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ORIGINAL CONTRIBUTION

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Efficacy and safety results of micellar water, cream and serum for rosacea in comparison to a control group

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Abstract

Background: Rosacea is a common inflammatory skin disorder with centrofacial erythema, flushing, telangiectasia, papules/pustules, and possible ocular or phymatous manifestation. Patients' skin is particularly sensitive to chemical and physical stimuli leading to burning, stinging, dryness, and skin tightness.

Objective: Dermatological evaluation of the efficacy and safety of skin care products designed for centrofacial erythema in rosacea patients, in comparison with a control group using objective measurements. Rosacea symptoms (itching, tension, warmth, burning, dryness) and quality of life were examined.

Methods: Sixty Caucasians with centrofacial erythema were enrolled in an 8-week prospective study, fifty of them exclusively using the study products (micellar water, cream, and serum) with ten participants randomly assigned to a control group. Patients were evaluated at baseline (V0), at 4 weeks (V1), and at 8 weeks (V2). Three-dimensional objective measurements (VECTRA®) as well as standardized questionnaires were used.

Results: Results were compared with the control group. A significant reduction of 16% in skin redness as indicated by VECTRA® analysis was seen in the intervention group comparing V0-V2. Furthermore, rosacea-associated symptoms diminished by 57.1%, while life quality of affected patients within the intervention group improved by 54.5% comparing V0-V2, respectively.

Conclusions: A skin care regime suitable for sensitive and redness-prone skin led to an enhanced clinical appearance, to a decrease of associated symptoms in rosacea patients, and to an improved life quality.

KEYWORDS

cosmeceutical, cosmetic dermatology, facial redness, rosacea, skin care

1 | INTRODUCTION

Rosacea is a common inflammatory dermatosis primarily affecting the central face, cheeks, forehead, chin, and nose. The condition shows diverse clinical presentation and is characterized by a relapsing course. Revised diagnostic criteria have recently been proposed, abandoning the previously used subtyping approach, favoring a phenotyping classification, in order to provide greater accuracy in diagnosis, to facilitate treatment, and to improve patient care.[1] Therefore, a persistent centrofacial erythema and phymatous changes represent diagnostic criteria for cutaneous rosacea.[2] Facial erythema may appear as an early symptom of rosacea and is often underdiagnosed.[3] If these findings are missing, two or more major features can be used for the diagnosis, namely papules and pustules, flushing (transient erythema), and telangiectasia. Minor features such as burning or stinging sensation, facial edema, and dry appearance can also contribute to diagnosis.[4] Apart from these cutaneous findings, ocular manifestation should not be overlooked.[5]

Rosacea manifestations can lead to a remarkable reduction of quality of life.[6,7] Mostly, fair-skinned individuals after the age of thirty are affected.[8] The development of rosacea is complex and multifactorial. Predisposing factors,[9,10] unspecific triggers (ultraviolet radiation, microbial stimuli of demodex and its symbiont endobacterium *C kroppenstedtii*,[11] heat, stress), dysfunction of the immune system, and neurovascular dysregulation can fuel the pathogenesis of rosacea.[12] Dilatation of the precapillary arterioles can cause characteristic flushing, and venular leak of plasma proteins can result in facial edema.[13] Especially, the role of the innate immune response seems to represent a major contributing factor. Studies have shown an overexpression of ligand-binding Toll-like receptors (TLR) in the membrane of epidermal keratinocytes. Activated through physical and chemical stimuli, these receptors activate a downstream pathway that upregulates an inflammatory response. Moreover, an increase in the biological activity of kallikrein 5 (KLK5), a serine protease responsible for the activation of cathelicidin (LL-37), has been found in lesional rosacea skin.[14]

Furthermore, disturbances in the epidermal barrier have been described in rosacea patients with an increased transepidermal water loss.[15] Rosacea patients' skin has been found to be more alkaline compared to healthy controls.[16] A decreased tolerance to topical agents such as soaps has also been detected.[17]

Therefore, a skin care regime suitable and specific for sensitive skin prone to redness should be used on a daily basis. Cleansing products that can be applied and removed without the use of water are preferred.[4] Topicals should be moisturizing and contain a light texture and sun protection factor.[18] Ideally, the application should result in an immediate relief of dry and burning discomfort and restore the natural skin barrier, while simultaneously protecting from possible triggers.

This study was performed to objectively evaluate whether the combined use of micellar water, cream, and serum could lead to a reduction of facial erythema, a decrease of symptoms, and an enhanced quality of life in rosacea patients.

2 | MATERIALS AND METHODS

2.1 | Study design

The study was designed as a single-center, controlled, 8-week prospective trial. The study protocol was approved by the ethics committee of the University Hospital Munich, LMU (Ref.-No.: 477-15). This study was conducted in compliance with the International Conference on Harmonisation, Harmonised Tripartite Guidelines for Good Clinical Practice 1996, Directive 91/507/EEC, the Rules Governing Medicinal Products in the European Community, and the Declaration of Helsinki. All participants provided written informed consent.

2.2 | Inclusion and exclusion criteria

The inclusion criteria comprised healthy Caucasians of both sexes with a persistent centrofacial erythema due to rosacea, who had not undergone any redness-relieving treatment for the past 3 months (no topical/systemic rosacea treatment or laser therapy). Exclusion criteria were minors, pregnancy, and breastfeeding, a known type IV hypersensitivity to any product ingredient, diseases that may provoke facial erythema and participation in any other clinical trial 4 weeks prior to inclusion in the study.

2.3 | Study visits

Each participant underwent three study visits (V): V0 (baseline), V1 (after 4 weeks of treatment), and V2 (after 8 weeks of treatment). Patients were randomized to the intervention (50 participants) and control group (10 participants).

At each study visit, data were obtained using three-dimensional objective measurements for facial erythema (VECTRA®) and subjective assessments (questionnaire regarding rosacea-associated symptoms, *Dermatology life quality index* (DLQI)). Moreover, undesirable effects were recorded and graded regarding their duration and severity (mild, moderate, and severe). (Figure 1).

2.4 | Study endpoints

The primary endpoint was defined as the assessment of facial erythema in both study arms (intervention and control group) between V0, V1, and V2. Secondary efficacy variables included the subjective evaluation of rosacea-associated symptoms and change in quality of life comparing at V0, V1, and V2. Furthermore, the safety of the products was addressed.

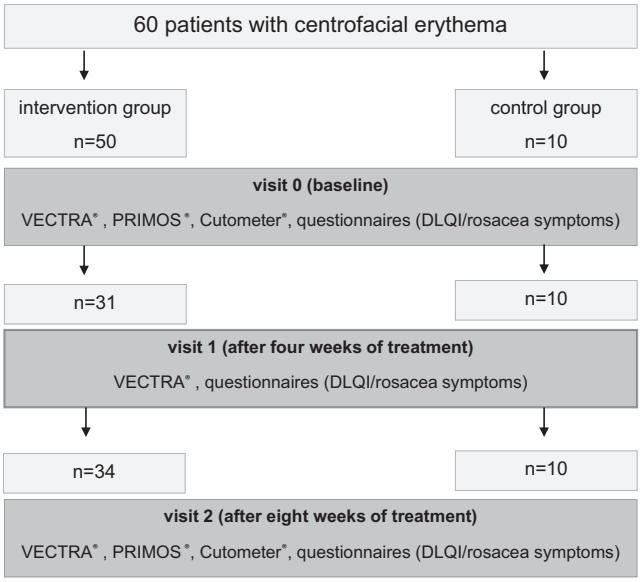

FIGURE 1 Study algorithm: Sixty patients were enrolled in the prospective study with 10 patients randomly assigned to the control group. Every patient underwent three study visits. Data were obtained using objective and subjective evaluation methods. (n = number, DLQI = Dermatology Life Quality Index, V = visit, V0 = baseline, V1 = after 4 wks of treatment, V2 = after 8 wks of treatment)

2.5 | Study products

Each patient within the intervention group received three skin care products: micellar water, cream, and serum (LETISR® (*sensitive and red skin*)) (ingredients [INCI]: Table S1). Products were provided by LETI® Pharma GmbH. Patients were not informed with regard to the name or the brand of the study products. Precise instructions for use were given. The face was cleansed in the morning and in the evening using the micellar water with the help of a cotton wool pad without the use of water. In the morning, patients applied the nontinted cream containing sun protection against UV-A and UV-B (SPF 20). In the evening, patients applied the serum with a gentle massage on clean and dry skin.[18]

Participants of the intervention and control group were instructed to strictly restrain from using any other rosacea treatment and to avoid excessive ultraviolet exposure. They were allowed to apply makeup, except on the days of the study visits. Within the intervention group, the use of the study products was assessed by weighing the tubes at each visit. Patients within the control group had to continue with their previous skin care regime. Their standard of care did not include any rosacea-specific products. Brand and name of products used in the control group were noted (data not shown).

2.6 | Data analysis

Data analysis was performed by a blinded professional statistician and an epidemiologist. Statistics were carried out using SAS®, release 9.3 (SAS Institute Inc, Cary, NC, USA) and Prism® software (GraphPad® Version 7.0b for Mac OS X, La Jolla, CA, USA) on a Microsoft® Windows® platform (Redmond, WA, USA). Variables mean, standard deviation, median, lower and upper quartile, and minimum and maximum were determined. In order to investigate tendencies over time, the nonparametric Wilcoxon signed rank test for dependent samples was applied on a test level of 5%. For comparison of treatment groups, the two-sided Wilcoxon rank-sum test was used on the 5% level.

2.7 | VECTRA®

VECTRA® (Canfield Scientific), a three-dimensional imaging device with eight cameras, was used to objectively evaluate patients' facial erythema. The measurements were performed by a blinded investigator without knowledge whether the respective patient belonged to the intervention or control group. First, high-resolution pictures of the skin surface were taken (*picture mode*). Second, the RGB (red-green-blue) color code was used to quantify the intensity of the color red per pixel as a dimensionless figure (ImageJ software, open source freeware, version 2.0.0-rc-43/1.51 g for Windows (*red-colour-depth-mode*[19])). Lighter shades of red were defined as an improvement in facial erythema. The values at V0 were set as the reference point, and the relative changes at V1 and V2 were given. (Figure 2).

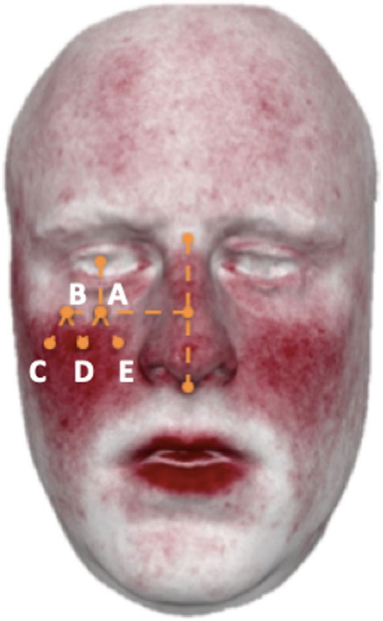

FIGURE 2 VECTRA® was used to quantify the intensity of facial erythema. Five defined points per cheek (A-E) were analyzed (point A: under the pupil, halfway up the nose; point B: lateral of point A, half-length of pupil and point A distance; point C: 60° downwards and lateral of point B; point D: 60° downwards in the middle of point A and point B; point E: 60° medial of point A). All points were added up to a final score

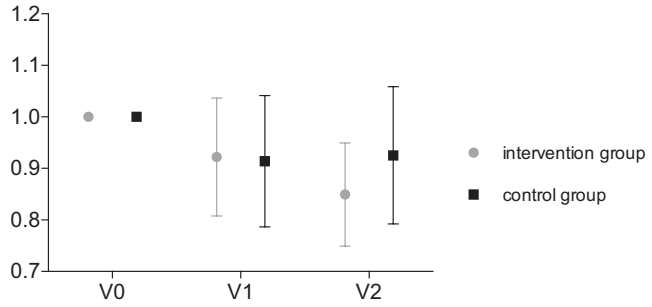

FIGURE 3 VECTRA® data showing the relative change in facial erythema within the intervention group and control group at V0, V1, and V2. Mean with standard deviation are shown. (Intervention group: V1-V0 $P = .0016$; V2-V0 $P \leq .0001$; V2-V1 $P = .0078$—control group: V1-V0 $P = .0195$; V2-V0 $P = .0195$; V2-V1 P = nonsignificant)

2.8 | Questionnaires

Patients were asked about their rosacea-related symptoms (itching, tension, warmth, burning, dryness). The presence of each of these five items was scored with one point. The sum was calculated and the mean determined.

The DLQI, the most commonly used dermatology-specific validated instrument assessing the extent of skin diseases' impact on patients' psychological well-being, on daily activities and social functioning was applied. Scores ranged from 0 (no impact) to 30 (maximum impact). Validated bands gave meaning to the scores as follows: 0-1 = no effect on patients' life; 2-5 = small effect; 6-10 = moderate effect; 11-20 = very large effect; 21-30 = extremely large effect.[20]

3 | RESULTS

3.1 | Patient population

A total of 60 patients (44 women [73%], 16 men [27%]), with a mean age of 43 years (range between 21 and 81 years) were included in this prospective study. The control group consisted of five women and five men, with a mean age of 30 years (range between 25 and 37 years). The intervention group therefore comprised 50 patients (39 women, 11 men), with a mean age of 45 years (range between 21 and 81 years).

Forty-four out of 60 patients (73%) of the cohort completed the study. 34 of 50 patients within the intervention group and all patients (10/10) within the control group were followed up until V2. Complete dropouts were seen after V0 (n = 13) and after V1 (n = 3). Reasons for discontinuing the study were incompliance: excessive exposure to ultraviolet radiation (n = 1), mild undesirable effects (n = 2), and a complete loss of follow-up (n = 13). Six patients did not show up for V1; however, they did show up for V2. Their data were included in the statistical analysis.

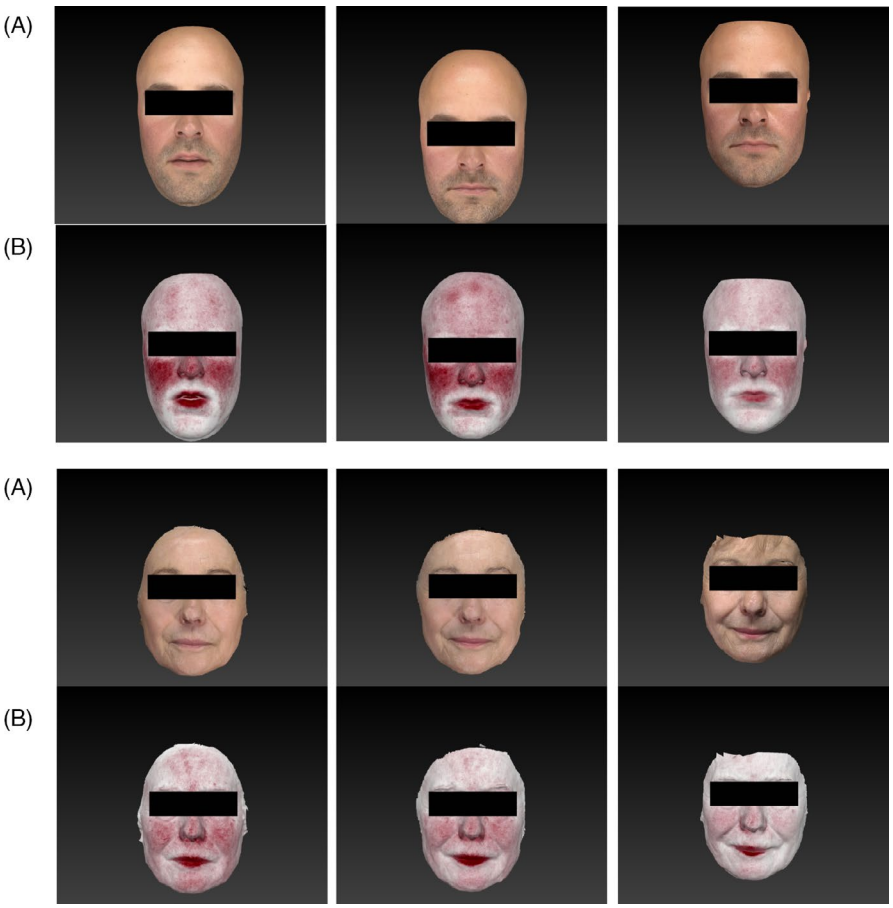

FIGURE 4 Two cases of the intervention group throughout the course of the study at V0 (left), V1 (middle), V2 (right), respectively, in *picture mode* (A) and *red-colour-depth mode* (B) using VECTRA®

Two mild undesirable effects within the intervention group were observed in the beginning of the study. Two females reported a slight aggravation of redness and pustules of the face alongside a burning sensation. No conclusion could be drawn as to the exact triggering product. The patients dropped out of the study. Patch tests were rejected by the patients.

Participants in the intervention group recorded a mean use of products at V2 as follows, showing adherence to the study design: 133.75 ± 44.42 g of micellar water, 20.06 ± 7.54 g of cream, and 16.48 ± 6.30 g of serum. (Figure 1).

3.2 | Facial erythema

Evaluation of VECTRA® technology presented a statistically significant reduction in facial erythema within the intervention group showing 0.92 ± 0.11 at V1 ($P = .0016$) and 0.84 ± 0.10 at V2 ($P \leq .0001$) compared to V0. This resulted in an improvement of 16% between V0 and V2. Analyzing the change in redness between V1 and V2, a statistically significant change of 0.08 was found ($P = .0078$).

Within the control group, skin redness was determined as 0.91 ± 0.12 at V1 ($P = .0195$) and 0.92 ± 0.13 at V2 ($P \leq .0195$), as compared to V0. Here, we found a relative improvement by 8% when comparing V0 and V2. No statistically significant change in skin redness was seen between V1 and V2. (Figures 3-5).

3.3 | Rosacea-associated symptoms and quality of life

Regarding subjective assessment of itching, tension, warmth, burning, and dryness within the intervention group, the mean score showed a decrease from 2.1 ± 1.0 points at V0, down to 1.5 ± 0.7 points at V1 and 0.9 ± 0.6 points at V2. This constituted to a relative improvement of 28.6% at V1 ($P = .0258$) and 57.1% at V2 compared to baseline measurements ($P \leq .0001$).

The overall mean DLQI score decreased significantly within the intervention group from 3.3 ± 3.6 points at V0, to 1.6 ± 1.6 points at V1, to 1.5 ± 2.0 points at V2. Thus, data show a relative improvement of 51.5% at V1 ($P = .0005$) and 54.5% at V2 compared to V0 ($P = .0149$).

Within the control group, the total score of subjective symptoms was 1.4 ± 0.5 points at V0, 1.5 ± 0.5 points at V1 and 1.5 ± 0.9 points at V2 (P = nonsignificant, respectively).

The overall mean DLQI score within the control group was 2.1 ± 2.1 points at V0, 2.0 ± 1.7 points at V1, 1.6 ± 1.5 points at V2. A relative improvement of 4.8% at V1 and of 23.8% at V2 compared

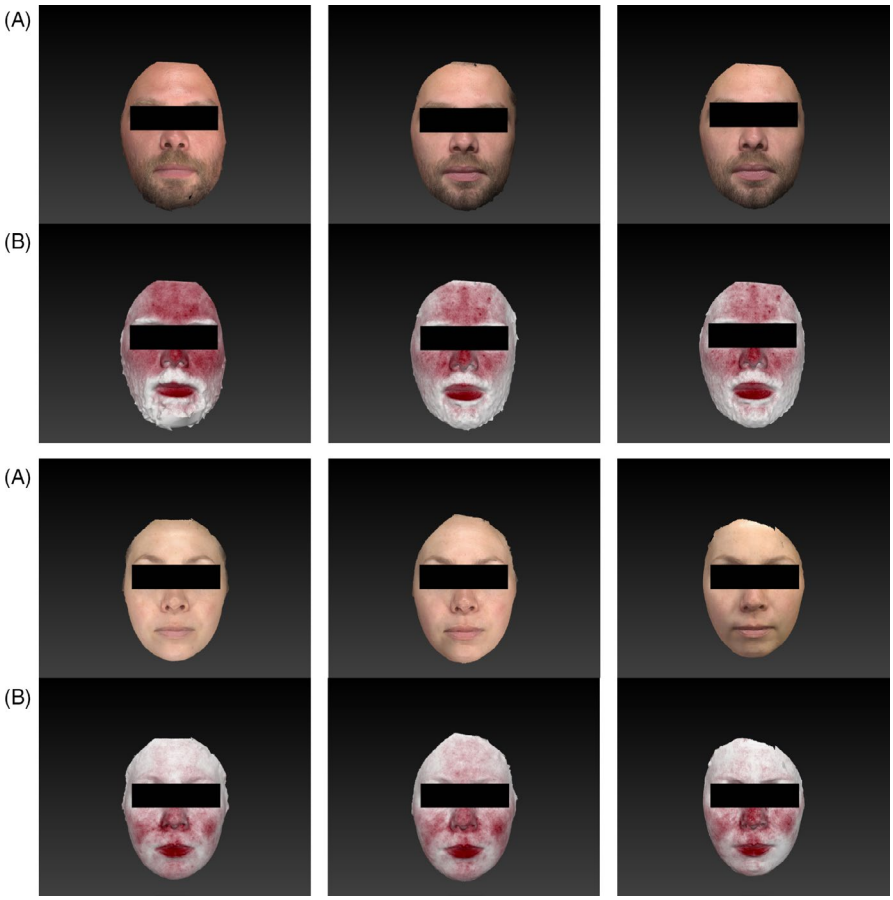

FIGURE 5 Two cases of the control group throughout the course of the study at V0 (left), V1 (middle), V2 (right), respectively, in *picture mode* (A) and *red-colour-depth mode* (B) using VECTRA®

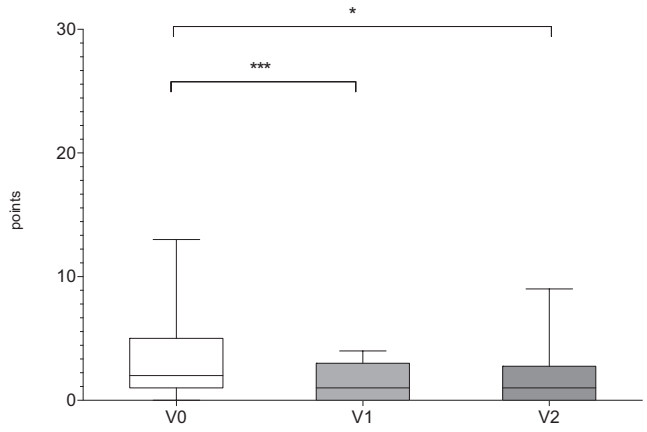

FIGURE 6 Subjective analysis of rosacea symptoms (itching, tension, warmth, burning, dryness) within the intervention group. Each item was scored with one point. Mean values with range are shown. (*P = .0258, ***P = <.0001)

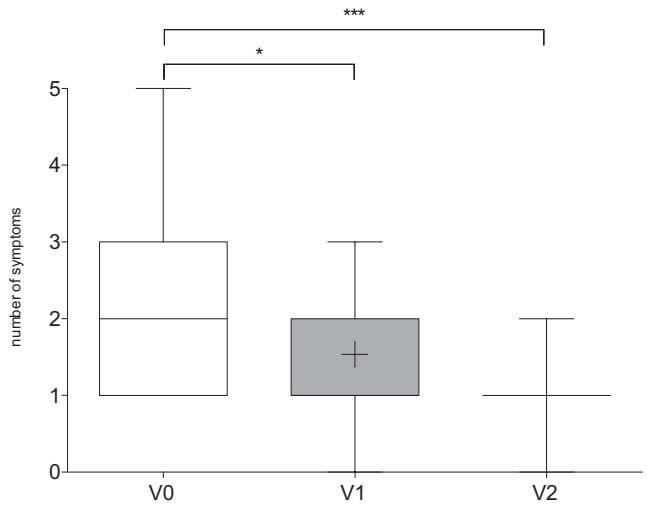

FIGURE 7 DLQI scores within the intervention group throughout the course of the study. Mean, minimum, and maximum are shown. (0-1 = no effect on patients' life; 2-5 = small effect; 6-10 = moderate effect; 11-20 = very large effect; 21-30 = extremely large effect; *P = .0149, ***P = .0005)

to baseline was found, however, not statistically significant (P = non-significant, respectively). (Figures 6 and 7).

4 | DISCUSSION

This clinical trial objectively evaluated the efficacy of a skin care series designed for sensitive and redness-prone skin as seen in rosacea patients, by quantifying improvement of facial erythema, rosacea-associated symptoms, and quality of life.

The study achieved its primary endpoint by showing a significant decrease in facial erythema in the intervention group by 16% comparing V0-V2. Hereby, an innovative method was introduced to objectively quantify the intensity of the color red. No comparative data have been described to date (Figures 3-5). Within the control group, a reduction in skin redness by 9% was seen. This change was observed between baseline and V1 with no further improvement compared to V2. The intervention group, however, showed a continuous improvement. This might indicate the superior efficacy of the study products.

In accordance with many previous studies explaining the skin barrier in rosacea patients,[21] negative sensations such as itching, tension, warmth, burning, and dryness were also present in both groups at the beginning of the study, but almost fully diminished within the intervention group comparing V0-V2. On the other hand, no significant change was seen in the control group. This underlines the importance of a suitable and specific skin care regime in the optimal care of rosacea patients.

Rosacea leads to a reduced quality of life.[7,22] As this study merely included healthy patients with mild symptoms of rosacea, as opposed to inflammatory or phymatous lesions, baseline overall quality of life was relatively high. However, due to the improved clinical appearance after treatment, patients´ quality of life increased significantly by 54.5% within the intervention group comparing V0-V2. Conversely, DLQI results of patients within the control group merely noted an improvement by 23.8% (not significant, ns).

Bearing in mind that patients with rosacea skin are sensitive to exogenous factors,[23] two mild undesirable effects were seen at the beginning of the study. A connection with the study products could not be proven as further diagnostics were advised but rejected by the affected participants.

The strength of the study lies within the prospective and controlled study design and the new objective evaluation method for the quantitative analysis of facial erythema. With countless available skin care products, in vivo studies with objective evaluation methods are necessary in order to prove their efficacy.[24,25] Kresken et al recently emphasized the high demand for dermocosmetics suitable for use in rosacea.[18] Especially the treatment of erythema represents a major challenge for practitioners in everyday clinical practice. An appropriate skin care regime can promote treatment adherence and can play a supportive role in the reduction of frequency of outbreaks. The limitation of this study lies within the fairly small control group of patients, who continued with their standard of care in the sense of an active control. Since rosacea patients show a high burden of burning and stinging sensations, abstaining from any skin care throughout the study would not have been practical. Moreover, the treatment period was relatively short. Also, it might be interesting to include a follow-up period in future studies and to elaborate the relevance of this skin care series if complementing a pharmaceutical approach. Although neither the name nor the brand of the study products was revealed to the patients and VECTRA® analysis was performed by a blinded investigator, a double-blinded study design would have added to the quality of the clinical trial.

The use of the three specialized products for the care of sensitive skin prone to redness resulted in a significant improvement of facial erythema, alleviated associated symptoms, and improved the quality of life of affected patients.

CONFLICT OF INTEREST

AG, NMJ, BCE, and AJW declare no conflict of interest. CC and AS are employees of LETI Pharma GmbH. MR has received fees as a speaker and as an advisor by LETI Pharma GmbH, Galderma, MEDA Pharma GmbH & Co. KG, Beiersdorf AG, Pierre Fabre, L'Oreal.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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