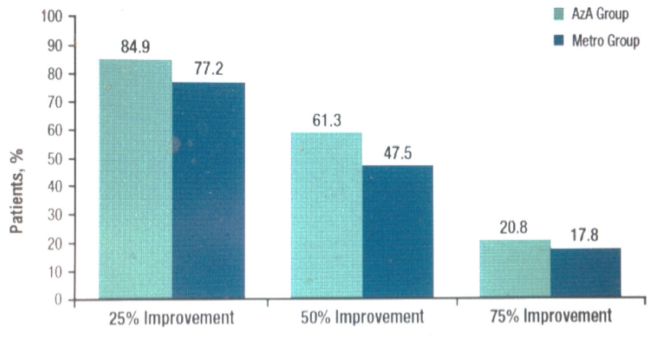
    - The percentage of patients achieving "treatment success" (IGA score of clear or minimal) was higher in the AzA 15% gel group compared with the metro 1% group at each time point. Statistical significance was reached at week 6 ($P$=.0097) (Figure 4).

The results of this study demonstrate comparable results in both groups, with support of an overall trend of quicker response and slightly greater efficacy in the AzA 15% gel treatment arm.[33]

## New Information on Possible Modes of Action of Azelaic Acid in Rosacea

In 2008, the American Acne and Rosacea Society (AARS) published recommendations on the medical management of rosacea based on the most current research and clinical data available.[18] These recommendations suggest the initial use of medical therapy that decreases the inflammation of rosacea (especially PPR) without the need for an antibiotic effect as there is no evidence that a bacterium is integral to the pathogenesis of rosacea, a concept that is well-supported based on currently available evidence.[6,11,13,18-20] Most recently, the AARS has published current recommendations on the management of rosacea that address the most common presentations of the disease – central facial erythema without papulopustular lesions (commonly referred to as erythematotelangiectatic rosacea) and central facial erythema with papulopustular lesions (commonly referred to as papulopustular lesions).[47] These

**FIGURE 3.** Percentage of subjects achieving 25%, 50%, and 75% or greater improvement in inflammatory lesion counts from baseline to week 2.[a]




AzA, azelaic acid 15% gel; Metro, metronidazole 1% gel.
[a]Subjects treated with doxycycline 40 mg modified-release once daily and either azelaic acid 15% gel or metronidazole 1% gel.

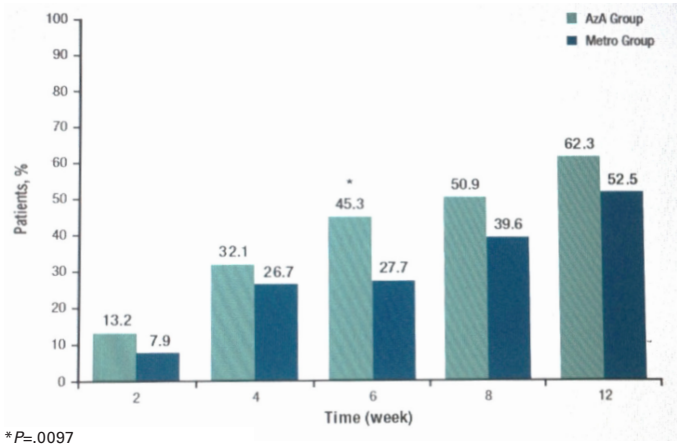
current AARS recommendations emphasize selecting therapy based on correlation with the clinical manifestations present in the individual patient and, as best as possible, the pathophysiologic mechanisms that are likely to be contributory.

Azaleic acid 15% gel was approved by the FDA on December 24 2002 for the treatment of papulopustular lesions of rosacea.[22] The statement "the mechanism(s) by which azelaic acid interferes with the pathogenic events in rosacea are unknown" was written in the approved product labeling over a decade ago.[40] Azaleic acid has been shown to exhibit multiple pharmacologic properties.[24,48] These include:

- Reduction in follicular keratinization in human skin in vivo and in vitro.
- In vitro evidence of antioxidant effects, including scavenger activity against hydroxyl radicals, inhibition of hydroxyradical-induced toxicity, and inhibition of oxyradical release from neutrophils.
- Competitive inhibition of tyrosinase and inhibition of mitochondrial respiratory enzymes in abnormal melanocytes.

Comedolytic activity and reduction in follicular keratinization support the development and FDA approval of AzA 20% cream for the treatment of inflammatory acne vulgaris. However, other than a possible contribution by antioxidant activity (if it occurs in vivo in rosacea-affected skin), none of the aforementioned pharmacologic effects of AzA are known to correlate with pathophysiologic mechanisms thought to be operative in rosacea. It is important to recognize that approved product labeling does not necessarily reflect current evidence related to how a given therapeutic agent may modulate the pathophysiology of disease, and that product labeling is not automatically updated by the FDA based on new evidence.

**FIGURE 4.** Percentage of patients achieving treatment success (investigator global assessment score of clear or minimal) at each time point.[a]




*$P$=.0097

AzA, azelaic acid 15% gel; Metro, metronidazole 1% gel.
[a]Subjects treated with doxycycline 40 mg modified-release once daily and either azelaic acid 15% gel or metronidazole 1% gel.

The augmented immune response and detection that is characteristic of rosacea-prone skin refers primarily to studies demonstrating upregulation of the cathelicidin (LL-37) production pathway in the facial skin of patients with PPR.[4,9-12]

The increased expression of toll-like receptor-2 (TLR2) is also consistent with the hyper-responsive nature of central facial skin of rosacea when exposed to exogenous trigger factors.[9] Interestingly, over the past 5 years, a series of in vitro studies performed with murine or human skin showed that AzA directly inhibited the following: (1) kallikrein 5 (KLK5) in cultured keratinocytes, (2) gene expression of KLK5, (3) TLR2 expression, and (4) cathelicidin (LL-37) formation.[12,49] An in vivo 16-week study performed in patients with PPR demonstrated that cathelicidin and KLK5 activity decrease with AZA 15% gel exposure; subjects with rosacea showed reduction in cathelicidin and KLK5 messenger RNA after treatment with AzA 15% gel twice daily.[49] These data performed in keratinocyte cell cultures, in murine skin, and in the facial skin of adult subjects with PPR support that inhibition of the upregulated cathelicidin pathway and possibly inhibition of TLR2 expression in rosacea-affected skin at least partially explain the therapeutic effects of AzA 15% gel in patients with PPR.

The efficacy of AzA 15% gel is greatest in those subjects with PPR who exhibit higher baseline levels of KLK5, further supporting this mode of action.[49]

This information on possible modes of action of AzA in PPR may also account to some extent for the observation of augmented benefit when AzA 15% gel is used in combination with doxycycline because this latter agent inhibits the upregulated cathelicidin pathway at a different step in the cathelicidin cascade of inflammation (inhibition of matrix metalloproteinases).[12,50]

### New Horizons With Azelaic Acid 15%

An oil-in-water emulsion foam formulation of micronized AzA 15% is under development and has been evaluated through the stage of Phase 3 clinical studies.[51] A randomized, double-blind, vehicle-controlled, multicenter, parallel-group study was conducted over 12 weeks with a 4-week follow-up period, evaluating the efficacy and safety of AzA 15% foam (n=198) applied twice daily compared with a vehicle foam (n=203) applied twice daily in adult subjects with moderate PPR (approximately 90% of subjects) or severe PPR (approximately 10% of subjects).[51] Primary efficacy variables assessed were IGA dichotomized into success and failure, and nominal change in inflammatory lesion count from baseline to end of treatment. The mean inflammatory lesion count at baseline was 21.6 in the AzA 15% foam group and 20.4 in the vehicle foam group.

- At week 12 (end of treatment), 43.4% of AzA 15% foam-treated subjects achieved treatment success (IGA score of clear or minimal) compared with 32.5% in the vehicle arm (*P*=.17).
- At week 12, the mean nominal inflammatory lesion reduction and mean percent reduction in inflammatory lesions were -13.4 and 65.4% respectively in the AzA 15% foam group, and -9.5 and 51% respectively in the vehicle foam group (*P*<.001, both parameters).
- Skin tolerability was favorable in both study groups. Application site burning sensation, stinging, and pruritus were reported as 1.5%, 2.5%, and 1.5% respectively in the AzA 15% foam study group, and as 0% for all 3 parameters in the vehicle foam study group. Importantly, this low number of subjects experiencing stinging and/or burning occurred despite the protocol not mandating use of designated gentle skin care products.[51]

Study outcomes show that the new foam formulation of AzA 15% is effective and well-tolerated in patients with moderate to severe PPR. Although no single formulation is appropriate for all patients, the availability of multiple vehicles assists the clinician in matching the needs and preferences of individual patients, especially given the favorable tolerability reported in the Phase 3 data with AzA 15% foam.[51]

## CONCLUDING REMARKS

Azelaic acid 15% gel boasts a long track record of both efficacy and safety for the treatment of PPR. The optimal use of AzA 15% gel is with concurrent proper skin care, either as monotherapy in patients with mild to moderate PPR, or in combination with oral therapy (ie, doxycycline) in patients with moderate to severe PPR. Once adequate control of PPR is achieved, AzA 15% gel can be continued without the oral agent to sustain the reduction in papulopustular lesions and associated inflammatory erythema.

There is some suggestive evidence that when used in combination with doxy-MR 40 mg QD, AzA 15% gel may provide a slightly quicker onset and greater magnitude of improvement of PPR overall than metro 1%. Although the differences are incremental based on study data, it may be clinically relevant in some patients who are anxious to see improvement, especially due to the chronicity of their disease.

There are new data supporting the anti-inflammatory activity of AzA through reduction of the cathelicidin pathway that is upregulated in rosacea-affected skin. If patients are not fully compliant and are using AzA 15% gel once daily instead of twice daily, there is comfort in knowing that once-daily application proved to be comparable to twice-daily application in patients with PPR. Lastly, the development of AzA 15% foam offers another vehicle option, and provides efficacy, safety, and a low incidence of skin tolerability reactions based on pivotal trial outcomes.

"Study outcomes show that the new foam formulation of azelaic acid 15% is effective and well-tolerated in patients with moderate to severe papulopustular rosacea."

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