Azelaic Acid 15% Gel: The Versatile Foundation of Combination Therapy in Mild to Moderate Rosacea in Various Patient Types

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Rosacea is a common, chronic dermatologic condition occurring predominantly in adult, white individuals of Celtic or Northern European ancestry. However, rosacea can also occur in people with skin of color and is often misdiagnosed in these patients. Rosacea is thought to have a multifactorial pathophysiology. Thus, an optimal foundation therapy should provide mechanisms of action that address these multiple pathophysiologic factors and have the ability to be easily combined with additional therapeutic modalities. Azelaic acid has anti-inflammatory and antimicrobial effects and has demonstrated clinical efficacy in treating both subtype 1 and subtype 2 rosacea in combination with other pharmacologic agents and laser therapy. It is also useful in addressing the hyperpigmented macules commonly seen in patients with skin of color who have inflammatory disorders such as rosacea. The objectives of this article are to review the rationale for first line use of azelaic acid and to evaluate the versatility of azelaic acid combined with various therapeutic regimens for mild to moderate rosacea in patients with different skin types.

Rosacea is commonly seen in clinical practice and can be a source of great embarrassment and emotional distress for those affected. It is a chronic skin disorder with various symptoms that usually affect the cheeks, chin, nose, and center of the forehead, which are the so-called convexities of the central face. The primary features of rosacea are flushing or blushing, with persistent redness of the face being the most common sign, with or without telangiectasias.[1-3] People with rosacea may also have acnelike papules or pustules. However, unlike acne vulgaris, the inflammation associated with rosacea papules can extend to facial skin well beyond the follicles, resulting in large, tender, red plaques.[4] There is a clear genetic predisposition to rosacea; it usually occurs in adults with fair skin, especially in those of Celtic or Northern European heritage.[2,3] Although facial rosacea is more frequent in individuals with fair skin, it has also been diagnosed in Asians and black individuals.[1] Indeed, it has been suggested that because of its greater prevalence in white individuals, rosacea may be underdiagnosed in people with skin of color.[5] Furthermore, skin pigmentation in people with skin of color can obscure signs of rosacea.[5]

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AZELAIC ACID AS FIRST-LINE THERAPY

As with the treatment of acne vulgaris, the optimal foundation treatment for rosacea would have multimodal effects that address the various pathophysiologic mechanisms purported to be involved in rosacea. Foundation therapies should also have the versatility and safety to be readily combined with additional therapeutic modalities. Azelaic acid is a naturally occurring, saturated, straight-chained dicarboxylic acid that appears to have anti-inflammatory and antimicrobial effects, as well as selective activity against hyperactive and abnormal melanocytes. These effects make azelaic acid a suitable treatment option for use in rosacea, acne, and certain cutaneous hyperpigmentary disorders.[6] The multimodal qualities of azelaic acid, along with its clinical safety and efficacy, make azelaic acid eminently suitable as a foundation therapy for patients with rosacea, including patients with skin of color and those in whom rosacea may be complicated by additional skin disorders, such as acne, postinflammatory hyperpigmentation (PIH), melasma, or seborrheic dermatitis.

AZELAIC ACID: CREAM VERSUS GEL

When azelaic acid was initially marketed as a dermatologic product, it was suspended at a 20% concentration in a cream formulation and topically applied to affected areas for use in the treatment of acne.[7] In general, cream preparations require a large amount of emulsifier to prevent separation of the water and oil-soluble ingredients.[7] Because emulsifiers tend to function as surfactants or detergents, the result is skin irritation along with a skin-whitening effect.[7] In contrast, gel formulations require less emulsifier since their oil-soluble ingredients are suspended in a structurally coherent matrix.[7] Earlier gel formulations used a cellulose matrix requiring acetone or alcohol, but the development of carbomers from polyacrylic acid has enabled gel formulations to be comprised of 70% water, with lipid concentrations as low as 3%.[7] With such a low lipid concentration, the emulsifier content is correspondingly low, ultimately resulting in less skin irritation.[7] In addition, gel formulations leave minimal residue compared with cream formulations, which translates into excellent skin aesthetics, while creating a cooling effect on the skin.[7]

In vitro testing of both azelaic acid cream and gel formulations has shown that the 20% cream formulation contains more micronized azelaic acid than the 15% gel formulation, yet more than 7 times the amount of azelaic acid is actually delivered to the viable skin with the gel formulation (25.3% for azelaic acid gel vs 3.4% for azelaic acid cream).[7] The key factor behind the development of azelaic acid gel is that gels are better vehicles for delivery because they require less azelaic acid in the overall formulation, while delivering more azelaic acid into the skin.[7]

SUBTYPES OF ROSACEA

The signs and symptoms of rosacea are variable. Not all people with rosacea have the same signs and symptoms, which leads to the concept that rosacea may be a syndrome rather than a single disease.[1-3] In 2002, the National Rosacea Society assembled a committee of thought leaders in the field of dermatology in order to develop a classification system for rosacea based on current scientific knowledge and morphologic characteristics.[1,4] The National Rosacea Society Expert Committee recommended that rosacea be divided into 4 major subtypes based on the type of signs present: erythematotelangiectatic rosacea (subtype 1); papulopustular rosacea (subtype 2); phymatous rosacea (subtype 3); and ocular rosacea (subtype 4) (Table 1).

PATHOPHYSIOLOGY OF ROSACEA

A number of theories about the pathogenesis of rosacea have been proposed over the years, but no definitive cause has been identified.[1-3] The pathophysiology of rosacea is believed to involve vasodilatory, inflammatory, and microbial components, aggravated by exposure to UV radiation (UVR) (Table 2).[2,3,8-13] Actinic damage may be part of the pathogenesis of rosacea, as UVR leads to collagen degradation, vasodilation, and the release of cytokines, which leads to inflammation and can result in the development of telangiectasias.[9] Solar elastosis is seen to a much greater degree in skin biopsy specimens from rosacea patients than in specimens from normal controls.[3,8,9]

ERYTHEMA AND FLUSHING: VASCULAR LABILITY

Flushing, a hallmark symptom of rosacea, occurs in response to changes in body temperature, ingestion of certain foods, emotion, or environmental triggers.[3,10,14] Vascular capacitance appears to be greater when blushing occurs in general, as demonstrated in a systemic study on flushing in normal subjects who were exposed to nicotinic acid and an oral thermal challenge. These subjects showed a proportionally greater increase in blood flow at the malar site.[10] The prevalence of flushing and blushing in rosacea patients, as well as the appearance of cutaneous blood vessels, may indicate an inherent vascular lability in people with rosacea.[2,10]

INFLAMMATORY MEDIATORS, UV EXPOSURE, AND REACTIVE OXYGEN SPECIES

Inflammatory mediators appear to be involved in both subtype 1 and subtype 2 rosacea. Inflammatory mediators

such as histamine, bradykinin, and prostaglandins have been implicated in the vasodilation seen in rosacea patients.[8,10] Individuals with rosacea have also been found to express abnormally high levels of the inflammatory mediator cathelicidin in their facial skin.[11] The proteolytically processed forms of cathelicidin peptides seen in rosacea patients differ from those in normal individuals and result from a posttranslational processing abnormality related to increases in the stratum corneum tryptic enzyme found in the epidermis.[11] Studies in mice have confirmed the role of cathelicidin in enabling skin inflammatory responses, offering a potential explanation of the pathogen.[11,15,16]

Exposure to UVR is also associated with inflammatory changes in the skin. UVR causes a release of cytokines and subsequently an infiltration of inflammatory cells, predominantly neutrophils, into the skin and the generation of reactive oxygen species (ROS), which play a major role in the changes seen in photoaged skin.[9] ROS are some of the most potent inflammatory mediators that immune cells (notably neutrophils) use to inactivate foreign objects or pathogens, which destroy collagen by

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Table 2

Proposed Pathophysiologic Components Underlying Rosacea[2,3,8-13]

Vasodilatory	Flushing in response to changes in body temperature, stress, environmental triggers; raises temperature at skin surface
Inflammatory	Antibodies to *Demodex* mites and some other bacteria found in sera of rosacea patients; ROS released by neutrophils to combat pathogens and also in response to UVR exposure; elevation of cathelicidins, which promote skin inflammation
Microbial	High proportion of *Demodex* mites as well as other skin microbes (eg, *Bacillus oleronius, Staphylococcus epidermidis, Propionibacterium acnes*)
UV radiation/ sun exposure	Solar elastosis more common in rosacea patients; UVR exposure leads to collagen degradation, vasodilation, development of telangiectasias, and release of cytokines

Abbreviations: ROS, reactive oxygen species; UVR, ultraviolet radiation.

TABLE 3
Therapeutic Options for Rosacea Subtypes 1 and 2

Drug Type	Agent
Topical	Azelaic acid 15% gel
	Metronidazole 0.75% gel and 1% gel
	Sulfur/sulfacetamide formulations
	Antibiotics (eg, clindamycin 1% gel)
Oral	Tetracycline
	Macrolide antibiotics

inactivating tissue inhibitors of matrix metalloproteinases.[9,12] Photoaged skin has reduced levels of antioxidant enzymes and thus, is less protected against ROS.[4,9,17] It has been proposed that people with rosacea have defects in their cutaneous antioxidant defense system, leading to a greater susceptibility to ROS-induced damage.[4,9,17]

INFLAMMATION AND MICROBIAL INVOLVEMENT

Clinical observations and histopathologic studies have also implicated microbes in the pathogenesis of rosacea.[2,13,18-22] *Demodex folliculorum*, a common skin mite, is seen in greater density in the skin of people with rosacea.[8,13,19,20] By mechanically blocking the follicles, acting as vectors for bacteria, or both, this increased density of mites may trigger inflammatory or specific immune reactions.[8,13] A recent study demonstrated a possible role for bacteria associated with *Demodex* mites in the development of papulopustular rosacea. The study demonstrated that *Bacillus oleronius* (a bacterium found within *Demodex* mites) stimulated an immune system response, inducing high levels of T lymphocytes in 79% of people with subtype 2 rosacea, compared with only 29% of people without rosacea.[21] It is relevant to note that *B oleronius* is susceptible to topical and oral antimicrobial agents, which demonstrates efficacy in rosacea.[21]

THERAPEUTIC OPTIONS FOR ROSACEA SUBTYPES 1 AND 2

Management of rosacea is multifaceted and should include an effective pharmacologic therapy, an appropriate supplementary skin care regimen, and patient education.[23] Fortunately, there are now many pharmacologic therapeutic options for rosacea, including topical[24-27] and oral[24-27] therapies (Table 3). Combination therapy involving a topical agent (eg, azelaic acid or metronidazole) and an oral antibiotic is now the standard of care for subtype 2 rosacea, while topical azelaic acid or metronidazole is the standard therapy for subtype 1 rosacea.[4,26] Topical metronidazole has been available for the treatment of rosacea since 1988 when it was approved by the US Food and Drug Administration (FDA).[2,27] Azelaic acid, previously available as a 20% cream for acne treatment, was approved as a 15% gel to treat rosacea in 2002.[27]

Both azelaic acid and topical metronidazole are clinically proven treatments for subtypes 1 and 2 rosacea, although some evidence suggests that azelaic acid may be more effective in addressing the erythema associated with both subtypes.[28-30] Azelaic acid has been reported to be effective in rosacea when used alone, or in combination with other topical agents, especially in patients with eczematous rosacea, seborrheic dermatitis, or both, and papulopustular rosacea.[28,31]

AZELAIC ACID PROPOSED MECHANISMS OF ACTION

The proposed mechanisms of action of azelaic acid in rosacea include antimicrobial, antibacterial, anti-inflammatory, antioxidant, and antikeratinizing effects (Table 4).[6,12,32,33] Azelaic acid appears to act selectively on hyperactive and abnormal melanocytes that are characteristic of hyperpigmentary disorders, while showing no depigmenting action on normal skin.[6] Azelaic acid displays bacteriostatic and bactericidal properties against a variety of aerobic and anaerobic microorganisms present on the skin of acne and rosacea patients.[6,18] Its antimicrobial action is apparently due to the inhibition of cellular protein synthesis because azelaic acid has been shown to produce marked inhibition of protein synthesis by *Staphylococcus epidermidis* and *Propionibacterium acnes*. Azelaic acid also decreases the free fatty acid content of skin surface lipids, further reducing the hospitable nature of the skin environment to microbial overgrowth.[6] Azelaic acid has shown antikeratinizing effects on normal and acne-affected skin.[6] Recent investigations have demonstrated that azelaic acid inhibits the generation and action of ROS in biologic systems, an effect that may contribute to the anti-inflammatory and diverse therapeutic properties of azelaic acid.[6,32] Additionally, azelaic acid has been shown to markedly decrease the free radicals generated by neutrophils by inhibiting cell metabolism and enzymatic activity within the cell membrane.[12,32]

CLINICAL EVIDENCE SUPPORTING THE USE OF AZELAIC ACID AS FOUNDATION THERAPY FOR ROSACEA

A number of double-blind, randomized, controlled trials support the efficacy of azelaic acid 15% gel in the treatment of papulopustular rosacea.[29,34,35] Although such randomized studies have not been conducted in patients with only subtype 1 rosacea, anecdotal case studies have

Table 4

Proposed Mechanisms of Action of Azelaic Acid in Rosacea[6,12,32,33]

Mechanism of Action	Properties of Azelaic Acid
Antimicrobial	Inhibits protein synthesis and reduces free fatty acid content in skin lipids, creating a hostile environment for microbes
Anti-inflammatory/Antioxidant	Decreases the production and release of ROS from neutrophils
Antikeratinizing	Incorporates into keratinocytes and disrupts mitochondrial activity and DNA synthesis

Abbreviation: ROS, reactive oxygen species.

shown that azelaic acid is effective in these patients also, with patients and investigators noting improvement in erythema.[28,34,36] In a case series of 6 patients with erythematotelangiectatic rosacea, azelaic acid was reported to be safe and effective in improving and resolving erythematotelangiectatic rosacea.[36] Marked improvement was noted in some patients as early as 2 weeks after treatment initiation.[36]

Two comparative trials of azelaic acid 15% gel, one versus metronidazole 0.75% gel and the other versus metronidazole 1% gel, showed that the efficacy of azelaic acid is similar to or better than that of metronidazole in treating rosacea.[29,37,38] Azelaic acid 15% gel maintained its effects over time in the first study, while the effects of metronidazole 0.75% gel appeared to plateau.[29] In this multicenter, randomized, double-blind, parallel-group study, patients in the azelaic acid 15% gel group showed a continuous decline in mean inflammatory lesion counts throughout the 15 weeks of treatment, with 18.1 lesions at baseline and 4.5 lesions at week 15. Although patients in the metronidazole 0.75% gel group showed a decline in lesions from baseline to week 8, with 19.4 lesions at baseline and 7.7 lesions at week 8, the lesion count stabilized after week 8 and no further reductions were seen through week 15.[29,37] The trial design has not been duplicated and further research is needed.[37]

Studies suggest that azelaic acid may have greater effects on erythema than metronidazole.[29,37] In the double-blind comparative study of azelaic acid 15% gel versus metronidazole 0.75% gel, azelaic acid 15% demonstrated significantly greater improvement in overall facial erythema ($P=.02$), with an improvement in erythema severity observed in 56% of the azelaic acid 15% gel group versus 42% of the metronidazole 0.75% gel group. Erythema continued to improve during the course of the 15-week study in the azelaic acid 15% group, but remained steady after week 8 in the metronidazole 0.75% gel group.[29,37]

An important consideration is that azelaic acid 15% gel is well tolerated in the treatment of rosacea, which is a condition associated with sensitive skin. In an analysis of the comparative trials presented at the 63rd Annual Meeting of the American Academy of Dermatology in 2005, the majority of patients in all treatment groups had comparable skin sensitivity at baseline, and almost half of each group reported skin dryness.[39] Additionally, more than 85% reported some degree of burning, tingling, itching, stinging, edema, scaling, or pain at baseline (Table 5).[39] The trials showed a high degree of compliance with azelaic acid 15% gel treatment and a low rate of discontinuation caused by local skin irritation (<5%).[39] Azelaic acid 15% gel has not been associated with systemic, photoallergic, or photosensitive reactions, and a statistically significant decrease in skin dryness has been reported with its use.[39] In most cases, patients experiencing neurosensory reactions to the application of azelaic acid 15% gel do not require an adjustment in therapy. The majority of these cases are mild to transient and do not result in discontinuation.[39] The use of an appropriate skin care regimen (eg, a cleanser and a moisturizer) is an important component of the effective management of rosacea and can address the occasional irritation associated with azelaic acid 15% gel.[4,33,39]

The Face and Mind Evaluation study, a real-world, practice-based evaluation of azelaic acid 15% gel used either as monotherapy or in combination with other rosacea treatments, examined both the clinical efficacy and the changes in quality of life resulting from treatment regimens for rosacea containing azelaic acid 15% gel.[40] Quality of life represents an important outcome parameter for dermatology patients, as the majority of conditions that dermatologists treat are not life threatening. They may, however, be considered life altering. RosaQoL is a rosacea-specific, quality-of-life instrument based on in-depth interviews with rosacea patients. In the Face and Mind Evaluation study, the RosaQoL findings were correlated with the

TABLE 5

Baseline Signs and Symptoms of Rosacea[39]

Clinical Characteristics	Azelaic Acid 15% Gel (n=124)	Metronidazole 0.75% Gel (n=127)
Skin dryness	62%	66%
Scaling	51%	58%
Itching	43%	51%
Edema	37%	32%
Burning	35%	33%
Stinging	30%	34%
Pain	18%	14%

investigator's global assessment (IGA), an 8-point measure widely used to determine the severity of rosacea.[40] Patients who were prescribed azelaic acid 15% gel in combination with other agents had significantly higher baseline IGA scores than those who were prescribed azelaic acid 15% gel as monotherapy. Furthermore, those who were prescribed an oral antibiotic as part of the combination regimen had significantly worse rosacea symptoms at baseline. Study results showed that, overall, patients had positive responses to their treatment regimens. The IGA score improved between baseline and follow-up for almost 79% of patients; only 1.8% of patients had a higher IGA score at follow-up than at baseline. Patients receiving combination therapy had a significantly greater decrease in rosacea symptoms than those receiving monotherapy ($P<.0001$), and patients given an oral antibiotic in combination with azelaic acid 15% gel showed the greatest improvement ($P<.05$).[40] A positive effect on quality of life was also seen over the course of the study, with all aspects of rosacea-related quality of life showing significant improvement with treatment ($P<.0001$).[40]

CONTINUED UTILITY OF AZELAIC ACID 15% GEL

Several exploratory studies have evaluated the efficacy and safety of azelaic acid 15% gel in dermatoses other than rosacea. In a double-blind, randomized, vehicle-controlled, exploratory, 6-week study of mild to moderate seborrheic dermatitis of the face, the results achieved with azelaic acid 15% gel were consistently better throughout the study than those achieved with the vehicle.[41] Local tolerability was rated as acceptable, good, or excellent by 93.6% of patients.[41]

Two recent randomized, multicenter, controlled trials compared the effects of azelaic acid 15% gel with those of topical benzoyl peroxide 5% gel or topical clindamycin 1% gel in the treatment of acne vulgaris.[42] Treatment with azelaic acid 15% gel resulted in a 70% to 71% median reduction in facial papules and pustules, compared with a 77% reduction with benzoyl peroxide 5% gel and a 63% reduction with clindamycin 1% gel.[42]

In a 1-year observational study in which dermatologists evaluated the efficacy and safety of azelaic acid 15% gel as monotherapy or in combination with other agents, 81.9% of physicians saw improvement in patients' symptoms after an average of 34.6 days, while 93.9% of physicians saw patient improvement after an average of 73.1 days.[42] Both physicians and patients considered azelaic acid 15% gel to be effective, with 74% of patients being very satisfied at the end of therapy.[42] Azelaic acid 15% gel was considered well tolerated or very well tolerated by 95.7% of patients.[42]

Studies of azelaic acid have demonstrated its efficacy and tolerability in melasma[43-45] as well as in other hyperpigmentary disorders, such as PIH.[46-48] Generally speaking, these studies have demonstrated that azelaic acid is at least as effective as hydroquinone in terms of untoward effects, such as irritation or the depigmentation of surrounding normal skin.[49] To date, most of the studies of azelaic acid in hyperpigmentary disorders have used 20% or 15% cream formulations.

Currently, azelaic acid 20% cream is FDA approved for the treatment of acne vulgaris and azelaic acid 15% gel is FDA approved for the treatment of inflammatory (papulopustular) rosacea. Because of its multiple mechanisms of action associated with potential therapeutic benefits, azelaic acid is a valuable therapeutic option for patients with rosacea, especially if they have concomitant dermatoses, such as seborrheic dermatitis, acne, melasma, or PIH.

RATIONALE FOR VARIOUS THERAPEUTIC COMBINATIONS, BUILDING ON TOPICAL AZELAIC ACID AS THE FOUNDATION

Given its efficacy, safety, and underlying mechanisms of action, there is a clear rationale for the inclusion of azelaic acid as part of combination therapy for rosacea subtypes 1 and 2. The use of topical azelaic acid with an oral antibiotic offers complementary pathophysiologic actions. Oral antibiotics provide antimicrobial (and sometimes anti-inflammatory) effects systemically, while azelaic acid applied topically complements the antimicrobial effects and also provides cutaneous anti-inflammatory and antioxidant effects. The combination of topical azelaic acid with topical metronidazole provides similar antimicrobial, anti-inflammatory, and antioxidant mechanisms of action, with the added benefit of the antikeratinizing action of azelaic acid. The inclusion of azelaic acid in a rosacea treatment regimen tailored to patients with skin of color is highly appropriate. Because of its antikeratinizing effects and ability to inhibit tyrosinase, which is the key enzyme of melanogenesis,[6] azelaic acid is likely to have beneficial effects on PIH, a comorbid condition occurring in people with skin of color who have inflammatory dermatologic disorders.[50] Azelaic acid can also be combined with procedures such as maintenance therapy following laser treatment (Figure).

In addition to the use of topical azelaic acid with other pharmacologic agents or procedures, the use of optimal cleansing and moisturizing products along with topical azelaic acid treatment may also improve the cosmetic condition of skin in rosacea patients. A 12-week, investigator-blinded, randomized study assessed the tolerability and potential additional benefits of a standardized skin care regimen containing gluconolactone, which is a polyhydroxy acid (PHA), compared with nonstandardized skin care regimens, during treatment with azelaic acid 15% gel for moderate rosacea.[51] Azelaic acid 15% gel reduced median lesion counts in both the standardized and the nonstandardized skin care groups, whereas significant decreases in erythema were experienced only by those in the standardized group.[51] Based on both investigator assessment and patient self-assessment, the PHA regimen was well tolerated, with fewer adverse events than the nonstandardized regimens.[51] Specifically, a statistically significant lower occurrence of skin dryness was seen with the standardized PHA regimen from week 4 to the end of the study, along with significantly better tolerability for neurosensory symptoms, such as itching and stinging.[51] Moreover, the additional benefit of skin smoothing and antiaging was observed among those using the gluconolactone-containing cleanser and moisturizer.[51] Findings from this study offer continued support for the 3-pronged approach to rosacea management, which includes pharmacologic therapy, proper skin care, and patient education.[23,33]

A 55-year-old woman with subtype 1 rosacea before treatment (A) and 3 months after treatment (B) with a combination of 532-nm green light laser treatment, followed by maintenance combination therapy with azelaic acid 15% gel and metronidazole 0.75% gel.

CONCLUSION

New research has increased our understanding of the pathophysiology of rosacea. Multiple factors appear to be involved in the pathophysiology of this chronic dermatologic disorder. Thus, agents or combinations of agents with multiple mechanisms of action should be most successful in its long-term treatment. Fortunately, a number of topical and oral pharmacologic agents as well as light-based therapies have demonstrated efficacy in the treatment of rosacea, not only in white individuals, who are the majority of rosacea patients, but also, less frequently, in patients with skin of color. Clinical studies continue to validate the clinical utility of topical azelaic acid 15% gel as foundation therapy for rosacea in a wide range of patients.

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