Diverse Skin Needs and the Tolerability of Azelaic Acid 15% Gel in Rosacea

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One of the major challenges in developing topical therapeutic agents for rosacea is meeting the diverse needs of the population affected by the disorder. Although phase 3 studies attempt to include populations that mimic real world clinical conditions, most enroll a relatively homogeneous group of participants based on inclusion and exclusion criteria. Oftentimes, these studies exclude individuals with sensitivities to ingredients, skin disease, sensitive skin, or other disorders and most do not analyze subpopulation. The US Food and Drug Administration recognizes the limitations of phase 3 testing and requests postapproval phase 4 studies to more accurately assess medication safety and tolerability in real world use.[1]

The performance of a rosacea agent can only be accurately assessed in a study population that realistically reflects the actual range of participants found in a clinical setting. Rosacea study populations should therefore include individuals with rosacea types appropriate for the agent under study and with varying disease severity, chronicity, and relapse rates. Additionally, the population should cover a broad range of ages, ethnicities, and skin types.[2,3] Finally, participants with concomitant skin disorders should be included because reports suggest that more than half of rosacea sufferers fall into that group.[4,5] Table 1 summarizes some possible considerations for building a diverse population in which to study rosacea medications.

This research developed a diverse population by enrolling participants of different ages and Fitzpatrick skin types with varying levels of sebum production. Table 2 summarizes the literature regarding skin variability. The study also enrolled participants with concomitant seborrheic dermatitis, eczema, and cosmetic intolerance syndrome.

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According to a survey of 1099 patients with rosacea, 56% of respondents had been diagnosed with at least one additional skin disorder, with 25% reporting concomitant seborrheic dermatitis and 21% reporting eczema (eg, contact dermatitis, atopic dermatitis, or both).[6] Of the patients being treated for those disorders, 37% said that therapy had exacerbated their rosacea. In another study, concomitant acne was reported in approximately 82% of participants and concomitant seborrheic dermatitis of the face or scalp in approximately 35% of participants with rosacea. Treatment for one of those conditions frequently exacerbated another.[7]

TABLE 1

Considerations for a Diverse Population

Skin type
Fitzpatrick skin types I–VI
Sebum production (dry, oily, combination, normal)
Gender
Age
Ethnicity
What constitutes diversity within a dermatologic disease group?
Severity
Chronicity
Relapse rate
Multiple concomitant skin diseases
What considerations are necessary for agent formulation?
Solubility of drug (water soluble vs oil soluble)
Skin barrier effects
Drug residue on skin surface (thick film vs thin film)
Ability of drug to spread over skin surface
Overall aesthetics

To help evaluate the performance of topical azelaic acid (AzA) 15% gel in a diverse population approaching actual clinical conditions, this phase 4 study was conducted in participants with a range of Fitzpatrick skin types, various levels of sebum production, and concurrent skin disorders.

TABLE 2

Cutaneous Differences Regarding Age and Ethnicity

	Type of Skin				
Variable	**White**	**Hispanic**	**Asian**	**Black**	**Mature**
Thickness, μ	7.2	N/A	N/A	6.5	Epidermal interface flattens, stratum corneum does not change; sun-exposed skin may thicken
Layers (mean No. at abdomen or trunk)	16.7	N/A	13.4	21.8	Possible increase, results variable
Transepidermal Water Loss					
Baseline	Less than Asian, Hispanic, or black	Not significantly greater than white, less than black	Significantly greater than white	Significantly greater than white	Lessens with age
After tape stripping	Less than Asian or black	N/A	Greater than white or black	Less than white, greater than Asian	N/A
After chemical irritation (SLS exposure)	2.0% SLS: lowest change vs baseline of those tested	2.0% SLS: higher than in white	0.25% SLS: change from baseline 7% lower vs white 0.5% SLS: change from baseline 29% higher vs white	2.0% SLS: Increased vs baseline, no significant change vs white	Less response to 5% SLS than younger participants
Sensitivity					
Vasodilation and/or vessel reactivity	Less than Asian, greater than black	Similar to white	Highest	Lowest	Possible age-related decrease; slower vessel recruitment and filling
Response to irritation	Erythema	Uneven skin tone or hyperpigmentation possibly masking erythema	Erythema	Uneven skin tone (eg, hyper- or hypo-pigmentation)	Slower to react, slower to resolve

Abbreviations: N/A, not applicable; SLS, sodium lauryl sulfate.

TABLE 3

Study Demographics Involving 40 Participants

Breakdown of Participants' Skin	n (%)
Fitzpatrick skin type	
Type I	20 (50)
Type II	15 (37.5)
Type III	5 (12.5)
Complexion/sebum type	
Dry	16 (40)
Oily	4 (10)
Combination	15 (37.5)
Normal	5 (12.5)
Cosmetic intolerance	13 (32.5)
Overlap syndrome	14 (35)
Facial eczema and rosacea	6 (15)
Facial seborrheic dermatitis and rosacea	4 (10)
Perioral dermatitis and rosacea	1 (2.5)
Facial seborrheic dermatitis, facial eczema, and rosacea	2 (5)
Facial eczema, eyelid dermatitis, and rosacea	1 (2.5)

Method

This single-center, open-label, prospective phase 4 clinical study was conducted from March to May 2008. Forty participants with diverse Fitzpatrick skin types applied AzA 15% gel to their facial rosacea twice daily for 4 weeks. Institutional review board–approval was obtained before initiation of the study, and each participant gave written informed consent upon enrollment before receiving the study medication.

The inclusion criteria required participants to be females aged 18 years or older with mild to moderate subtype II (papulopustular) rosacea defined as facial erythema, telangiectasia, and having 8 to 50 inflammatory papules and pustules. Pregnant women and those with known hypersensitivity to the study medication were excluded.

All participants were instructed to discontinue use of oral and topical agents indicated for rosacea 4 weeks prior to the study. Other medications were permitted. At baseline, each participant's Fitzpatrick skin type and sebum-related skin type were assessed by the investigator. The investigator also determined presence of overlap syndrome, which was defined as concurrent seborrheic dermatitis, eczema (atopic dermatitis), and other dermatologic disorders not interfering with skin evaluation. Presence of cosmetic intolerance syndrome, defined as heightened neurosensitivity with burning or stinging following application of facial cosmetics and skin care products, was also assessed. Compliance was determined from participants' diary sheets.

Three primary end points were specified: tolerability, defined as investigator's determination of skin irritation at study end; efficacy, determined by lesion count; and safety, determined by adverse events. Observations were conducted at baseline and at weeks 2 and 4. At those times, the investigator performed facial lesion counts and assessed erythema, desquamation, stinging, burning, itching, irritation, and overall rosacea severity based on an ordinal grading scale where 0=none; 1=minimal; 2=mild; 3=moderate; and 4=severe. A second set of observations based on participants' evaluation of their own facial redness, peeling, dryness, stinging, burning, and overall rosacea severity was obtained at those same times using the same ordinal scale. Lesion counts were analyzed using the *t*-test. Other findings (intrasubject comparison of 2- and 4-week scores vs baseline and comparison between subgroups of change from baseline) were analyzed using the 2-tailed Mann-Whitney nonparametric test. Statistical significance was defined as $P<.05$.

Results

Of the 40 enrolled participants, 40 successfully completed the 4-week study. The characteristics of the participant population are presented in Table 3. Table 4 presents baseline versus mean data of week 4 for other investigator-assessed signs and symptoms.

The mean lesion count at baseline was 11.15, and highly significant mean decreases were noted at week 2 (mean count, 6.63; $P<.001$) and at week 4 (mean count, 2.70; $P<.001$). Significant improvement versus baseline was also seen in erythema scores at weeks 2 and 4 ($P<.001$). Similarly, significant decreases in desquamation were seen at week 4 ($P<.0001$). No significant change versus baseline was seen at week 4 for other investigator-assessed signs and symptoms. No significant changes were present at week 2 except for an increase in stinging score ($P<.001$). No statistically significant increase in itching or irritation scores occurred during the study.

Subject-assessed variables demonstrated that participants perceived the AzA 15% gel formulation to be efficacious and tolerable. Scores were similar to those assessed by the investigator, with no increase in symptomatology. At week 2, participants reported statistically significant

TABLE 4

Investigator-Assessed Signs and Symptoms

	Desquamation			Stinging			Itching			Irritation		
	Baseline	Wk 4	*P* value	Baseline	Wk 4	*P* value	Baseline	Wk 4	*P* value	Baseline	Wk 4	*P* value
Full population	1.5	0.2	<.0001	0.05	0.25	≤.25 (NS)	0.05	0.15	≤.67 (NS)	0.0	0.03	≤.8 5 (NS)
Complexion/Sebum Type												
Dry	1.9	<0.1	≤.004	<0.1	0.6	≤.37 (NS)	0.06	0.3	≤.78 (NS)	0.0	0.0	NS
Oily	0.5	0.0	≤.43 (NS)	0.0	0.0	NS	0.0	0.0	NS	0.0	0.0	NS
Combination	1.5	0.3	≤.01	<.1	0.2	≤.55 (NS)	0.1	0.1	NS	0.1	0.1	≤.8 (NS)
Normal	0.6	0.6	≤1 (NS)	0.0	0.6	≤1 (NS)	0	0.6	≤1 (NS)	0.0	0.0	NS
Overlap Syndrome												
Facial eczema	3.6	0.4	<.0002	0.1	0.2	≤.45 (NS)	0.11	0.11	NS	0.11	0.0	≤.45 (NS)
Facial seborrheic dermatitis	2.2	0.7	≤.18 (NS)	0.0	0.2	≤1 (NS)	0.0	0.0	NS	0.0	0.0	NS
Cosmetic intolerance	1.9	0.3	<.001	2	0.8	≤.76 (NS)	0.2	0.8	≤.76 (NS)	.1	0.0	≤.76 (NS)

Abbreviation: NS, not significant.

improvements from baseline in scores for redness (1.9 vs 2.5; $P=.002$) and peeling (0.3 vs 0.8; $P=.006$). At week 4, significant improvement versus baseline was seen in redness (1.4 vs 2.5; $P<.001$), peeling (0.2 vs 0.8; $P=.002$), and dryness (0.9 vs 1.7; $P=.001$). No statistically significant increase in stinging was reported, although the score had decreased versus baseline by week 4 (0.8 vs 0.6).

For other investigator-assessed signs and symptoms, none of the subgroups had worsening of signs or symptoms at week 4 versus baseline; however, some had improvement. The majority of participants had no significant change in stinging, itching, or irritation at either weeks 2 or 4. Significant ($P<.05$) improvement in desquamation was found at week 4 in the subgroups with dry and combination skin, cosmetic intolerance, and eczema. At week 2, stinging only increased significantly ($P<.05$) in the subgroups with seborrheic dermatitis and cosmetic intolerance.

A subgroup analysis was also performed to better understand the different responses of participants with rosacea, other concomitant diseases, and varying amounts of sebum production. Overall assessment scores significantly decreased from baseline versus weeks 2 and 4 in the subgroup with dry skin (2.3 vs 0.8 for both weeks; $P=.0014$) and the subgroup with cosmetic intolerance (2.5 at baseline vs 1.2 at week 2; $P<.005$ and 1.00 at week 4; $P=.0008$) and only decreased at week 4 in the subgroup with combination skin (1.7 vs 0.7; $P=.01$). No participant experienced an adverse event during the study period.

Summary

This study enrolled 40 participants with diverse skin needs to better understand the ability of AzA 15% gel with various skin types beyond the homogeneous group that was enrolled in prior phase 3 studies.

Two features of type II (papulopustular) rosacea, lesion count and erythema, were addressed in this study and the findings supported the known efficacy of AzA 15% gel. Throughout this diverse group, twice daily application of AzA 15% gel was associated with reduction in these 2 variables at every time point versus baseline in both the entire population and in all subgroups (4 sebum types, 2 concomitant disorders, and cosmetic intolerance). The difference in lesion count and erythema was significant for every group and subgroup at week 4 ($P<.05$). Significance ($P<.05$) was present in all but 2 subgroups, oily skin and cosmetic intolerance, at week 2. Findings for other study variables (eg, stinging, itching, desquamation) support the tolerability of topical AzA 15% gel both in the entire population and in all subgroups.

It should also be noted that, although observer-assessed stinging worsened at week 2 in many of the groups, no increased stinging was observed at the study end. Furthermore, participant-assessed stinging decreased throughout the study period.

Interestingly, the results support the barrier-preserving effects of the AzA 15% gel formulation. A majority of significant improvements from baseline in erythema, desquamation, redness, and dryness (signs or symptoms associated with barrier disruption) were found in participants with baseline conditions associated with barrier disruption. This included dry skin, combination skin, eczema, and seborrheic dermatitis.

This study, approximating actual clinical practice, examined the effects of AzA 15% gel in a diverse population of participants who have mild to moderate rosacea. This population included participants with differing skin pigmentation, varying sebum production, concomitant facial skin disease, and cosmetic intolerance syndrome. The AzA 15% gel formulation showed statistically significant reductions in lesion count and rosacea symptoms as well as high tolerability, with no signs or symptoms worsening and several of them improving across all subgroups. The findings suggest that this formulation is highly tolerable in a wide variety of patients with rosacea. Further studies addressing clinical therapy in diverse populations are needed to refine and extend understanding of the effectiveness of topical medications in actual clinical use.

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