An Open-Label, Intra-Individual Study to Evaluate a Regimen of Three Cosmetic Products Combined with Medical Treatment of Rosacea: Cutaneous Tolerability and Effect on Hydration

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ABSTRACT

Introduction: Although rosacea management includes general skincare, previous studies have not evaluated comprehensive skincare regimens as adjuvants to other treatments.

Methods: The primary objective of this open-label, intra-individual study of subjects with rosacea was to evaluate the cutaneous tolerability of a regimen consisting of Cetaphil PRO Redness Control Day Moisturizing Cream (once daily in the morning), Cetaphil PRO Redness Control Night Repair Cream (once daily in the evening) and Cetaphil PRO Redness Control Facial Wash (foam once in the morning and once in the evening). Secondary objectives were to evaluate the effect on transepidermal water loss (TEWL) and cutaneous hydration and to determine the subjects' evaluation of efficacy, tolerability and future use. A dermatologist examined subjects and measured TEWL and cutaneous hydration on day (D) 0, D7 and D21, when subjects ranked symptoms. Subjects completed a questionnaire on D21.

Results: The per-protocol population consisted of 42 subjects receiving treatment for rosacea.

Eleven subjects developed adverse events, none of which were considered to be related to the skincare products. Five subjects showed signs or symptoms that were potentially associated with the skincare products that might suggest poor cutaneous tolerability; these were generally mild. TEWL decreased significantly by a mean of 17% on D7 and a mean of 28% on D21 compared with baseline (both $P < 0.001$). Skin hydration increased significantly by a mean of 5% on D7 ($P = 0.008$) and a mean of 10% on D21 ($P < 0.001$) compared with baseline. Subjects reported that the regimen was pleasant (98%) and effective (95%) and that it offered various benefits; 90% of subjects reported that they would like to continue to use the regimen and would buy the products.

Conclusion: The skincare regimen improved skin hydration and skin barrier function in subjects receiving medical treatment for rosacea and was well tolerated.

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Keywords: Moisturizing cream; Rosacea; Skincare regimen

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INTRODUCTION

Approximately 5–10% of the population suffers from rosacea, a chronic inflammatory skin disorder [1, 2], which can have a marked psychological impact and undermine health-related

quality of life [3–6]. Treatment depends on the phenotype and is supported by general skincare, which includes using sunscreen, gentle cleansers and frequent application of moisturizers [7]. According to recently published treatment guidelines, general skincare is also the main strategy to manage secondary features, such as dry appearance and dry and stinging sensations [7].

In people with rosacea, moisturizers can repair and maintain barrier function, enhance skin hydration, reduce the likelihood of skin irritation, relieve dry skin and improve dermatological characteristics (such as softness and suppleness) [8]. Skin care products for people with rosacea should block ultraviolet (UV) light; sun exposure is reported as a contributory factor by 61–81% of rosacea subjects [3, 9].

People with rosacea, however, often experience dry facial skin that can exacerbate symptoms [8] as well as heightened skin sensitivity [10]. For example, in a study of 65 people with rosacea and 60 healthy subjects, 30.8 and 10.0%, respectively, showed a positive reaction to at least one item in the 57-item Chemotechnique Diagnostics Cosmetic Series [11]. The reactive skin characteristic of rosacea seems to arise from activation of cutaneous nerves, a dysfunctional innate immune response and impaired epidermal barrier function [11].

As a result, skin care regimens should be assessed in people with rosacea. While moisturizers can be combined with other systemic and topical rosacea therapies [8], so far as we are aware, no previous studies have evaluated a comprehensive skincare regimen consisting of more than one product as an adjuvant to medical treatment of rosacea. This is, therefore, the first study to evaluate the cutaneous tolerability and effect on hydration and skin barrier function of a regimen of three cosmetic products—Cetaphil PRO Redness Control Day Moisturizing Cream (sun protection factor 30), Cetaphil PRO Redness Control Night Repair Cream and Cetaphil PRO Redness Control Facial Wash (all Galderma S.A., Lausanne, Switzerland)—during 21 days of use in subjects receiving concomitant medical treatment for rosacea. We hypothesized that the use of a comprehensive skincare regimen, as an adjuvant to medical treatment,

would improve the skin characteristics of patients with rosacea.

METHODS

Study Design

This open-label, intra-individual study was performed by DermScan Poland (Gdansk, Poland). Measurements and evaluations were taken before and after application of the regimen. Therefore, subjects were their own controls.

Subjects applied Cetaphil PRO Redness Control Facial Wash ('wash foam') once in the morning and once in the evening, the Cetaphil PRO Redness Control Day Moisturizing Cream ('sunscreen cream'), a beige emulsion, once daily in the morning and the Cetaphil PRO Redness Control Night Repair Cream ('night cream'), a white emulsion, once daily in the evening. Subjects applied the regimen for 21 days to their face. Patients were asked not to apply any product on the evening before each study visit. Washing with water was allowed.

Inclusion and Exclusion Criteria

The study aimed to enroll at least 40 female or male subjects, aged between 25 and 75 years, with Type I or Type II rosacea presenting with mild to moderate non-transient erythema. The skin color of the subjects was classified as ranging from Fitzpatrick phototype I to IV. A maximum of 20% of subjects were older than 60 years. Subjects received an oral or topical rosacea treatment for at least 4 weeks before enrollment. Subjects were not permitted to change their rosacea treatment in the 4 weeks before enrollment and were otherwise healthy. Female subjects of childbearing potential were asked to use precautions to avoid pregnancy.

Exclusion criteria included: starting, stopping or changing hormonal treatment (including contraception) during the 3 months before and during the study; a history of skin cancer; vaccination during the previous 2 weeks or intending to be vaccinated during the study;

and active skin disease (except rosacea) at the test area.

Subjects were also excluded if they used topical medication or over-the-counter treatments on the test area (excluding rosacea treatment), systemic immuno-suppressive drugs or antihistamines in the 4 weeks before or during the study. Subjects were excluded if they took anti-inflammatories and analgesics (except for minor pain relief medicine, such as acetylsalicylic acid or paracetamol) within 3 days of the start of study, reported excessive sun exposure 2 weeks before or during the study, or underwent procedures such as laser treatment or electrocoagulation in the 6 weeks before or during the study. Subjects with a history of adverse reactions to cosmetics or other common triggers were also excluded.

Objectives

The primary objective was to evaluate the cutaneous tolerability of a skincare regimen consisting of a wash foam, daily sunscreen cream and night cream after 21 days as an adjuvant to medical treatment for rosacea. The secondary objectives were to evaluate the effect of the skincare regimen on transepidermal water loss (TEWL) and cutaneous hydration, and to determine subjects' subjective evaluation of the efficacy, tolerability and their likely future use of the skincare regimen.

Cutaneous Tolerability

The same dermatologist examined each subject's face on day (D) 0, D7 and D21 and ranked each of the following using a five-point scale: erythema; edema; desquamation and dryness; roughness; other signs (Table 1). In the latter case, the dermatologist specified the sign (e.g., telangiectasia, papules, and pustules). On D7 and D21, the dermatologist evaluated global tolerability (defined as the least favorable result) based on the clinical examination and subject reports. The dermatologist assessed itching, irritation and subjective rosacea symptoms by asking the patient.

On D0, D7 and D21 subjects ranked each of the following using a five-point scale (0: none; 1: very mild; 2: mild; 3: moderate; 4: severe): tightness; stinging; itching; warm or burning sensation; dryness; other. Again, the subject specified any other signs.

TEWL and Cutaneous Hydration

Transepidermal water loss was measured using a Tewameter® TM 300 measuring device (Courage & Khazaka GmbH, Cologne, Germany) on D0, D7 and D21 after 30 min of acclimatization in ambient conditions (temperature 22 ± 2 °C, relative humidity of between 35 and 55%). Measurements were taken in one area on the left or right jaw line (alternating sides between consecutive subjects).

Measurements of cutaneous hydration were performed using a Corneometer® CM 825 skin hydration measurement instrument (Courage & Khazaka GmbH) on D0, D7 and D21 after 30 min of acclimatization in ambient conditions (see above) on the same facial area as the TEWL measurement. The same area was used throughout the study for both measurements.

Subjects' Subjective Evaluation

Subjects completed a questionnaire on D21 asking for their opinions about the efficacy, tolerability and their likely future use of the skincare regimen.

Ethical Approval

The protocol was approved by the Internal Ethic Committee at DermScan Poland. The study was conducted according to Good Clinical Practice and the Declaration of Helsinki (1964) and its successive updates were followed. Informed consent to participate was obtained from all participants. According to cosmetic regulations (as all products tested in this study were cosmetics rather than drugs), the study did not require registration.

Table 1 Scale for dermatologist's assessment of cutaneous tolerability

Outcome	Severity (score)				
	None (0)	Very mild (1)	Mild (2)	Moderate (3)	Severe (4)
Erythema	Not present	Fairly detectable, discreet pinkness	Definite pinkness	Clearly distinguishable, dull red	Deep dark or fiery bright red
Edema	Not present	Palpable, barely visible	Palpable and visible	Obvious edema (thickness < 1 mm), with or without papule(s) or vesicle(s)	Severe edema (thickness > 1 mm), with or without vesicle(s) or blister(s)
Desquamation/dryness	Normal skin, regular cutaneous surface, absence of scale	Cutaneous surface slightly dull, little scales only with light scratching or rubbing	More obvious scales with a slightly whitish aspect	Numerous marked scales	Heavy scale production
Roughness	Surface perfectly smooth and supple	Slight irregularity and mild roughness to the tangential touch	Markedly irregular and rough appearance and ability to feel by vertical touch slight skin roughness	Very marked feeling of roughness and irregularity	Presence of very important irregularities, dehydrated sensation
Other signs	None	Very mild	Mild	Moderate	Severe

Statistical Analysis

Paired Student *t* tests compared TEWL and cutaneous hydration values before, during and after treatment. A *P* value of ≤ 0.05 was considered to be statistically significant. Statistical analyses were performed using Excel 2010 (Microsoft Corp., Redmond, WA, USA). Based on the bilateral confidence interval of a proportion, a more than 65.4% agreement in responses to questions in the subjects' subjective evaluation was considered to be statistically significant.

RESULTS

Subject Disposition and Demographics

A total of 44 subjects were enrolled, of whom 42 (37 females; mean age 48 years; range 25–68 years) completed the study (Table 2). Eighteen patients had type 1 rosacea; the remainder had type 2 rosacea. All subjects received medical treatment for rosacea for at least 30 days before enrollment in the study. Of these, 20 subjects received more than one medical treatment for rosacea (median 1; range 1–4). The

Table 2 Demographics of the per-protocol population ($n = 42$)

Variable	Value
Age (years)	
Mean	48
Median	25
Range	25–68
Sex (n)	
Female	37
Male	5
Fitzpatrick phototype (n)	
I	6
II	22
III	12
IV	2
Facial skin type (n)	
Dry	20
Normal	6
Combination	14
Greasy	2
Rosacea type	
I	18
II	24
Medical treatments for rosacea (n) ^a	
Metronidazole	32
Ivermectin	13
Clindamycin	5
Azelaic acid	4
Lymecycline	3
Tacrolimus	3
Erythromycin	2
Adapalene plus benzoyl peroxide	1
Azelaic acid plus lactobionic acid	1
Benzoyl peroxide	1
Brimonidine	1

Table 2 continued

Variable	Value
Clindamycin plus tretinoin	1
Clotrimazole	1
Niverosin ^b	1

^a Subjects could receive more than one treatment^b Niverosin: branded combination of diosmin, rutoside and hesperidin

safety population consisted of 44 subjects who applied the study products at least once. Of these, 42 subjects constituted the per-protocol population, who were analyzed for cutaneous tolerability and completed the questionnaire.

One subject was lost to follow-up after D7 and was excluded from the analysis. One subject withdrew on D7 after developing the following symptoms: moderate erythema on the cheeks, nose and chin; moderate desquamation, dryness and roughness on the whole face; and reporting a severe warm, burning sensation on the cheeks. This subject had changed rosacea treatment 1 week before the start of the study, but neglected to inform the investigator. Due to this serious protocol violation, which made assessing causality with the study products impossible, the subject was excluded. This was the only serious protocol violation.

Values for TEWL were recorded for 39 subjects on D7 and 42 subjects on D21. Cutaneous hydration was recorded for 41 subjects on D7 and D21. The other values were deemed aberrant due to technical issues during measurement based on the investigator's experience (values did not correlate with variations in skin hydration or clinical examination) and, therefore, excluded.

Adverse Events and Cutaneous Tolerability

Twelve subjects reported a total of 15 adverse events, most commonly colds or flu ($n = 4$),

runny nose ($n = 3$) and headache ($n = 2$). None of the adverse events were considered to be related to the skincare products. No serious adverse events were observed. Five subjects showed signs or symptoms that might suggest poor cutaneous tolerability; these were potentially associated with the skincare products (Table 3). These symptoms were generally mild. In addition, based on the subjective evaluation questionnaire, 26% of subjects reported cutaneous irritation during the study.

TEWL and Cutaneous Hydration

Transepidermal water loss decreased significantly by a mean of 17% on D7 and a mean of 28% on D21 compared with baseline (both $P < 0.001$) (Table 4; Fig. 1). Hydration of the superficial layers of the epidermis increased significantly by a mean of 5% on D7 ($P = 0.008$) and a mean of 10% on D21 ($P < 0.001$) compared with baseline (Table 5; Fig. 2).

Subjects' Subjective Evaluation

Subjects reported that the skincare regimen was pleasant (98%) and effective (95%). The questionnaire results suggested a range of benefits on, among other outcomes, dryness, moisturizing and stinging (Table 6). Subjects found the skincare products to be gentle and appropriate for use with medical treatments for rosacea (Table 6). Indeed, 90% of subjects reported that they would like to continue to use the skincare regimen; the same proportion would like to buy the products, regardless of the price. All results exceeded 65.4% agreement and are, therefore, statistically significant.

DISCUSSION

A skincare regimen encompassing sunscreen, gentle cleansers and frequent application of moisturizers is a cornerstone of rosacea management [7]. The combination of the three

Table 3 Symptoms that might suggest poor cutaneous tolerability and potential association with the skincare regimen

Subject number	Study period	Adverse event
28	D1–D12	Subject reported moderate tightness on the cheeks, which lasted 14 h, beginning immediately after application of the day cream
30	D14–D21	Subject reported moderate tightness and dryness on the whole face, which lasted 1 h, beginning immediately after application of the day cream
38	D1–D6	Subject reported severe tightness on the cheeks and chin, which lasted a few hours, beginning 1 h after application of the day cream
	D7–D20	Subject reported mild tightness on the cheeks and chin, which lasted 3 h, beginning 1 h after application of the day cream
	D21	Dermatologist observed very mild desquamation and dryness on the chin
39	D21	Dermatologist observed very mild desquamation and dryness on the cheeks and chin
41	D0–D6	Subject reported mild tightness on the nose, cheeks and forehead, which lasted the whole day, beginning 5 min after application of the day cream
	D5 and D6	Subject reported moderate burning sensation on the nose, which lasted 1–2 h, beginning 5 min after application of the day cream
	D21	Dermatologist observed very mild desquamation and dryness, and roughness on the nose

D Day

Table 4 Transepidermal water loss

Study period	Mean $\pm$ SEM (g m ⁻² h ⁻¹)	Change (%)	<i>P</i> value	Subjects with improved TEWL (%)
D0	13.4 $\pm$ 0.7			
D7	11.1 $\pm$ 0.5			
D21	9.7 $\pm$ 0.5			
Δ D7–D0	– 1.8 $\pm$ 0.4	– 17	< 0.001	74
Δ D21–D0	– 3.7 $\pm$ 0.5	– 28	< 0.001	93
Δ D21–D7	– 1.8 $\pm$ 0.4	– 13	< 0.001	82

Δ Change, *SEM* standard error of the mean, *TEWL* transepidermal water loss

Fig. 1 Mean transepidermal water loss (*TEWL*) over time**Table 5** Cutaneous hydration

Study period	Mean $\pm$ SEM (AU)	Change (%)	<i>P</i> value
D0	56 $\pm$ 2		
D7	59 $\pm$ 2		
D21	61 $\pm$ 2		
Δ D7–D0	3 $\pm$ 1	5	0.008
Δ D21–D0	6 $\pm$ 1	10	< 0.001
Δ D21–D7	3 $\pm$ 1	4	0.003

Δ Change, *SEM* standard error of the mean, *AU* Arbitrary units

products assessed in this study (wash foam, daily sunscreen cream and night cream) meet these needs. Despite many people with rosacea

reporting heightened skin sensitivity with skin care and personal hygiene products [10, 11], to the best of our knowledge, no previous studies have evaluated a comprehensive skincare regimen as adjuvant to the medical treatment of rosacea. This is, therefore, the first study to evaluate the cutaneous tolerability and effect on hydration and skin barrier function of a regimen of three cosmetic products in subjects receiving concomitant medical treatments for rosacea.

Despite the subjects having heightened skin sensitivity [10, 11], the skincare regimen assessed here (Cetaphil PRO Redness Control Day Moisturizing Cream, Cetaphil PRO Redness Control Night Repair Cream and Cetaphil PRO Redness Control Facial Wash) showed good cutaneous tolerance when used daily with concurrent topical or systemic treatments for rosacea for 21 days. While a few subjects reported signs and symptoms that might indicate poor cutaneous tolerability, these were generally mild and usually related to the day cream. However, as subjects used a variety of medical treatments, assessing causality is difficult. Moreover, 26% of subjects reported cutaneous irritation during the study. The questionnaire did not enquire about the severity of the irritation. Moreover, 12% of subjects showed signs or symptoms (most of which were mild) that might suggest poor cutaneous tolerability, with these signs and symptoms potentially associated with the skincare products. However, 98% of subjects reported that using the skincare regimen was pleasant. The high level of

Fig. 2 Mean cutaneous hydration over time. AU Arbitrary units

acceptance suggests that the irritation was not sufficiently serious to influence the subjects' perception of the product.

Moisturizers relieve dry skin, improve dermatological characteristics, such as softness and suppleness, and repair defective barrier function [8]. Despite subjects receiving concurrent

topical or systemic treatments for rosacea, 21 days use of the skincare regimen significantly reduced TEWL and increased cutaneous hydration. These results suggest that the skincare regimen repaired the cutaneous barrier in rosacea subjects over and above any effect of the concurrent topical or systemic treatments.

TEWL and cutaneous hydration improved significantly on D21 compared with D7, and prolonged use of this skincare regimen may further improve outcomes. Studies with longer-term follow-up could ascertain whether and for how long the cutaneous barrier continues to repair.

Ninety percent of subjects valued the skincare regimen and, tellingly, wanted to continue use after the study ended. A product that is well accepted is likely to help ensure good adherence, especially during long-term use, although further studies with longer follow-up are needed.

The study was open label, un-randomized and performed at one center. Therefore, this study could be replicated in a larger, more

Table 6 Subjects' subjective evaluation of efficacy of the skincare regimen after D21

Characteristic	Percentage of subjects who fully agree or agree	Percentage of subjects who fully agree	Percentage of subjects who agree
Protects the skin from drying out	92	40	52
Provides long-lasting moisturization and relief	93	43	50
Safe to use in combination with systemic or topical drugs for rosacea	100	60	40
Decreases symptoms associated with dry appearance, dry sensation, stinging sensation	93	50	43
Complimentary for use with redness and/or rosacea treatments	86	36	50
Non-irritating for redness-prone skin	100	52	48
Gentle enough for everyday use	98	60	38
Helps alleviate dryness associated with rosacea treatments	92	52	40
Leaves skin feeling moisturized and comfortable	93	50	43

diverse, randomized, double-blind sample. Moreover, future studies could determine any interactions between the medical treatments and the skincare regimen and use biometric outcomes to characterize skin condition in addition to the subjective evaluations by patients and experienced physicians.

Furthermore, the population was not homogenous in terms of demographics, disease severity or drug treatment. However, a highly homogenous population may reduce the external validity of the study. Our study represents the wider, demographically diverse population of subjects with rosacea who, in clinical practice, receive a range of treatments. Despite this variation, the regimen improved skin hydration and barrier function, suggesting broad clinical applicability. The study could be repeated, however, in a population selected by more tightly defined inclusion and exclusion criteria, such as infestation with *Demodex* mites. Subjects with rosacea show a significantly higher prevalence (odds ratio 9.0) of infestation and density of *Demodex* mites (standardized mean difference 1.6) compared with control patients. A causal relationship has not, however, been established [12].

CONCLUSIONS

The skincare regimen of Cetaphil PRO Redness Control Day Moisturizing Cream, Cetaphil PRO Redness Control Night Repair Cream and Cetaphil PRO Redness Control Facial Wash improved skin hydration and barrier function in subjects who were receiving medical treatment for rosacea. Subjects reported that the skincare regimen was pleasant, effective and offered a range of benefits. Considering the skin reactivity of rosacea subjects, the skincare regimen's tolerability was extremely favorable, underscored by the fact that most participants reported that they would purchase and recommend the products. These findings suggest that this skincare regimen could improve outcomes for people receiving medical treatments for rosacea.

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Compliance with Ethics Guidelines. The protocol was approved by the Internal Ethic Committee at DermScan Poland. The study was conducted according to Good Clinical Practice and the Declaration of Helsinki (1964) and its successive updates were followed. Informed consent to participate was obtained from all participants. According to cosmetic regulations (as all products tested in this study were cosmetics rather than drugs), the study did not require registration.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available because they are commercially sensitive, but are available from the corresponding author on reasonable request.

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