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ORIGINAL CONTRIBUTION

Efficacy and tolerability of a cream containing modified glutathione (GSH-C4), beta-Glycyrrhetic, and azelaic acids in mild-to-moderate rosacea: A pilot, assessor-blinded, VISIA and ANTERA 3-D analysis, two-center study (The "Rosazel" Trial)

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Abstract

Background: Rosacea is a very common, chronic inflammatory disease characterized by flushing, erythema and inflammatory lesions. Increased oxidative stress plays a relevant pathogenetic role in Rosacea. Intracellular Glutathione (GSH) is the main scavenger protective mechanism against increased oxidative stress. An altered GSH metabolism in Rosacea has been described. GSH-C4 is a modified GSH molecule characterized by a better intracellular bioavailability and longer half-life. A daily cream (E-AR) containing GSH-C4 (0.1%) with beta-Glycyrrhetic (0.5%) and azelaic acids (10%), with an SPF of 30, is available.

Aim: In a pilot, prospective, two-center, assessor-blinded study we evaluate the efficacy and the tolerability of E-AR cream in subjects with mild to moderate Rosacea treated for 8 weeks.

Patients and Methods: The main outcomes were the Investigator Global Assessment (IGA) 7-point score (from 0, completely clear; to 6, severe) and the clinical and instrumental erythema severity score (ESS) (from 0 to 4) evaluated in a blinded fashion (randomly coded photographs) at baseline, after 4 (only clinical) and 8 weeks (clinical and instrumental). VISIA evaluation for erythema and lesion counts and ANTERA 3D analysis for skin haemoglobin concentration (a parameter associated with inflammation) were also performed at the same time points. Analysis of primary outcomes was performed on an intention-to-treat basis. Tolerability was evaluated at week 4 and 8 recording spontaneously reported side effects.

Results: Thirty subjects (22 women and 8 men; mean age 38 years) were enrolled after their written informed consent. Twenty-six (87%) subjects completed the study phases. Four subjects stopped prematurely the trial due to low skin tolerability (n=3) or lost to follow-up (n=1). At baseline, mean (SD) IGA score was 2.6 (0.9). At week 4, IGA score decreased (NS) to 2.3 (1.2). IGA score decreased significantly (p=0.0001) at week 8 to 1.2 (1) (mean difference 1.3; 95% CI of the difference from 0.9 to 1.7) in comparison with the baseline. The inflammatory mean (SD) lesion count, evaluated clinically, were 5.1(2.5) at baseline, 2.8 (1.9) at week 4, and 1.9 (1.7) at week 8 (P=0.0001; ANOVA Test), representing a 63% reduction. This reduction was confirmed by inflammatory lesions count

performed on VISIA pictures (from 4.5 at baseline to 1.7 lesions at week 8). Similar evolution was observed for the clinical and instrumental ESS with a reduction of 56% (clinical) and 48% (VISIA), respectively, at week 8 in comparison with the baseline. ANTERA 3D photographs confirmed the positive evolution observed clinically with a significant reduction (-24%) in hemoglobin content: from 1.88 at baseline to 1.44 at week 8.

Conclusion: This new GSH-C4, beta-glycyrrethic and azelaic acids cream has shown to be efficacious in mild to moderate rosacea subjects. Local tolerability is in line with other anti-rosacea treatments.

KEYWORDS

assessor-blinded, clinical trial, modified glutathione, Rosacea

1 | INTRODUCTION

Several experimental and clinical studies have demonstrated that increased oxidative stress plays a relevant pathogenetic role in rosacea.[1-3] Intracellular glutathione (GSH) is the main scavenger protective mechanism against increased oxidative stress,[4,5] and an altered GSH metabolism in rosacea has been described.[6] GSH-C4 is a modified GSH molecule characterized by a better intracellular bioavailability[7] and longer half-life.[8] A daily cream (E-AR) containing C4-GSH (0.1%) with beta-glycyrrhetic (0.5%), azelaic acids (10%) with an SPF of 15 has recently been available.

2 | STUDY AIM

In a pilot, prospective, two-center, assessor-blinded, instrumental evaluation study, we tested the efficacy and the tolerability of E-AR cream in subjects with mild-to-moderate inflammatory papulopustular rosacea.

3 | SUBJECTS AND METHODS

3.1 | Population and study design

Between January and December 2019, 55 subjects were assessed and screened for inclusion in the trial. Twenty-five subjects were excluded for different reasons. The study took place in two Dermatology Italian clinics (Catania and Modena). The study protocol was approved by each participating center (Eutr. 01/2018) on November 2018. The trial was conducted according to the Declaration of Helsinki and the International Conference on Harmonization-Good Clinical Practice Guidelines.[9] Thirty subjects, meeting inclusion and exclusion criteria, with mild-to-moderate facial papulopustular rosacea (IGA score >2 and <5; with less than 50 inflammatory lesions) were enrolled, after their written informed consent, in a prospective 8-week assessor-blinded study. Main exclusion criteria were inflammatory skin diseases other than rosacea, known allergies or intolerance to one of the components of the tested product, pregnancy, or breastfeeding, recent (<8 weeks) treatments with oral or topical products used in rosacea therapy. ER cream was applied twice daily (morning and evening) on the entire face.

3.2 | Outcomes

The main outcomes were as follows: 7-point Investigator Global Assessment score[10] (IGA; the primary endpoint of the study) (from 0, completely clear; to 6, severe) and the clinical Erythema Severity Score (ESS) (from 0 to 4) evaluated in a blinded fashion (randomly coded photographs) at baseline, after 4 and 8 weeks. Twenty subjects (Catania Center) were also evaluated with VISIA for erythema and lesion counts calculation and ten subjects (Modena Center) with ANTERA3D (Miravex, Dublin Ireland) analysis for skin hemoglobin concentration (a parameter associated with inflammation) and vascular pattern. In more details, instrumental erythema severity was evaluated by cross-polarized images obtained by RBX™, via VISIA-CR system (Canfield, USA) using a 5-point scale, 0 = no erythema; 1 = very mild erythema; 2 = mild erythema; 3 = moderate erythema; and 4: severe erythema. Instrumental evaluations (VISIA and ANTERA 3D) were performed at baseline and after 8 weeks. Permissions for the use, after de-identification procedures, of face pictures of enrolled subjects to document clinical evolution were obtained from each patient. All the subjects have provided written informed consent for the images to be published. Tolerability was evaluated at weeks 4 and 8 recording spontaneously reported side effects.

3.3 | Statistical analysis and sample size calculation

Statistical analysis was performed using GraphPad statistical software ver. 13.0 (La Jolla, CA, USA). The primary endpoint of the trial was the evolution of IGA score from baseline to week 8 (end of treatment). The Wilcoxon and ANOVA tests were used for the analysis of the study outcomes. Differences were considered significant when $P < .05$. The efficacy analysis evaluated

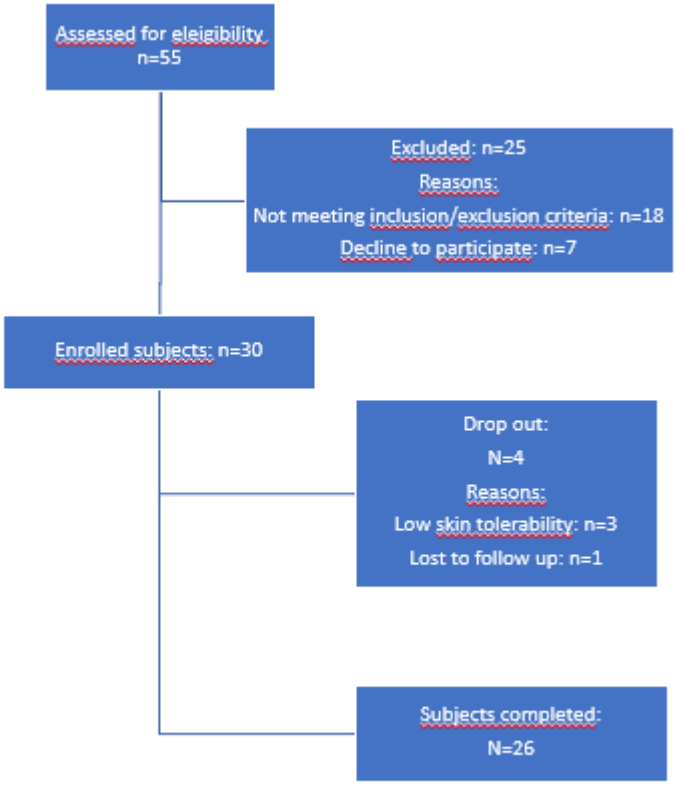

FIGURE 1 Study's flow

the hypothesis if the tested cream would be able to reduce significantly the IGA score (the primary endpoint of the study). Therefore, sample size calculation was performed on the hypothesis that the tested treatment could reduce the IGA score, in comparison with the baseline value, with an effect size of at least 0.8. With an alpha value of 0.05 and a power of 95%, a total of at least 30 subjects should be enrolled to detect this difference. The sample size was calculated using G-Power statistical software version 3.9 (Kiel, Germany). The analysis was performed based on the intention-to-treat principle, using the last observation carried forward (LOCF) methods. We summarized continuous variables by mean ± standard deviation (SD), calculating also the 95% confidence intervals (CI) for the observed differences.

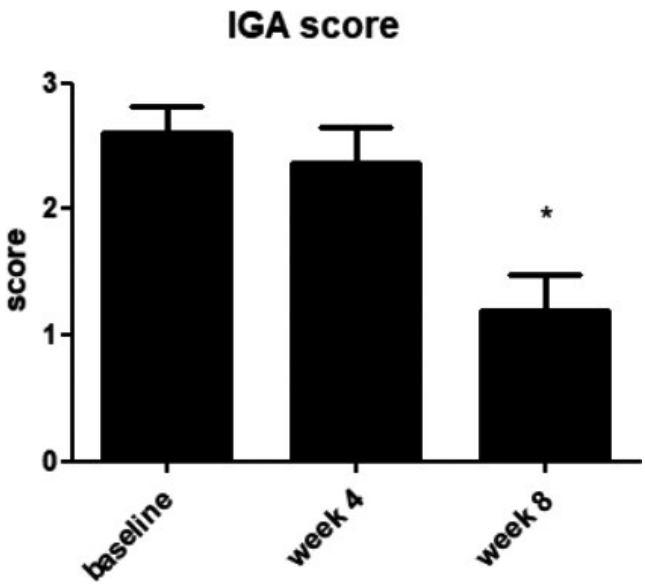

FIGURE 2 Investigator Global assessement Score (IGA)

4 | RESULTS

Thirty subjects (22 women and 8 men; mean age 38 years) were enrolled after their written informed consent. Twenty-six (87%) subjects completed the study phases. Four subjects stopped prematurely the trial due to low skin tolerability (n = 3; 10%) or lost to follow-up (n = 1). Figure 1 shows the study's flow. At baseline, mean (SD) IGA score was 2.6(0.9) (range: 2-5). At week 4, IGA score decreased not significantly to 2.3(1.2). IGA score decreased significantly ($P = .0001$) at week 8 to 1.2(1) (mean difference 1.3; 95% CI from 0.9 to 1.7) in comparison with the baseline, representing a 54% reduction (Figure 2). Similar evolution was observed for the clinical (n = 30) and instrumental (n = 20) ESS with a reduction of 56% at week 8 in comparison with the baseline. Clinical ESS at baseline was 2.6 (1), and it was significantly ($P = .0001$) reduced to 1.2 (1) (absolute difference: 1.4; 95% CI from 0.89 to 1.9) after week 8. The reduction in clinical ESS at week 4 was not significantly

different from the baseline value. The inflammatory mean (SD) lesion count evaluated clinically were 5.1 (2.5) at baseline, 2.8 (1.9) at week 4, and 1.9 (1.7) at week 8 ($P = .0001$; ANOVA Test) (Figure 3). This reduction was confirmed by inflammatory lesions count performed on VISIA pictures (from 4.5 at baseline to 1.7 lesions at week 8; $P = .0001$; a 63% reduction). Figure 4 reports VISIA pictures at baseline and after 8 weeks of treatment for IGA and erythema score evaluation. ANTERA 3D photographs confirmed the positive evolution observed clinically. A significant reduction (−24%) ($P = .05$) in hemoglobin content was observed: from 1.88 AU at baseline to 1.44 AU at week 8. ANTERA 3D pictures also documented a significant improvement in inflammatory lesions and telangiectasia pattern. Figure 5 reports three cases evaluated by ANTERA 3D at baseline and after 8 weeks.

5 | DISCUSSION

Chronic inflammation, like rosacea, is associated with oxidative stress.[11] Oxidative stress occurs when the amount of reactive oxygen species (ROS) exceed the buffer capability of endogenous antioxidative defense system.[12] Several studies have demonstrated that oxidative stress is strongly involved in the pathogenesis of rosacea.[13] In skin biopsies from rosacea patients, ROS levels are higher than healthy controls.[14] Rosacea subjects present increased levels of ROS and a decrease in antioxidants such as ascorbic acid also in the blood.[15] These data have been confirmed by Tisma et al[16] showing that serum peroxide levels were significantly higher and serum total antioxidative potential levels were significantly lower in rosacea patients than in healthy controls. UV radiation, a very well-known trigger and aggravating factor of rosacea,[17] is a potent inducer of ROS formation in the skin.[18] ROS are mediators of cytokines induction in human keratinocytes.[19] Topical metronidazole,[20] azelaic acid,[21] and systemic doxycycline[22] can counteract the

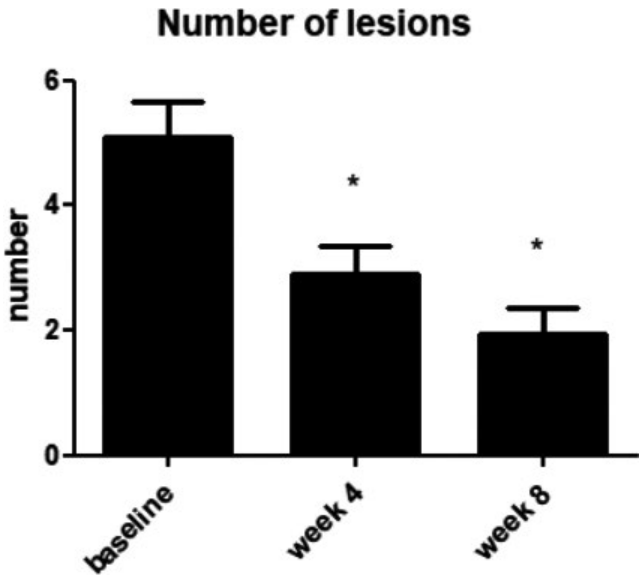

FIGURE 3 Evolution of inflammatory lesion count evaluated clinically. *$P = .0$

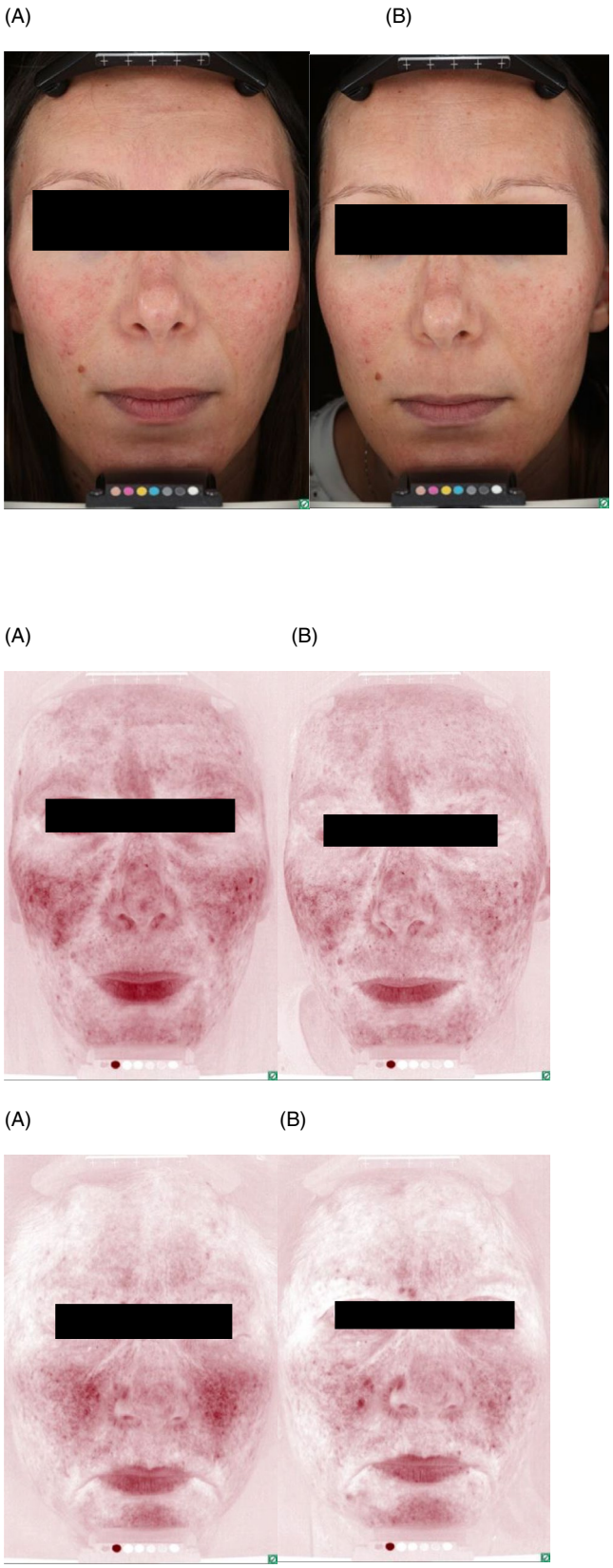

FIGURE 4 (1) IGA score evaluation at baseline (A) and at week 8 (B) 2) Erythema evaluation with cross-polarized images obtained by RBX™ VISIA (two subjects) at baseline (A) and after 8 weeks (B)

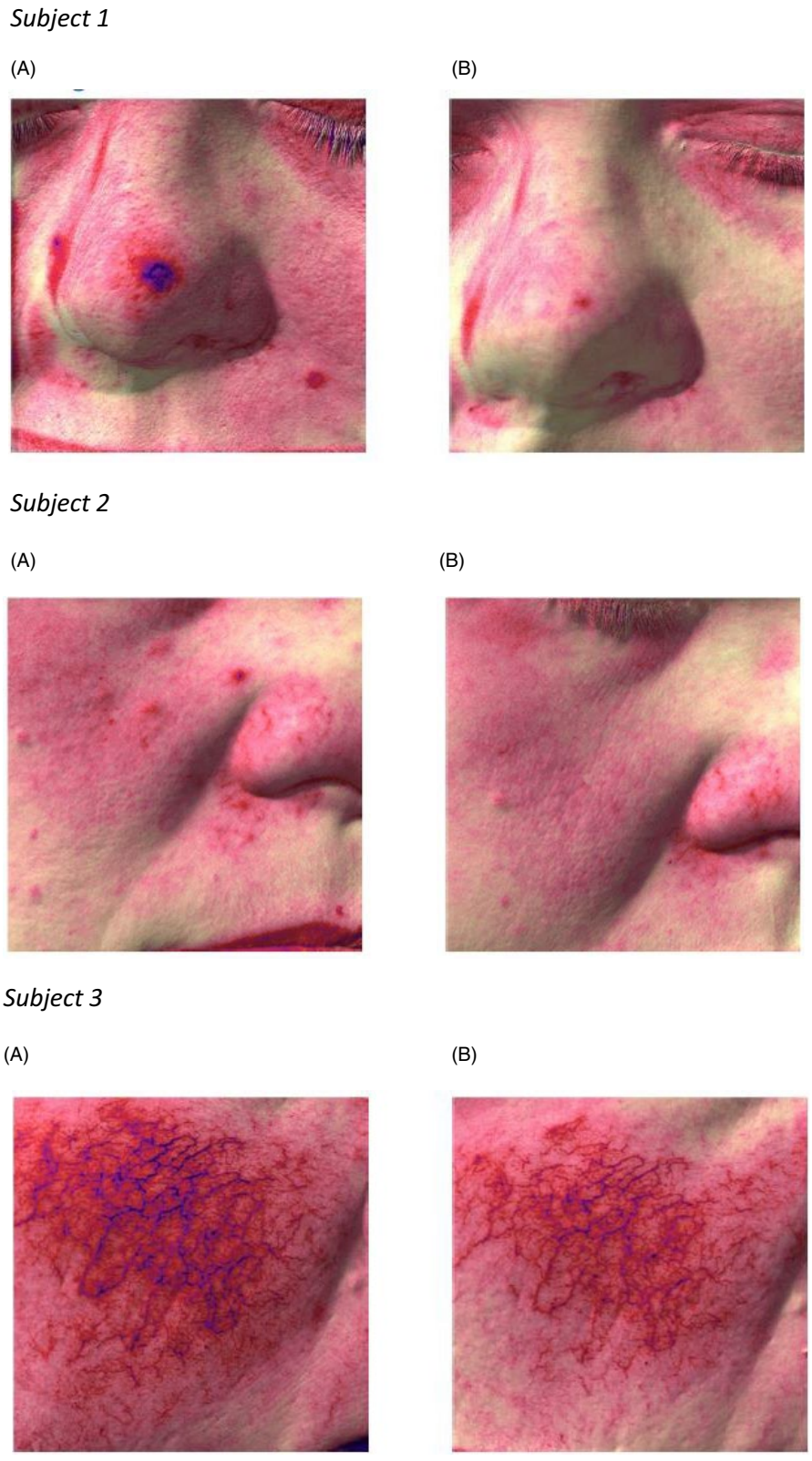

FIGURE 5 ANTERA 3D pictures of three subjects (1, 2, and 3) at baseline and at week 8 showing evolution of erythema and inflammatory lesions and grade of teleangectasis (A: baseline; B: week 8)

pro-inflammatory action of ROS, and this effect could explain, at least in part, the clinical efficacy of these drugs in rosacea treatment. Physiological antioxidant mechanisms include superoxide dismutase, catalase, and glutathione peroxidase, a powerful hydrogen peroxide detoxifier.[23] Glutathione (GSH), a tripeptide formed by L-glutamate, cysteine, and glycine, is the most abundant low-molecular-weight thiol in animal cells.[24] GSH is present in millimolar concentrations in virtually all normal cells[25]; therefore, GSH is the principal intracellular antioxidant buffer against oxidative stress and mainly exists in the forms of reduced glutathione (GSH) and oxidized glutathione (GSSG).[26] The

availability of intracellular GHS is a key factor for an effective antioxidant defensive mechanism.[27] GSH deficiency contributes to oxidative stress.[28] In more than 40% of rosacea subjects, there is a genetic defect in the production of glutathione transferase. Furthermore, in rosacea patients an altered ratio GSSG/GSH, an accurate indicator of the oxidative status of the cell, is significantly higher in comparison with healthy controls.[29] For these reasons, therapeutic strategies with the aim to increase GSH intracellular levels could be, at least theoretically, an interesting tool counter fighting the pathogenetic role of oxidative stress in rosacea. However, GSH has a very low capability to cross cell membrane.[30] Intracellular levels of GSH are, in fact, mainly the result of inside synthesis.[31] Therefore, from a pharmacological point of view, the addition of exogenous GSH (systemic or topical) should be considered ineffective. A modified GSH molecule (GSH-C4) has been synthetized and patented.[32] GSH-C4 is a butanoyl derivative of GSH. This modification does not alter the antioxidant activity of the new molecule.[33] GSH-C4 is more lipophilic, and it can cross the cell membrane faster and more effectively than GSH.[8] Inside the cell, GSH-C4 has also a longer half-life than GSH. More important, an experimental study has shown that GSH-C4 significantly increases the intracellular pool of GSH and it is able to express anti-inflammatory action.[34] A cream containing GHS-C4 and hyaluronic acid has shown to be effective in seborrheic dermatitis patients.[35] In this study, we evaluated the clinical efficacy of 8-week treatment of a new cream containing GSH-C4 (0.1%), azelaic acid (10%), and beta-glycyrrhetic acid (0.5%) with an SPF of 15 (therefore suitable for the use during summer season), in patients with mild-to-moderate rosacea. This cream has demonstrated a significant reduction of the erythema score, assessed both clinically and instrumentally (−54%) and of the lesion count (−63%). Azelaic acid alone is considered an effective treatment of rosacea.[36] Topical azelaic acid (20%) used for 12 weeks has shown to reduce erythema score on average by 36% with a reduction of lesion count of 66%.[37] Therefore, it is improbable that the clinical efficacy we have observed in our study could be completely and exclusively ascribed to azelaic component alone (present in this cream at 10% concentration) of the tested formulation. Full clinical efficacy of azelaic acid topical treatments and other anti-rosacea drugs is observed after 12-16 weeks.[38] Our study lasted 8 weeks only. Azelaic acid concentrations >15% could have a low local tolerability profile.[39] It is possible that azelaic acid could have a synergistic effect with GSH-C4, explaining the good clinical results we have seen in this trial. Both molecules could reduce, in different ways, the expression of TLR2[40,41] which play a pivotal pathogenetic role in rosacea. The additional component of the tested cream is glycyrrhetic acid. It has a steroid-like structure and is believed to have immunomodulatory and anti-inflammatory properties.[42] Glycyrrhetic acid is the principal metabolite of glycyrrhizic acid, a triterpenoid saponin glycoside, the major water-soluble constituent of licorice root.[43] Some limitation should be taken in account in interpreting the results of this pilot trial. The study was an open noncontrolled trial. To improve internal validity, we adopted a primary outcome (IGA score evolution) assessor-blinded evaluation study design. Furthermore, the study protocol has included an objective instrumental evaluation (VISIA and ANTERA 3 D) of other two relevant clinical outcomes: facial erythema and lesions count. Another study limit of our study is the fact that we have evaluated a relatively small sample size. However, the present study should be considered a pilot trial and future clinical evaluations in a larger rosacea population are warranted. In addition, it should be taken in account that we have decided to enroll 30 subjects performing a sample size calculation with a prespecified hypothesis of the clinical effect of this cream. Therefore, in relation with the primary outcome, the sample size of this trial should be considered adequately powered.

6 | CONCLUSION

This new GSH-C4, beta-glycyrrhetic, and azelaic acids cream has shown to be efficacious in mild-to-moderate Ros subjects. Local tolerability is in line with other anti-Ros treatments.

CONFLICT OF INTEREST

MM is an employee of Cantabria Labs Difa Cooper. The other authors report no other conflicts of interest in this work.

AUTHOR CONTRIBUTIONS

FDO and MP contributed toward enrollment of subjects and data collection. GM and MM performed the results analysis and prepared the drafting of the paper. All the authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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