

Azelaic Acid Gel 15% in the Management of Papulopustular Rosacea: A Status Report on Available Efficacy Data and Clinical Application

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Azelaic acid (Aza) gel 15% is approved by the US Food and Drug Administration (FDA) for the treatment of papulopustular rosacea (PPR). Its efficacy and safety as monotherapy have been demonstrated. Release of active drug from the gel formulation is superior to the cream. The combination of Aza gel 15% with oral doxycycline appears to expedite and augment response, especially in cases of PPR of greater severity, and Aza gel 15% maintains control of PPR over 6 months as compared to vehicle. Adjunctive skin

care is recommended to augment the therapeutic outcome of PPR and reduce the potential for irritation that can occur with topical therapy.

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Rosacea is a bucket term encompassing a group of heterogenous clinical phenotypes. Papulopustular rosacea (PPR) is a common clinical subtype of rosacea characterized most often by the presence of central facial erythema, inflammatory lesions (papules, pustules), and telangiectases.^{1,2} Papulopustular rosacea differs from erythematotelangiectatic rosacea (ETR) in that the latter is characterized by central facial erythema and telangiectases without inflammatory lesions. Both the PPR and ETR subtypes most commonly affect adults, usually fair-skinned white individuals, and wax and wane in intensity intermittently. Phymatous rosacea, most commonly affecting the nose, is a less common subtype of rosacea that affects males most frequently and often is seen in association with PPR.^{1,2} Lastly, ocular rosacea has been reported to affect up to 30% of patients with rosacea, including concurrent involvement with PPR, and can present as blepharitis; conjunctivitis; and in more severe cases, keratitis and papillary hypertrophy. Symptoms of ocular rosacea often include a sense of grittiness, dryness, pruritus, blurred vision, and photophobia.^{1,3} Importantly, there is a correlation between the severity of cutaneous rosacea and ocular rosacea, and their exacerbations may occur simultaneously or at different points in time.³

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Although PPR is less common than ETR, all of the therapies approved by the US Food and Drug Administration (FDA) for the treatment of rosacea were submitted to the FDA based on pivotal trials completed in participants with only PPR subtype (on-label indication),^{4,5} which is likely because the presence of inflammatory lesions in this subtype allows for determining severity grading and efficacy end points that can be assessed in a quantifiable manner. Medical therapies that are FDA approved for the treatment of PPR are topical metronidazole (Metr) 0.75% and 1% in multiple formulations, azelaic acid (AzA) gel 15%, and doxycycline 40-mg modified-release (Doxy-MR) capsules (subantimicrobial-dose doxycycline).⁵ Although not formally approved by the FDA for use in rosacea based on new drug application submission coupled with the required phases of pivotal trial support, sodium sulfacetamide 10%/sulfur 5% topical formulations are available for use in the treatment of acne, seborrheic dermatitis, and rosacea based on the drug efficacy study implementation. The drug efficacy study implementation program, started by the FDA in the 1960s, was developed to classify pre-1962 drugs after the Kefauver-Harris Amendment to the Food Drug and Cosmetic Act required all drugs to be efficacious and safe.⁶

Azelaic acid gel 15% was FDA approved in the United States in December 2002, released into the US marketplace in March 2003, and is indicated for the topical treatment of inflammatory papules and pustules of mild to moderate rosacea.⁷ Perilesional erythema associated with PPR also decreases with use of AzA gel 15%.^{7,8} This article emphasizes the clinical efficacy data on the use of AzA gel 15% for PPR, in addition to discussing relevant information regarding the vehicle, bioavailability, and optimal clinical application.

What are believed to be the modes of action of AzA gel 15% in the treatment of PPR?

Several pathophysiologic mechanisms have been suggested as being operative in PPR, including augmented innate immunity, generation and release of reactive oxygen species (ROS) in neutrophils causing inflammation secondary to oxidative tissue destruction, depletion of cutaneous superoxide dismutase (antioxidant reserve) correlated with greater disease severity, increased vascular hyperreactivity, innate stratum corneum dysfunction characterized by augmented central facial transepidermal water loss (TEWL), increased levels of cutaneous cathelicidins, upregulated expression of cutaneous serine protease activity (eg, kallikrein 5 [KLK-5]), and increased

levels of proinflammatory cathelicidin peptides (eg, LL-37 and variant peptides).^{1,8-16}

Azelaic acid has been shown to exhibit several pharmacologic properties such as scavenger activity of hydroxyl radicals; inhibition of ROS (oxyradical) release from neutrophils; antikeratinizing activity on follicular epidermis; anticomedolytic properties; inhibition of tyrosinase; concentration-dependent reduction in KLK-5 activity (human keratinocytes); and decreased expression of KLK-5, cathelicidins, and toll-like receptor 2 messenger RNA (murine skin).^{8,17,18} Among these properties, inhibition of ROS release from neutrophils; reduced KLK-5 activity; and decreased expression of KLK-5, cathelicidins, and toll-like receptor 2 are most likely to explain, at least in part, the effectiveness of AzA gel 15% for PPR.

Are there clinically relevant differences between the 15% gel and 20% cream formulations of AzA?

Azelaic acid—a saturated, straight-chain, medium-length dicarboxylic acid—is a white, odorless, crystalline powder that is poorly soluble in water and naturally occurring in many foods, such as barley, wheat, and rye.⁸ Azelaic acid gel 15% is FDA approved for the treatment of mild to moderate PPR.⁷ Azelaic acid cream 20% is FDA approved for the treatment of mild to moderate inflammatory acne vulgaris.¹⁹ Prior to FDA approval of both formulations for their respective indications, no dosage-ranging studies were completed, with both formulations studied in clinical trials using a twice-daily application frequency. As a result, the recommended application frequency for both formulations is twice daily according to FDA-approved product labeling.^{7,8,19} A subsequent multicenter, double-blind, randomized, 12-week study of adults with mild to moderate PPR showed that AzA gel 15% applied twice daily (n=37) or once daily (n=35) demonstrated equivalent efficacy in inflammatory lesion reduction, investigator global assessment (IGA) of clinical response, cosmetic acceptability, and tolerability.²⁰

Although AzA cream 20% has a higher amount of active drug per gram of final product, a greater percentage of AzA is solubilized in the 15% gel formulation as compared to the cream vehicle.⁸ The AzA gel is aqueous based (70% water) and adjusted to the approximate pH of the skin (pH 4.8), with polyacrylate polymers used to create a 1-phase system containing evenly suspended and uniformly micronized particles of AzA.^{8,21} The advances made in incorporating AzA into the gel vehicle, despite a lower concentration than the cream base, appear to markedly influence the cutaneous bioavailability

of active drug. Importantly, it has been shown that a higher concentration of AzA remains on the skin surface after application of the 20% cream (68.4%) compared to the 15% gel (56.7%), indicating greater release and penetration of AzA from the gel vehicle.^{8,21} In addition, percutaneous absorption and penetration of AzA from both the 15% gel and 20% cream vehicles was evaluated at 24 hours after fixed-dose (milligram per square centimeter) application to murine skin.²¹ Results showed an 8-fold higher delivery of AzA into viable skin from the 15% gel (25.3%) compared to the 20% cream (3.4%). However, the skin pass-through rate of AzA, reflective of potential for systemic exposure, was lower for the 15% gel (5.8%) than the 20% cream (16.3%). These latter findings are consistent with results obtained from a human urinary excretion study, which demonstrated that twice-daily application of either AzA gel 15% or AzA cream 20% did not alter the normal daily endogenous excretion of AzA compared to nontreated participants consuming a regular diet.²¹

Scarification testing, a methodology used to investigate irritation potential of topical products, was completed in 20 human participants using AzA gel 15%, AzA cream 20%, their respective vehicles, and benzoyl peroxide gel 5%. Both AzA formulations exhibited lower irritation potential than benzoyl peroxide gel 5%, and all scored between very low and mild.²¹

Does AzA gel 15% exhibit any clinically relevant effects on the function or integrity of the stratum corneum (epidermal permeability barrier) in patients with PPR?

Increased central facial TEWL has been noted in PPR and also in ETR, reflecting altered function of the stratum corneum, commonly referred to as epidermal permeability barrier dysfunction.¹³ A 2-week study was completed in 50 female participants with PPR and/or ETR treated with AzA gel 15% once or twice daily, evaluating both skin hydration (using corneometry measurements) and TEWL (using an open-chamber evaporimeter). The results demonstrated that AzA gel 15%, applied once or twice daily in patients with PPR and/or ETR, does not cause impairment of stratum corneum permeability barrier function based on TEWL measurements and does adversely affect skin hydration based on corneometry.²²

What are the efficacy results from clinical trials evaluating AzA gel 15% in the initial treatment of PPR?

Literature reviews have included clinical studies evaluating AzA gel 15% in the treatment of PPR,

including monotherapy, combination therapy, and comparative studies.^{23,24} The results of these individual studies are detailed here.

Pivotal Trials—The results of 2 multicenter, randomized, double-blind, parallel-group, vehicle-controlled phase 3 trials of participants with moderate PPR (N=664) demonstrated statistically significant superiority of AzA gel 15% compared to vehicle in reducing inflammatory lesion count (study 1, $P=.0001$; study 2, $P=.0208$); improving mean erythema rating (study 1, $P=.0017$; study 2, $P=.0005$); and increasing the percentage of participants achieving a rating of clear, minimal, or mild at study end point (study 1, $P<.0001$; study 2, $P=.0127$).²⁵

Comparison to Topical Metronidazole—Two multicenter, randomized, blinded studies were completed comparing AzA gel 15% twice daily versus Metr gel 0.75% twice daily or Metr gel 1% once daily in adult patients with PPR.^{26,27} In a multicenter, double-blind, randomized, parallel-group, 15-week study, AzA gel 15% twice daily (n=124) and Metr gel 0.75% twice daily (n=127) were compared in adults with moderate PPR.²⁶ Azelaic acid gel 15% demonstrated statistically significant superiority in all outcome measures, including mean percentage reduction from baseline in inflammatory lesion counts (-72.7% vs -55.8% ; $P<.001$), improvement in erythema score compared to baseline (56% vs 42%; $P=.02$), and IGA scores ($P=.02$) and physician-rated overall improvement compared to baseline ($P=.005$). A notable observation from this trial based on the mean percentage lesion reduction and the percentage of patients experiencing at least a 1-grade improvement in erythema rating was that a marked divergence between the 2 study arms occurred after week 8. In the AzA-treated group, continuous improvement in both the lesion reduction and erythema parameters was noted throughout the duration of the study, whereas a plateau effect was noted in the Metr-treated group from week 8 through week 15 with both parameters.²⁶

In a multicenter, randomized, investigator-blinded, parallel-group, 15-week, noninferiority study, AzA gel 15% twice daily (n=78) and Metr gel 1% once daily (n=82) were compared in adults with moderate PPR. Efficacy comparisons between the 2 groups were not statistically significantly different at study end point, including median percentage reduction in inflammatory lesion counts (80% AzA; 77% Metr; intent-to-treat population; $P=.264$), erythema severity score of 0 or 1 based on a 5-point scale (42.3% AzA; 42.7% Metr; $P>.1$), and treatment success (percentage cleared or almost cleared) based on investigator global severity score (56.4% AzA; 53.7% Metr; $P>.4$).²⁷

Combination Therapy Studies—Multiple studies include the use of AzA gel 15% in combination with oral agents, primarily different formulations of oral doxycycline in the management of PPR.²⁸⁻³⁰ Although the study objectives differed based on protocol design, some clinically relevant information may be gleaned from the outcomes of these trials.

An exploratory, multicenter, investigator-blinded, randomized, 12-week study evaluated either AzA gel 15% twice daily (n=106) or Metr gel 1% once daily (n=101), in combination with Doxy-MR 40-mg capsules administered once daily in patients with moderate PPR and persistent erythema.²⁸ Progressive improvement was observed in both treatment groups over the entire course of the study based on multiple conventional efficacy parameters used in studies of PPR. In addition to evaluating relative efficacy over the course of the study, differences in onset of clinical efficacy were assessed. The change in mean number of inflammatory lesions at week 2 did not differ significantly between the 2 groups (−10.5 AzA; −9.4 Metr; $P=.38$), with comparable nominal lesion reductions noted throughout the course of the study. Evaluations of the proportion (%) of patients achieving 25% or greater, 50% or greater, and 75% or greater inflammatory lesion reduction revealed a positive trend toward the AzA-treated group; the outcome that approached statistical significance between study arms was 50% improvement in inflammatory lesion counts (61.3% AzA; 47.5% Metr; $P=.0515$). The percentage of participants who were rated as responders (clear, minimal, or mild) based on IGA at study end point was 78.3% in the AzA group and 72.3% in the Metr group. The investigator rating of improvement as excellent based on comparison to baseline was 46.6% in the AzA group and 42.3% in the Metr group. Overall, this study demonstrated comparable efficacy with either topical agent when used in combination with Doxy-MR in moderate PPR, with a possible trend toward more rapid onset and greater global efficacy in the AzA-treated group. The latter trend observations were not fully supported by statistical methodology in this study, warranting further evaluation in additional larger trials.²⁸

A long-term, open-label, observational study evaluated AzA gel 15% alone or in combination with other conventional therapies in patients with mild to moderate PPR (N=583).²⁹ The primary physician-rated evaluation was based on IGA with the time between baseline and follow-up visits noted to be 48.6 days. In the combination therapy group (n=307), 205 participants received AzA gel 15% with an oral antibiotic. Although the

patient subset treated with AzA gel 15% and an oral antibiotic exhibited greater severity of PPR based on mean IGA at baseline, this group demonstrated significantly greater improvement than the group treated with AzA gel 15% with combination therapy not including an oral antibiotic ($P<.05$). Important conclusions noted in this study were that patients with greater severity of rosacea were more likely to be prescribed a combination regimen from the outset of therapy ($P<.0001$), the combination regimen when prescribed usually included an oral antibiotic with a topical agent ($P<.001$), patients treated with combination therapy demonstrated much greater improvement than those treated with monotherapy ($P<.0001$), and patients given an oral antibiotic along with the primary topical treatment used in this study (AzA gel 15%) exhibited the greatest improvement ($P<.05$).²⁹

Another study that includes data on treatment with AzA 15% gel in combination with oral doxycycline will be discussed in the next section.³⁰

What information is available on maintenance treatment of PPR with AzA gel 15%?

A 2-phase, multicenter study was completed to evaluate treatment response of adult participants with PPR of at least moderate severity.³⁰ In the first phase of the study (phase 1)—completed in a nonrandomized, open-label fashion—AzA gel 15% twice daily and doxycycline 100 mg twice daily were used in combination for a minimum of 4 weeks up to a maximum of 12 weeks (n=172). Those participants who achieved 75% or greater inflammatory lesion count reduction in phase 1 with the combination treatment used for at least 4 weeks were offered the opportunity to continue into phase 2, a double-blind, randomized study evaluating the ability of AzA gel 15% twice daily (n=67) versus vehicle gel twice daily (n=69) to maintain control of PPR over the ensuing 24 weeks. By week 12 of phase 1, 81.4% of participants achieved 75% or greater reduction in inflammatory lesion count and 64% of participants achieved treatment success, defined as an IGA rating of clear, minimal, or mild. In phase 2, relapse was defined as a 50% deterioration in lesion count improvement achieved at the end of phase 1, or an increase in erythema intolerable to the participant or failure to adequately maintain control of PPR as deemed by the participant and/or the investigator. By the end of phase 2, 75% of participants treated with AzA gel 15% maintained adequate remission of PPR, which equated to a relative risk reduction for relapse that was 33% greater than participants treated with vehicle gel twice daily.³⁰

Are there any notable safety and cutaneous tolerability concerns with the use of AzA gel 15% for PPR?

Available data from multiple studies support a lack of major safety concerns or systemic toxicities with the use of AzA gel 15%.^{4,5,8,20,23-30} Cutaneous tolerability reactions to AzA gel 15% have been summarized in several publications, with approximately 25% to 38% of participants noting burning, stinging, or tingling.^{8,24,26} Most participants report these reactions as transient and mild to moderate in intensity, with severe stinging or burning noted in less than 1% of participants.^{8,25} Discontinuation of treatment due to cutaneous tolerability reactions has been uncommon in studies of AzA gel 15%, with incorporation of controlled skin care recognized as an important adjunctive treatment to reduce both signs and symptoms innate to PPR and to decrease the frequency and/or intensity of tolerability reactions related to topical therapy.^{4,8,31-33}

A multicenter, open-label, split-face, 1-week study evaluated the impact of a specified skin care regimen in adults with PPR undergoing treatment with AzA gel 15% twice daily (N=102).³² The variable was use of a designated moisturizer cream twice daily on the same side of the face after application of AzA gel 15%. Subjective scores for severity and duration of stinging, burning, tingling, and itching were recorded in the morning and evening. It was noted that cumulative symptom scores demonstrated a statistically significant decrease on the side where moisturizer was applied ($P=.015$).³² Additionally, in an *in vitro* Franz diffusion cell human skin penetration assay incorporating radiolabeled AzA, the impact of the order of application of moisturizer lotion and AzA gel 15% on the bioavailability of AzA in human skin was studied. The application of any of 3 different commonly recommended moisturizer lotions applied before AzA gel 15% did not retard or reduce the penetration of AzA into skin, suggesting that any of these moisturizers may be applied before or after application of AzA gel 15%.³⁴

What concluding remarks may be made about the use of AzA gel 15% in PPR?

Azelaic acid gel 15% has been extensively studied in the treatment of PPR. The aqueous, polyacrylate polymer-based gel allows for greater active drug release and greater cutaneous penetration of AzA than the cream vehicle. Most studies have assessed results with twice-daily application, though once-daily use has been shown to be effective. Combination use of AzA gel 15% with an oral agent, usually doxycycline (including subantimicrobial-dose

doxycycline), has been shown to be efficacious and appears to expedite response to therapy, especially in patients with moderate to severe PPR. The systemic safety profile of AzA gel 15% is excellent. Although cutaneous tolerability of AzA gel 15% is favorable overall, a subset of patients experience burning, stinging, or tingling that usually is transient and not severe. Adjunctive skin care using a gentle cleanser and moisturizer is recommended to reduce both signs and symptoms characteristic of rosacea, and to decrease the frequency and/or intensity of tolerability reactions related to topical therapy.

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