The Appearance of Facial Foundation Cosmetics Applied After Metronidazole Gel 1%

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The purpose of this study was to assess the cosmetic appearance of commonly marketed facial cosmetics when used after the application of metronidazole gel 1%. An observational, open-label, single-site study was conducted with women (N=30) aged 20 to 75 years and diagnosed with moderate papulopustular rosacea (investigator global severity score of 3). After cleansing the face with a gentle skin cleanser, participants applied metronidazole gel 1% once daily before applying their usual facial foundation. Two surveys were conducted: (1) investigator assessment of cosmetic appearance; and (2) participant assessment of cosmetic appearance. The investigator also evaluated erythema, disease severity, and tolerability at baseline and week 2. Adverse events were collected. The 28 per-protocol (PP) participants had a mean age (standard deviation [SD]) of 54.0 (10.3) years and a mean duration (SD) of rosacea of 15.4 (13.2) years. The median response score for both the investigator and participant assessments of cosmetic appearance was 10 (best) for each survey question. Signs and symptoms of rosacea did not increase with use of metronidazole gel 1% and the participants' selected cosmetic regimen. At baseline all 28 participants were classified as having moderate erythema. At week 2, 18 (64%) participants were classified as having moderate erythema and 10 (36%) mild. At baseline all 28 (100%) participants were classified as having moderate rosacea according to the investigator global severity score. At week 2, 10 (36%) participants were classified as mild and 18 (64%) moderate. In addition, few participants reported cutaneous irritation during the study. At week 2, 10 participants had dryness, 2 had itching, 8 had scaling, and 2 had stinging/burning.

According to surveys completed by the investigator and the participants themselves, most participants had a good cosmetic appearance with their facial foundation cosmetics that were applied after metronidazole gel 1%. The use of various cosmetic regimens after application of metronidazole gel 1% did not cause rosacea symptoms to worsen and treatment was well-tolerated.

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Rosacea is a chronic inflammatory disease of the skin; its etiology remains unknown.[1,2] The proposed mechanisms for this disease can be divided into a number of diverse groups including chemicals and ingested agents, climatic exposures, matrix degeneration, microbial organisms, pilosebaceous unit abnormalities, and vasculature.[1] The primary features of rosacea include transient erythema (flushing), nontransient erythema, papules, pustules, and telangiectases.[3-5] Burning, dry appearance, edema,

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ocular and peripheral manifestations, phymatous changes, and stinging also can be observed. A number of risk factors have been associated with rosacea including the use of topical corticosteroids, chronic actinic damage, tendency for flushing, genetic factors, and northern or eastern European heritage.[1,6,7] In addition, several common triggers have been reported in the literature including alcohol, chemical irritation, cosmetics, exposure to extreme temperatures, heavy exercise, humidity, spicy food, stress, sunlight, and wind.[3,4,8]

The National Rosacea Society estimates that more than 16 million individuals in the United States are affected by rosacea. According to the National Rosacea Society, a recent gallup poll found that 78% of Americans are unaware of this disease or its treatment.[9] The prevalence of rosacea appears to be increasing in the United States, which may be the result of aging in the baby boom generation.[10,11] One study (N=2933) found that rosacea prevalence was 16% in white women in the United States.[12] Efforts by the National Rosacea Society have raised awareness of this skin disorder.[9] In Europe, it is estimated that as much as 10% of the population is affected by this disease.[13,14] The onset of rosacea typically occurs after the age of 30 years and the disease is more common in women but tends to be more severe in men.[3,15]

Rosacea is known to adversely affect a patient's quality of life.[4] It can cause anxiety, embarrassment, and decreased self-esteem.[16] Avoidance of social situations also occurs in some cases.[17] Professional relationships can be affected and patients have even reported losing their jobs.[18] In some instances, a correlation between rosacea and depression can exist.[19] All of the factors underscore the importance of medical treatments for this disease that are safe, effective, and acceptable for the patient to include in his/her daily skin care routine. Therefore, treatment regimens should be designed to address individual signs and symptoms as well as disease subtype and severity.[20]

Topical metronidazole has been used for the treatment of rosacea since the early 1980s.[21,22] This compound is one of the most effective agents for improving the lesions of rosacea.[4] It is used both alone and in combination with other products, such as oral antibiotics and anti-inflammatory agents.[23,24]

Little information currently is available regarding the acceptability of metronidazole gel 1% when used with cosmetic foundations. Rosacea patients are known to experience hypersensitivity to some cosmetics and medications.[25] Ideally, rosacea patients should be able to use their topical medications and then apply facial foundation as well as other cosmetic products as desired. Cosmetics help maintain a favorable appearance for the patient. In general, cosmetic foundations help to provide some level of camouflage for the underlying red skin.[7] The purpose of this observational study was to determine the cosmetic appearance of commonly marketed facial cosmetics when used after the application of metronidazole gel 1%.

Methods

Study Population—This open-label, single-site study involved 30 participants.[26] Women aged 20 to 75 years of any race were included if they were diagnosed with moderate rosacea (investigator global severity score of 3 [classified as moderate erythema with several small or large papules/pustules and up to 2 nodules]), willing to stop current rosacea medication for at least 2 weeks, willing to use the study-provided cleanser and not change skin care products or cosmetics during the study, and in good general health according to medical history. Participants were required to have an established routine of cosmetic application of at least 3 months. If they used medications to treat a concurrent medical condition, the type and dosage must have been stable for at least 3 months prior to study entry. All participants read and signed the approved informed consent form after the nature of the study had been fully explained and prior to any study-related procedures. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements.

Individuals who were pregnant or breastfeeding or planned to become pregnant during the course of the study, had known allergies or sensitivities to ingredients contained in the test products, or failed to undergo a washout period of 14 days for the use of topical rosacea therapy were not allowed to participate in the study. Individuals were excluded if they did not routinely wear facial foundation or if they were unwilling to stop their current rosacea medication for 2 weeks. They were free to discontinue participation in the study at any time for any reason.

Treatment—Each participant was instructed to wash the face with the provided Cetaphil® Gentle Skin Cleanser, rinse, and pat dry. They then were told to apply metronidazole gel 1% once daily (morning) and wait 10 minutes for it to dry before applying their usual facial foundation (no particular foundation was used), powder, and eye shadow. This regimen continued for 2 weeks. The first and last doses of metronidazole gel 1% and cosmetic applications were applied under the supervision of study staff at the study site during the baseline visit and the final visit at week 2.

Compliance—The study product was collected and weighed at baseline and week 2 to document

treatment compliance. Participants were questioned regarding their use of study medication.

Cosmetic Appearance—Cosmetic appearance was evaluated in the per-protocol (PP) population, which excluded participants considered not evaluable due to major deviations from the study protocol. Participants self-assessed the cosmetic appearance of their facial foundation when it was applied after metronidazole gel 1% treatment. They also maintained a diary of their impressions. The investigator assessed cosmetic appearance at baseline and week 2. One survey was used to capture the investigator's assessment of the participant's cosmetic appearance; another survey was used to capture each participant's assessment of her own cosmetic appearance. In both surveys, respondents gave answers based on a scale of 1 (worst) to 10 (best). Participants were photographed at each visit (baseline and week 2) to document their cosmetic appearance.

Symptom Severity—The erythema severity score was based on a 5-point scale (0=none; 1=very mild; 2=mild; 3=moderate; 4=severe) and served to evaluate the entire face. The investigator global severity score, based on a 5-point scale (0=clear; 1=almost clear; 2=mild; 3=moderate; 4=severe), was used to evaluate the participant's disease severity. All participants had papules and/or pustules at the baseline visit. The investigator assessed rosacea signs and symptoms using erythema and global severity scores at baseline and week 2.

Tolerability and Safety—Tolerability assessments for dryness, itching, scaling, and stinging/burning were evaluated on a 4-point scale (0=none; 1=mild; 2=moderate; 3=severe). All adverse events were monitored and reported. Tolerability and safety assessments were conducted in the safety population, which included any participant who had received at least 1 dose of study medication.

Statistical Analysis—The end point analyses were based on the PP population. The primary end point was the investigator assessment of cosmetic appearance at week 2. A Wilks-Shapiro test was used to determine the normality of the total score of the assessments of cosmetic appearance. The significance level was set at $\alpha=.05$. Descriptive statistics included mean, median, standard deviation (SD), minimum, and maximum scores.

Results

Participant Demographics—Table 1 shows the baseline demographics for the study participants. Thirty participants were included in the safety population. Two participants were excluded from the PP analysis: 1 participant violated the inclusion/exclusion criteria, and 1 participant had a study visit that was more than 3 days off schedule. All participants in the PP population were white females (N=28; 100%) with either Fitzpatrick skin type I (16/28 [57%]) or II (12/28 [43%]). The mean age (SD) of the participants was 54.0 (10.3) years and the mean duration (SD) of rosacea in these participants was 15.4 (13.2) years (Table 2). All participants had moderate erythema and investigator global severity scores at baseline.

Table 1.

Summary of Baseline Demographic Characteristics

	Safety/ITT Population (N=30)	PP Population (N=28)
Age, y		
Mean (SD)	53.8 (10.0)	54.0 (10.3)
Median (Minimum, Maximum)	55.0 (29.0, 69.0)	55.5 (29.0, 69.0)
Gender, n (%)		
Female	30 (100)	28 (100)
Race, n (%)		
White	30 (100)	28 (100)
Fitzpatrick skin type, n (%)		
I	17 (57)	16 (57)
II	13 (43)	12 (43)

Abbreviations: ITT, intent to treat; PP, per protocol; SD, standard deviation.

Compliance—The PP participants were 100% (N=28) compliant with their metronidazole regimen (no missed doses) and 96% (27/28) compliant with their makeup regimens.

Cosmetic Appearance—The median response score for the investigator assessment of cosmetic appearance at baseline and week 2 was 10 (best) for each survey question (Table 3). Across all questions in this investigator assessment, 68% (19/28) to 100% (28/28) of participants received a score of 10 (best). Similarly, the median response score for the participant

assessment of cosmetic appearance at baseline tand week 2 was 10 (best) for each survey question (Table 4). Sixty-eight percent (19/28) to 93% (26/28) of participants scored 8 or higher on the cosmetic evaluation survey.

Symptom Severity—At baseline all 28 (100%) participants were classified as moderate for the erythema severity and investigator global severity scores (Table 5). At week 2, 10 (36%) participants were classified as mild and 18 (64%) moderate for both severity scores.

Tolerability—Most participants did not experience cutaneous irritation during the study. At week 2, 10 participants had dryness, 2 had itching, 8 had scaling, and 2 had stinging/burning (Table 6).

Safety—Three participants reported adverse events; 2 were not considered to be related to the study drug (upper abdominal pain and dizziness) and the acne reported by 1 participant was classified as possibly related to the study medication.

Table 2.

Summary of Baseline Characteristics

	PP Population (N=28)
Duration of rosacea, y	
Mean (SD)	15.4 (13.2)
Median (Minimum, Maximum)	10.0 (1.0, 50.0)
Erythema severity score, n (%)	
Moderate	28 (100)
Investigator global severity score, n (%)	
Moderate	28 (100)

Abbreviations: PP, per protocol; SD, standard deviation.

Comment

Topical metronidazole is widely used today for treating rosacea. It was the first topical agent approved by the US Food and Drug Administration to treat this disease.[27] Metronidazole gel 1% is currently the leading topical medication prescribed for rosacea.[28] Following cleansing of the skin, the patient applies a thin film of metronidazole gel 1% once daily to the entire affected area(s). Cosmetics are then applied to the skin.

Studies suggest that topical rosacea medications vary regarding tolerability and side-effect profiles.[29,30] Colón et al[31] reported that azelaic acid showed a greater potential for irritation than metronidazole gel 0.75%. More patients reported stinging and burning with azelaic acid, while more patients had moderate scaling with metronidazole.[31] A considerably lower mean cumulative irritancy index was found by Ziel et al[30] for metronidazole gel 0.75% versus azelaic acid gel 15%. Another study with rosacea patients reported that 7% on metronidazole (n=127) and 26% on azelaic acid (n=124) experienced facial skin signs and symptoms.[29]

Prior studies have shown that metronidazole gel 1% is well-tolerated.[16,21,23,32-36] Colón et al[31] reported that the 1% gel formulation has a lower potential for irritation than its predecessor, the 0.75% gel. In fact, the 1% preparation showed a mean cumulative irritancy index score (0.0222) that was similar to white petrolatum (0.0018).[31] The 1% formulation of metronidazole contains hydrosolubilizing agents (HSA-3®) that make the gel highly spreadable and easy to use.[31,37] Allergic contact dermatitis with this medication is rare (1.3% in the package insert).[38-40] In a clinical trial of 557 participants, a low incidence of adverse events was reported with metronidazole gel 1%, typically consisting of dryness (25.4%), scaling (24.6%), pruritus (15.8%), stinging/burning (10.3%), headache (2.2%), nasopharyngitis (3.1%), and upper respiratory tract infections (2.5%). The majority of the cutaneous signs and symptoms reported have been mild in severity.[40]

Little information currently is available regarding patients' perception of metronidazole when used with their facial cosmetics. The primary end point of the current study was the investigator assessment of cosmetic appearance at week 2. The median response score for this assessment was 10 (best) for each survey question, indicating that most participants had a favorable cosmetic appearance in the opinion of the investigator. Regarding ease of application of metronidazole gel 1% and cosmetics, the investigator indicated that participants did not appear to have any difficulty in applying the medication or their cosmetics afterward.

The majority of the participants felt that their cosmetic appearance was good at week 2. The median response score was 10 (best) for each survey question. However, the participant and investigator responses differed somewhat. The mean score tended to be slightly lower for the participants than the investigator scores. At least 1 participant rated their experience

Table 3.

Investigator Assessment of Cosmetic Appearance (N=28)[a]

Survey Question	Baseline		Week 2		Survey Score at Week 2, n (%)		
	Mean (SD)	Median (Minimum, Maximum)	Mean (SD)	Median (Minimum, Maximum)	10	9	8
Did the subject appear to have difficulty in applying MetroGel® 1%?[b]	10 (0.0)	10.0 (10.0, 10.0)	10 (0.0)	10.0 (10.0, 10.0)	28 (100)	0 (0)	0 (0)
Did the subject appear to have difficulty in applying her foundation after using MetroGel 1%?[b]	9.9 (0.4)	10.0 (8.0, 10.0)	10 (0.0)	10.0 (10.0, 10.0)	28 (100)	0 (0)	0 (0)
Did the facial foundation appear to be smooth after application?[c]	9.8 (0.5)	10.0 (8.0, 10.0)	9.3 (1.2)	10.0 (5.0, 10.0)	19 (68)	2 (7)	5 (18)
Rate the subjects overall appearance after application of MetroGel 1% and facial foundation[d]	9.8 (0.5)	10.0 (8.0, 10.0)	9.4 (1.0)	10.0 (7.0, 10.0)	19 (68)	2 (7)	6 (21)

Abbreviation: SD, standard deviation.

[a]Cosmetic appearance based on a scale of 1 (worst) to 10 (best). Number of investigator responses for scores of 1 to 7 are not shown.

[b]Rated from 1 (very difficult) to 10 (not difficult at all).

[c]Rated from 1 (foundation was flaked, rough, or not smooth at all) to 10 (very smooth [even, no flakes or roughness]).

[d]Rated from 1 (poor appearance [blotchy, uneven application, flaky]) to 10 (good appearance [smooth, even application without flaking or blotchiness]).

as a 1 (worst) for experiencing problems with facial foundation application, ability to apply the cosmetics smoothly over metronidazole gel 1%, and assessment of overall appearance of the skin. In general, patient perceptions tend to be more critical compared to physicians. For the most part, the study participants did not have difficulty applying metronidazole gel 1% or their foundation after using metronidazole gel 1%.

The purpose of the current study was not to evaluate efficacy but rather cosmetic compatibility with metronidazole gel 1% treatment. However, the signs and symptoms of rosacea also were evaluated to document

Table 4.

Participant Assessment of Cosmetic Appearance (N=28)[a]

	Baseline		Week 2		Survey Score at Week 2, n (%)		
Survey Question	Mean (SD)	Median (Minimum, Maximum)	Mean (SD)	Median (Minimum, Maximum)	10	9	8
Did you experience any problems when applying MetroGel® 1%?[b]	9.9 (0.4)	10.0 (8.0, 10.0)	9.6 (1.4)	10.0 (4.0, 10.0)	25 (89)	0 (0)	1 (4)
Did you experience any problems with your facial foundation application after using MetroGel 1%?[b]	9.4 (1.0)	10.0 (7.0, 10.0)	8.7 (2.6)	10.0 (1.0, 10.0)	21 (75)	0 (0)	2 (7)
Were you able to apply your cosmetics smoothly over the MetroGel 1% after the 10-minute drying time?[c]	9.6 (0.9)	10.0 (7.0, 10.0)	8.3 (3.2)	10.0 (1.0, 10.0)	19 (68)	2 (7)	1 (4)
How is your overall appearance of your skin after application of MetroGel 1% and your facial foundation?[d]	9.7 (0.7)	10.0 (8.0, 10.0)	8.3 (2.5)	10.0 (1.0, 10.0)	16 (57)	1 (4)	2 (7)

Abbreviation: SD, standard deviation.

[a]Cosmetic appearance based on a scale of 1 (worst) to 10 (best). Number of participant responses for scores of 1 to 7 are not shown.

[b]Rated from 1 (very problematic) to 10 (no problems).

[c]Rated from 1 (application was not smooth) to 10 (very smooth application).

[d]Rated from 1 (not happy with appearance) to 10 (very happy with appearance).

that they did not worsen with the use of cosmetics after the application of metronidazole gel 1%. At the start of the trial all 28 participants were classified as having moderate erythema. At week 2 only 18 (64%) participants were classified as having moderate erythema and the other 10 (36%) participants had

Table 5.

Erythema Severity and Investigator Global Severity Scores (Per-Protocol Population; N=28)

	Participants, n (%)	
Assessments	**Baseline**	**Week 2**
Erythema severity score		
Mild	0 (0)	10 (36)
Moderate	28 (100)	18 (64)
Investigator global severity score		
Mild	0 (0)	10 (36)
Moderate	28 (100)	18 (64)

Table 6.

Analysis of Tolerability Assessments (Safety/Intent-to-Treat Population; N=30)

	Participants, n (%)	
Responses	**Baseline**	**Week 2**
Dryness		
None	25 (83)	20 (67)
Mild	3 (10)	7 (23)
Moderate	2 (7)	3 (10)
Severe	0 (0)	0 (0)
Itching		
None	30 (100)	28 (93)
Mild	0 (0)	1 (3)
Moderate	0 (0)	1 (3)
Severe	0 (0)	0 (0)
Scaling		
None	30 (100)	22 (73)
Mild	0 (0)	5 (17)
Moderate	0 (0)	3 (10)
Severe	0 (0)	0 (0)
Stinging/Burning		
None	30 (100)	28 (93)
Mild	0 (0)	1 (3)
Moderate	0 (0)	1 (3)
Severe	0 (0)	0 (0)

mild erythema. At baseline all 28 (100%) participants were classified as having moderate rosacea. At week 2, however, 10 (36%) participants were classified as mild and 18 (64%) participants were classified as moderate.

The combination of metronidazole gel 1% and cosmetic foundation was well-tolerated. Three nonserious adverse events were reported, including 1 that was possibly related to the study medication (acne).

This study has some limitations that should be taken into consideration when drawing conclusions. It was a small, open-label, single-site study involving 30 participants. There was no vehicle control group. However, this study provides real-world data on the use of a rosacea treatment and facial cosmetics. Additional multicenter, blinded trials could provide further evidence regarding patient acceptance of this type of therapeutic regimen.

Conclusion

This 2-week study provides useful information regarding patient acceptability of a topical rosacea treatment with routine skin care. According to surveys completed by the participants and the investigator, most participants had a good appearance with the facial foundation cosmetics that were applied after metronidazole gel 1%. Erythema and investigator global severity scores remained stable over the course

of the study. The use of cosmetics after the application of metronidazole gel 1% was well-tolerated. The high degree of patient acceptance of this therapeutic regimen could be expected to have a favorable effect on patient compliance and treatment outcomes.

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