Noxious Sensory Perceptions in Patients With Mild to Moderate Rosacea Treated With Azelaic Acid 15% Gel

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Patients with rosacea form a unique subset of the sensitive skin population because of the barrier defects inherent in this condition and the increased propensity for burning/stinging from topical products. This propensity for burning/stinging when medications, skin care products, or cosmetics are applied to the facial skin has been frequently documented but never quantified. The objective of this 2-week study was to determine the prevalence of heightened neurosensory perceptions of burning/stinging in a random population of 40 women with mild to moderate rosacea defined as 15 or fewer inflammatory papules or pustules. Also evaluated was the effect of azelaic acid 15% gel on barrier function and facial stinging utilizing transepidermal water loss (TEWL), corneometry, and lactic acid facial sting tests as noninvasive measurement criteria. At baseline, the incidence of lactic acid stinging among these rosacea subjects was 62.5%, which is substantially higher than observed in the general population. Two weeks after application of azelaic acid 15% gel, no evidence of barrier damage was noted on TEWL or corneometry tests. Moreover, there was no statistical relationship between lactic acid stinging and a stinging response that is occasionally reported with exposure to azelaic acid 15% gel.

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Rosacea is a chronic skin condition characterized by flushing, erythema, telangiectasia, and inflammatory papules and pustules.[1,2] Rosacea presents a therapeutic challenge for the dermatologist because the clinical manifestations may be accompanied by skin sensitivities such as itching, burning/stinging, and dryness. These noxious sensory perceptions are reported with prescription medications, over-the-counter cosmetics, and skin care products. Even though this phenomenon is well recognized clinically, quantification of the problem has never been performed. This heightened neurosensory phenomenon may be related to issues of skin barrier defects or possibly to an altered perception of stimuli that induce skin irritation. The condition of the skin barrier can be assessed by measuring the water inside of and exiting the skin. Evaluating skin stinging is more difficult because this is a subjective evaluation on the part of the patient.

Within the cosmetics and skin care industries, the lactic acid facial sting test has been validated as a technique for evaluating facial stinging. In this test, facial sweating is induced via a steam sauna, then a lactic acid 5% aqueous solution and normal saline are placed into opposing nasolabial folds in a randomized fashion. Patients are asked to determine if stinging is present at 30 seconds and then 5 minutes. Those who experience stinging with the lactic acid contact form a unique group who are likely to perceive sensations of stinging with cosmetic products that produce no noxious sensory stimuli in the general population. It is difficult to accurately quantify what percentage of the normal population is predisposed to stinging with lactic acid, though the range is from 5% to 20% depending on race and region of the country. When patients with rosacea

are exposed to the facial sauna, they experience both sweating and flushing of the face. Many of the patients who are found by the cosmetics industry to be lactic acid "stingers" are identified with rosacea. For this reason, rosacea patients are frequently selected to evaluate cosmetic products that might cause stinging in the sensitive skin population.

The lactic acid facial sting test has been adapted from the cosmetics industry to assess the effect of topical medications for rosacea, including azelaic acid, on the skin. Some reports of stinging have been associated with the use of azelaic acid for the treatment of rosacea. This study was designed to gain some insight into the prevalence of facial stinging among patients with mild to moderate facial rosacea, as well as to assess the effects of azelaic acid 15% gel on skin sensitivity, barrier function, and facial stinging in these patients.

Table 1.

Measurement of TEWL and Skin Hydration Before and After Application of Azelaic Acid 15% Gel*[4]

	TEWL, mean±SD	Corneometry, mean±SD
Baseline	11.13±4.50	381.6±84.8
After 2 weeks of treatment	12.00±3.82	364.7±103.0
P value	.148	.087

*TEWL indicates transepidermal water loss.

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Methods

This 2-week study enrolled 40 women aged 18 to 80 years with mild to moderate facial rosacea defined as the presence of 15 or fewer inflammatory papules or pustules. All subjects were required to sign an Institutional Review Board–approved consent form. One hour prior to baseline evaluation, the women washed their face with an open-weave textured face cloth for sensitive skin. At this time, they completed an entry questionnaire detailing their skin care habits and practices and any prior experience with facial skin itching, burning/stinging, and dryness. At baseline, a dermatologist investigator assessed the degree of facial erythema and telangiectasia, the inflammatory lesion count, and the overall rosacea severity on a 5-point scale (with 5 being the most severe).

Several noninvasive assessment techniques were used to determine the condition of the skin before and after exposure to azelaic acid 15% gel. To determine the state of the skin barrier, transepidermal water loss (TEWL) measurements were taken in duplicate from the left and right sides of the face. Corneometry measurements were taken to assess skin hydration. To determine the presence or absence of heightened neurosensory stimuli, the women underwent a lactic acid facial sting test.[3] They were exposed to a moist heat facial sauna until a state of profuse facial sweating and accompanying flushing and erythema was achieved. Using a cotton-tipped applicator, lactic acid 10% was applied to one randomized blinded nasolabial fold while normal saline was applied to the other fold. At 30 seconds and 5 minutes after product application, the women were asked if either nasolabial fold experienced stinging. The normal saline application was used as a control because it generally does not induce facial stinging; lactic acid 10% has been found to induce facial stinging reproducibly in a subpopulation of patients with sensitive skin, often called "stingers." In this study, it was hypothesized that azelaic acid stinging might be increased in the women with enhanced TEWL, decreased skin hydration, and heightened neurosensory perceptions.

To visually document the condition of each subject's rosacea at baseline and week 2, photographs were taken of the front face and of the right and left face at a 45° angle using a stereotactic device and a digital camera.

Following completion of the enrollment procedures, the women were provided with azelaic acid 15% gel to be applied to the face twice daily for 2 weeks. A diary also was supplied to document compliance and to record any facial stinging that may have been experienced with product use.

After 2 weeks, the subjects returned to the research facility to complete an exit questionnaire and to be photographed the same as at baseline. A dermatologist investigator evaluated any changes in facial erythema, telangiectasia, inflammatory lesion count, and overall rosacea severity. The noninvasive TEWL, corneometry, and lactic acid tests were repeated to determine the effect of treatment with azelaic acid 15% gel. The women performed an aesthetic assessment of azelaic acid 15% gel based on a 5-point scale, with 5 representing the highest rating. They also were asked to reassess their facial skin itching, burning/stinging, and

dryness after 2 weeks of treatment with azelaic acid 15% gel.

Results

All 40 women successfully completed the study with no intercurrent or adverse events reported. On the lactic acid 10% facial sting test, 62.5% (25/40) of the women received a positive score, confirming the perception that most rosacea patients possess sensitive skin. Using the Fisher exact test, no statistically significant relationship was demonstrated between a positive result on the lactic acid sting test and subsequent stinging with azelaic acid. Only 6 of 8 women who experienced stinging during treatment with azelaic acid 15% gel were identified as lactic acid stingers.

Following application of azelaic acid 15% gel, there was no statistically significant change in either TEWL or skin hydration (corneometry) measurements from baseline to week 2 on the left or right face (paired Student *t* test)(Table 1).[4] These results indicate that azelaic acid 15% gel did not induce barrier degradation, an effect sometimes seen with topical medications that contain penetration enhancers designed to improve efficacy.

The subjects' aesthetic assessment scores of azelaic acid 15% gel were generally favorable, with a mean score of 4.4 for texture, 4.2 for smell, 3.7 for feel, and an overall score of 3.7. After only 2 weeks of treatment, the women reported a mean score for rosacea improvement of 3.4. Analysis of the women's assessment of facial skin itching, burning/stinging, and dryness (Mann-Whitney 1-tailed *t* test) indicated no statistically significant change in patient-rated itching and burning/stinging from baseline to week 2 (Table 2).[4] The data confirm the results of the TEWL and corneometry measurements, which indicated the absence of barrier damage from azelaic acid 15% gel. A statistically significant reduction in facial dryness (P=.0036) was observed with the use of azelaic acid 15% gel, indicating a patient-perceived moisturization benefit.

The dermatologist investigator assessment of rosacea determined that 2 weeks of therapy with azelaic acid 15% gel resulted in a statistically significant decrease in facial erythema (P=.0016) and a statistically significant improvement in the global rosacea severity assessment (P=.001)(Mann-Whitney 1-tailed *t* test). No statistically significant change was seen in telangiectasia or inflammatory lesion count (Table 3). These results were expected because 2 weeks is much shorter than the recommended course of treatment for a topical therapy, and all topical therapies are known to be ineffective against telangiectasia.[4]

Comment

To gain a better understanding of the skin sensitivity associated with rosacea, this study examined the prevalence of lactic acid stinging among a subset of rosacea patients and then evaluated the barrier, neurosensory, and therapeutic effects of a novel azelaic acid 15% gel on rosacea. The most interesting data were the results of the lactic acid facial sting test. The percentage of rosacea subjects who were found to be lactic acid stingers in this randomly

Table 2.

Patient Assessment After 2-Week Treatment With Azelaic Acid 15% Gel[4]

	Itching	Burning/Stinging	Dryness
Change from baseline after 2 wk, % (n)			
-2, -3 (marked improvement)	10.0% (4)	10.0% (4)	27.5% (11)
-1 (mild improvement)	15.0% (6)	15.0% (6)	35.0% (14)
0 (no change)	37.5% (15)	37.5% (15)	20.0% (8)
+1 (mild worsening)	20.0% (8)	25.0% (10)	7.5% (3)
+2, +3 (marked worsening)	17.5% (7)	12.5% (5)	10.0% (4)
Mean baseline score	0.8	0.9	1.5
Mean follow-up score	1.1	1.1	0.8
P value	.095	.247	.0036

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Table 3.

Physician Assessment After 2-Week Treatment With Azelaic Acid 15% Gel[4]

	Erythema	Telangiectasia	Inflammatory Papules	Global Rosacea Severity
Change from baseline after 2 wk, % (n)				
-2, -3 (marked improvement)	5.0% (2)	2.5% (1)	0%	2.5% (1)
-1 (mild improvement)	62.5% (25)	12.5% (5)	22.5% (9)	62.5% (25)
0 (no change)	30.0% (12)	82.5% (33)	75.0% (30)	30.0% (12)
+1 (mild worsening)	2.5% (1)	2.5% (1)	2.5% (1)	5.0% (2)
+2, +3 (marked worsening)	0%	0%	0%	0%
Mean baseline score	2.8	2.4	1.2	2.5
Mean follow-up score	2.1	2.2	1.0	1.9
P value	.0016	.2264	.1399	.001

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selected group of 40 women with mild to moderate rosacea was 62.5% (25/40). This number is considerably higher than in the general population, which explains the sensitive skin issues that present serious challenges in the selection of appropriate medication and skin care products for rosacea patients. However, this preexisting sensitive skin was not influenced by any barrier defects created by the azelaic acid 15% gel, as demonstrated by the lack of any statistically significant change in TEWL (Table 1).[4] This conclusion is further confirmed by the statistically significant decrease in skin dryness reported by women using the azelaic acid formulation (*P*=.0036).

The study also demonstrated some evidence of the clinical effectiveness of azelaic acid 15% gel. On the investigator's assessment, a highly statistically significant therapeutic improvement in facial erythema (*P*=.0016) and global rosacea severity (*P*=.001) were noted after only 2 weeks of therapy. However, the study could not employ a placebo arm because of the primary goal of assessing skin stinging.

The study demonstrated that lactic acid stinging was not a predictor of azelaic acid stinging, suggesting that the azelaic acid 15% gel formulation is appropriate for sensitive skin patients. However, it is worthwhile to postulate why some patients experience transient stinging when azelaic acid is applied to the face. The 3 major causes of noxious sensory stimuli in sensitive skin are barrier defects, increased neurosensory awareness, and heightened immune responsiveness. Based on the results of the corneometry and TEWL evaluations, the study demonstrated that azelaic acid facial stinging is not due to a barrier defect. No heightened neurosensory awareness to azelaic acid was demonstrated through the lactic acid facial sting test, and there was no heightened immune responsiveness seen in the facial rosacea assessments. The study demonstrated that the transient azelaic acid stinging is not medically significant because increases in facial erythema or barrier deficits were not identified.

In summary, the cause of azelaic acid facial stinging remains unknown. It could be postulated that it is a patient-specific phenomenon that is medically insignificant and not characterized by any currently available cutaneous noninvasive techniques.

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