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Improvement in Skin Moisturization and Lack of Barrier Damage Following Treatment With Clascoterone Cream 1%

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ABSTRACT

Background: Topical medications commonly prescribed for the treatment of acne vulgaris may be limited by application-site dryness, which can result in skin barrier damage. This study aimed to evaluate the effects of clascoterone cream 1% on skin barrier properties in acne-prone individuals.

Methods: Participants ≥18 years of age with acne-prone skin were enrolled in a single-center, split-face study and randomized to twice-daily treatment with clascoterone cream 1% (approximately 0.5 g) to the right or left side of the face for 2 weeks. The primary and secondary endpoints were the changes in corneometry reading and transepidermal water loss (TEWL), respectively, between treated and untreated sides at week 2. Tolerability was evaluated from the severity of dryness, erythema, scaling, irritation, tightness, stinging, itching, and burning for each side using a 5-point scale from 0 (none) to 4 (severe).

Results: This study enrolled 50 participants (female, n = 38) with a mean ± standard deviation (SD) age of 31.1 ± 8.9 years. The mean ± SD corneometry reading was significantly higher for the treated vs untreated side at week 2 (131.3 ± 42.9 vs 113.9 ± 36.6; $P<0.001$). There was no difference in TEWL between treated and untreated sides at any time point assessed. All tolerability parameters evaluated were rated as absent or minimal through week 2 for both sides.

Conclusion: Twice-daily treatment with clascoterone cream 1% for 2 weeks was associated with increased moisturization and maintenance of skin barrier function as assessed by corneometry and TEWL and was otherwise well tolerated.

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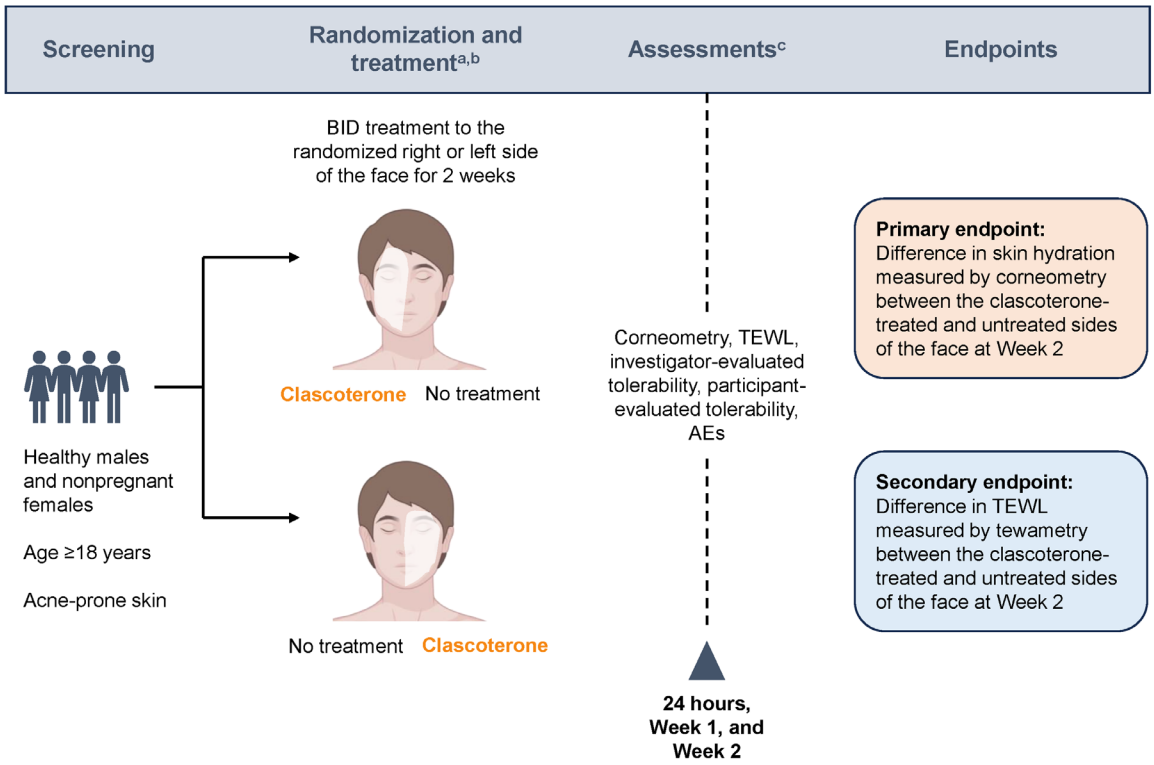
INTRODUCTION

Acne vulgaris is one of the most prevalent dermatologic conditions in the US and worldwide.[1,2] Although acne typically presents during adolescence, it is a chronic condition that can persist into adulthood.[1] The physical and psychological impacts of acne are often consequential for patients and can include pain, erythema, scarring, anxiety, and depression,[3,4] highlighting the importance of early and effective treatment for patients with acne. Despite the range of acne treatments available, limitations in tolerability may contribute to the high rate of nonadherence to acne medications,[5-7] which can impact efficacy and treatment success.[8]

As outlined in the American Academy of Dermatology guidelines, topical treatments are recommended as first-line agents in the treatment of acne vulgaris; however, therapies such as retinoids (eg, adapalene) and benzoyl peroxide may be limited by adverse effects, including dryness and irritation that can result in skin barrier damage and decreased patient adherence.[4,9-14] Topical agents with improved, less irritating vehicle formulations[15] or concomitant use of moisturizers[11,16] can improve tolerability and mitigate skin barrier damage during acne treatment, but adverse effects may still be a concern—particularly with combinations of 2 or more topical agents.[17] Several new and effective topical treatment options for acne introduced within the past decade may provide better tolerability and therefore improve patient adherence.[18,19]

Clascoterone cream 1%, a topical androgen receptor inhibitor, is a first-in-class therapy approved in the US in 2020 (with subsequent approvals in Canada and Australia) for the treatment of acne vulgaris in patients ≥12 years of age.[20-23] The effect of clascoterone is attributed to competition with dihydrotestosterone for binding to androgen receptors within the skin, thereby preventing the transcription of androgen-responsive genes and decreasing sebum production.[24] The efficacy and safety of clascoterone cream 1% were established in two 12-week, randomized, double-blind, phase 3 clinical

FIGURE 1. Study design.



[a]Participants were not permitted to alternate application of clascoterone cream 1% between different sides of the face during the study.
[b]Participants were permitted to continue using a self-selected cleanser and sunscreen, which had been used for 30 days prior to study enrollment, with equal application to both sides of the face during the study.
[c]Corneometry, TEWL, and tolerability assessments were also performed at baseline.
AE, adverse event; BID, twice daily; TEWL, transepidermal water loss.

trials and a 9-month extension study, in which adverse effects such as application-site pain, dryness, and irritation were not commonly reported.[23,25] No head-to-head studies have been conducted to directly compare the efficacy and safety of clascoterone to those of other topical acne medications; however, the efficacy of clascoterone cream 1% was similar to that of topical retinoids including trifarotene and tazarotene in a recent meta-analysis.[26]

Although low reported rates of dryness and cutaneous irritation in clinical trials of clascoterone cream 1% treatment suggest that it may have low potential for skin barrier disruption, the effect of clascoterone treatment on the integrity of the skin barrier has not been clinically evaluated. This study aimed to evaluate changes in skin barrier properties induced by treatment with clascoterone cream 1% in acne-prone individuals.

MATERIALS AND METHODS

Study Design and Participants

This single-center, split-face study evaluated changes in skin barrier properties following treatment with clascoterone cream 1% in participants with acne-prone skin. Male and nonpregnant female participants ≥18 years of age with all Fitzpatrick skin types who self-identified as having sensitive, acne-prone skin and who were in generally good physical and mental health were eligible for enrollment. Individuals with any dermatologic disorder that in the investigator's opinion could interfere with the evaluation of skin characteristics, a previous hypersensitivity reaction to any of the ingredients in clascoterone cream 1%, clinically meaningful unstable medical disorders, a history of psychological illness or immunosuppressive/immune deficiency disorders, or who had planned surgeries and/or invasive medical procedures during the study were excluded, as were those who currently use or frequently used high doses of anti-inflammatory drugs or immunosuppressive medications.

The study was conducted in accordance with the principles described in the Declaration of Helsinki, Good Clinical Practice guidelines, and all local, legal, and regulatory requirements. Institutional review board (Allendale Institutional Review Board, Old Lyme, CT) approval was obtained for the study protocol and the informed consent form. All patients were required to provide written informed consent to participate in the study.

Treatments

Participants were randomized to treatment with clascoterone cream 1% twice daily to the right or left side of the face for 2 weeks, which represents 1 complete stratum corneum turnover cycle[27]

(Figure 1). Participants were instructed to apply clascoterone cream 1% (approximately 0.5 g, half of the 1-g twice-daily recommended dose for the whole face in the clascoterone cream 1% Prescribing Information[20]) to the entire right or left side of the face (including the forehead, cheek, and jawline) following cleansing every morning and evening and were not permitted to alternate application of clascoterone cream 1% between sides during the study. The assessing dermatologist was blinded as to which side of the face was receiving clascoterone cream 1% treatment. Participants were permitted to continue using a self-selected cleanser and sunscreen, which had been used for 30 days prior to study enrollment, with equal application to both sides of the face during the study; the use of any topical medications or facial skincare products other than sunscreen and cleanser was not allowed. Participants were not permitted to introduce any new colored cosmetics (lipstick, eye shadow, facial foundation, blush, or powder) during the study.

Assessments and Endpoints

All planned assessments were performed at baseline and during the treatment period at 24 hours, week 1, and week 2 (Figure 1). The primary endpoint was the difference in skin hydration measured by corneometry between the clascoterone-treated and untreated sides of the face at week 2. The secondary endpoint was the difference in transepidermal water loss (TEWL), a measure of epidermal barrier permeability, measured by tewametry between the clascoterone-treated and untreated sides of the face at week 2. Tolerability was evaluated by recording the severity of dryness, erythema, scaling, irritation, tightness, stinging, itching, and burning for each side of the face using a 5-point scale from 0 (none) to 4 (severe). Erythema, scaling, and irritation were assessed by the dermatologist investigator, whereas tightness, stinging, itching, and burning were assessed by the participant; dryness was assessed by both the investigator and the participant. Safety was also assessed by the monitoring of adverse events (AEs) at 24 hours, week 1, and week 2.

Statistical Analyses

No formal sample size calculations were performed due to the exploratory nature of this study. The sample size selected was based on the estimation of the number of participants required to achieve statistical significance. Ordinal tolerability assessment data were analyzed using Wilcoxon signed-rank test and sign test for paired comparisons at different time points; corneometry and tewametry data were confirmed to be normally distributed and then analyzed using paired *t*-tests performed using Microsoft Excel. No transformations were applied to the data. All statistical tests were 2-sided, and $P<0.05$ was accepted as significant with no adjustment for multiple comparisons. Statistical analyses included all enrolled participants; missing data were not imputed.

RESULTS

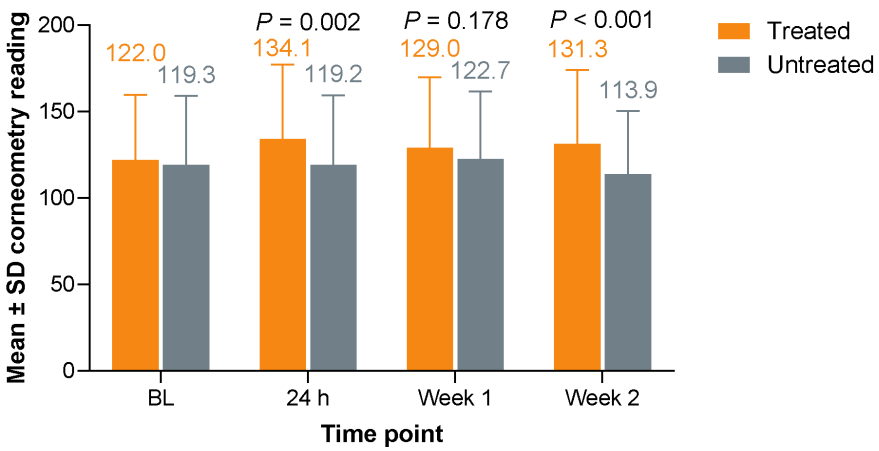
Patient Demographics

The study enrolled 50 participants (male, n = 12; female, n = 38), of whom 49 completed the study. The mean ± standard deviation (SD) age was 31.1 ± 8.9 (range, 19–45) years. Most of the participants were White (60%), 38% were Black or African American, and 2% were Hispanic.

Efficacy Outcomes

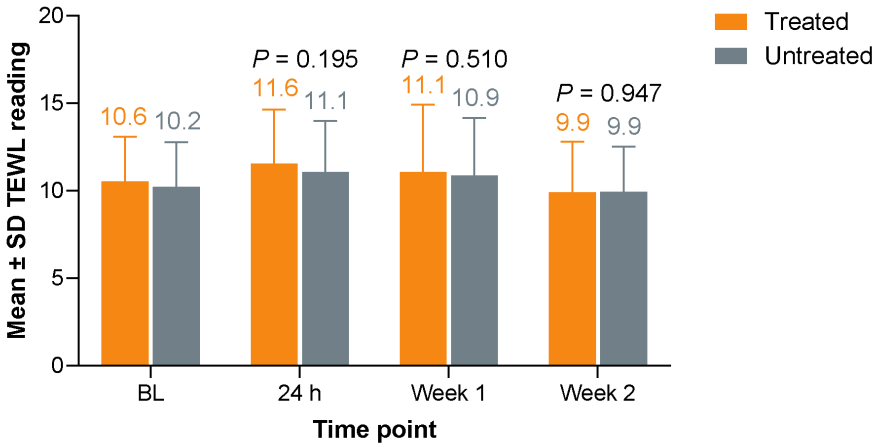
From baseline to week 2, the mean ± SD corneometry reading for the clascoterone-treated side of the face increased from 122.0 ± 37.7 to 131.3 ± 42.9, whereas it decreased for the untreated side from 119.3 ± 39.7 to 113.9 ± 36.6 (Figure 2). The difference in corneometry reading for the clascoterone-treated vs untreated side was 15.0 ($P=0.002$) at 24 hours, 6.3 ($P=0.178$) at week 1, and 17.3 ($P<0.001$) at week 2 of treatment. Consistent with these findings, the treatment difference in the change from baseline in corneometry reading favored the clascoterone-treated vs untreated side at 24 hours (12.3; $P=0.041$), week 1 (3.6; $P=0.531$), and week 2 (14.8; $P=0.004$) of treatment. The mean ± SD TEWL readings for the clascoterone-treated side were 10.6 ± 2.5 at

FIGURE 2. Facial corneometry readings by visit from baseline to week 2.



BL, baseline; h, hours; SD, standard deviation.

FIGURE 3. Facial TEWL readings by visit from baseline to week 2.



BL, baseline; h, hours; SD, standard deviation; TEWL, transepidermal water loss.

baseline and 9.9 ± 2.9 at week 2, which were similar to those for the untreated side (10.2 ± 2.6 at baseline and 9.9 ± 2.6 at week 2; Figure 3). There was no statistically significant difference in mean TEWL between the clascoterone-treated and untreated sides of the face at 24 hours (0.5; *P*=0.195), week 1 (0.2; *P*=0.510), or week 2 (0.02; *P*=0.947) of treatment.

Tolerability Assessments

There was no statistically significant difference in any of the investigator-evaluated tolerability parameters (dryness, erythema, scaling, and irritation) between the clascoterone-treated and untreated sides of the face, all of which were rated as 0 (not present) at 24 hours, week 1, and week 2. Similarly, the mean severity rating for each of the participant-assessed

TABLE 1.

Summary of Participant-Evaluated Tolerability Assessments

	24 hours N = 50	Week 1 N = 50	Week 2 N = 49
Dryness			
Treated	0.08 ± 0.27	0.06 ± 0.24	0
Untreated	0.14 ± 0.40	0.12 ± 0.33	0.08 ± 0.28
P-value	0.502	0.311	0.058
Tightness			
Treated	0.04 ± 0.20	0.02 ± 0.14	0.02 ± 0.14
Untreated	0.02 ± 0.14	0	0
P-value	0.596	0.436	0.436
Stinging			
Treated	0	0.02 ± 0.14	0
Untreated	0	0	0
P-value	1.000	0.436	1.000
Itching			
Treated	0.04 ± 0.28	0.04 ± 0.28	0
Untreated	0.02 ± 0.14	0	0
P-value	0.990	0.436	1.000
Burning			
Treated	0	0.02 ± 0.14	0
Untreated	0	0	0
P-value	1.000	0.436	1.000

Data are shown as mean ± SD. Responses to each parameter were scored on a 5-point scale from 0 (not present) to 4 (severe) for each side of the face. Data were analyzed using Wilcoxon signed-ranked test and sign test for paired comparisons at different time points. SD, standard deviation.

tolerability parameters (dryness, tightness, stinging, itching, and burning) ranged from 0 to 0.14 through week 2, with no statistically significant differences between the clascoterone-treated and untreated sides of the face (all $P>0.05$; Table 1).

Safety Outcomes

One AE of a fever, suspected to be from COVID-19, was reported in 1 participant; the participant was discontinued at the final study visit due to concerns about transmission to other study participants.

DISCUSSION

This study provides the first clinical evaluation of the effects of clascoterone cream 1% on skin barrier function in acne-prone individuals. Corneometry readings increased with no change in TEWL readings for the side of the face treated with clascoterone cream 1% twice daily for 2 weeks compared with the untreated side of the face, indicating increased moisturization and maintenance of skin barrier function, respectively, during treatment. The severity of each of the tolerability parameters was rated as none to minimal by the investigators and/or participants throughout the 2-week study period. These findings demonstrate that treatment with clascoterone cream 1% for 2 weeks did not disrupt the skin barrier in individuals with acne-prone skin and was otherwise well tolerated.

The term "epidermal barrier" generally refers to the ability of the stratum corneum to retain moisture, regulate and adapt to changes in TEWL, and maintain the selective permeability of the skin to exogenous and endogenous substances.[28] TEWL, a measure of epidermal barrier disruption, is significantly increased in patients with acne compared with healthy controls.[29] Topical acne medications such as benzoyl peroxide and topical retinoids can further exacerbate barrier disruption, leading to cutaneous side effects such as peeling, scaling, and erythema.[9-14] These side effects may contribute to poor adherence to acne medications.[6] Several randomized controlled trials have demonstrated that the concomitant use of moisturizers or other adjunctive products can limit the extent of skin barrier damage and reduce the severity of cutaneous side effects during acne treatment.[11,16,30] However, the impact of adjuvant barrier repair therapies on clinical outcomes in acne treatment is contingent upon good adherence to both the medication and adjuvants,[8] and the use of more complex treatment regimens (eg, involving a higher number of medications) may negatively impact patient adherence.[31,32]

Improvements in vehicle design (eg, creams vs gels or the addition of emollients) have helped to mitigate the negative barrier impacts and cutaneous side effects of topical acne medications.[15,33] Differences in tolerability and patient satisfaction following treatment with 2 distinct formulations of tretinoin—a 0.05% lotion and a 0.05% generic cream—were evaluated in a split-face study in patients ≥18 years of age with acne.[15] Following 2 weeks of once-daily treatment, tretinoin lotion produced significantly less irritation and was associated with higher rates of patient satisfaction compared with tretinoin cream.[15] These findings highlight the importance of well-designed formulations to the development of topical acne medications, as the formulation can have a significant impact on tolerability and patient satisfaction and, in turn, adherence to medication.[15]

A limitation of this study is the comparison of changes in corneometry and TEWL between clascoterone cream 1% and no treatment, rather than a comparator, which would allow for direct comparison of the barrier properties of clascoterone vs other topical formulations. Nonetheless, the results of the current study demonstrate that clascoterone cream 1% provides a well-tolerated treatment option for patients with acne vulgaris, with a low potential for skin barrier damage and without the need for concomitant moisturizers or adjunctive barrier repair therapies. These properties increase the likelihood that patients will demonstrate good adherence to treatment with clascoterone cream 1%. However, future studies are needed to demonstrate adherence and patient satisfaction with clascoterone cream 1% treatment.

CONCLUSION

Twice-daily treatment with clascoterone cream 1% was associated with increased moisturization and maintenance of skin barrier function through 2 weeks of treatment in acne-prone individuals. Clascoterone cream 1% provides a treatment option for patients with acne vulgaris that is well tolerated and has low potential for skin barrier disruption, which may increase patient adherence.

DISCLOSURES

ZDD was an investigator on this study and received a grant from Sun Pharma. KK and NS are employees of Sun Pharmaceutical Industries, Inc.

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