Management of Rosacea-Prone Skin: Evaluation of a Skincare Product Containing Ambophenol, Neurosensine, and La Roche-Posay Thermal Spring Water as Monotherapy or Adjunctive Therapy

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ABSTRACT

Objective: The objective of these studies was to investigate whether a skincare product containing Ambophenol, Neurosensine, and La Roche-Posay thermal spring water formulated in a highly protective packaging can have an impact in the management of rosacea-prone skin subjects.

Methods: Several studies were performed to evaluate the efficacy of this product in the management of rosacea prone skin, as either monotherapy or adjunctive therapy or to maintain the efficacy of a Metronidazole treatment. The first study was performed on 37 women aged 18-45 with added stage 2 erythro-couperosis, who applied test formula as monotherapy twice a day for 4 weeks. During a second study, a dermatological evaluation was performed on patients with stage I or II rosacea, a questionnaire containing information about patient characteristics, tolerance, clinical signs, symptoms and skin reactivity to "trigger factors" was completed by dermatologists at baseline and 2 months after treatment with the test formula as either monotherapy or adjunctive therapy. Finally, in a third study, 65 patients finishing a Metronidazole treatment applied once daily and the tested formula twice daily were divided into 2 groups using the test formula or vehicle control, twice a day for 8 weeks for the evaluation of efficacy as adjunctive therapy.

Results: We noted that the test formula, as an adjunctive therapy, helped prolong the efficacy of a Metronidazole treatment. In monotherapy, there was a significant efficacy of the test formula associated with an excellent tolerance. A significant improvement of all the clinical signs and symptoms of rosacea and a reduction of the skin reactivity to "trigger factors" were shown.

Conclusions: These studies highlight the interest value and impact of a skincare product containing Ambophenol, Neurosensine, and La Roche-Posay thermal spring water formulated in a highly protective packaging in monotherapy or in combination with or after a therapeutic treatment in the management of patients suffering from rosacea.

J Drugs Dermatol. 2013;12(8):920-924.

INTRODUCTION

Rosacea is commonly described as a chronic inflammatory cutaneous disorder, primarily affecting the central facial zone (cheeks, chin, nose and central forehead). It is characterized by various cutaneous symptoms such as flush, erythema, telangiectasia, oedema, papules, pustules, etc. Rosacea occurs in both genders, but two to three times as many women as men are affected.[1,2] It is most commonly apparent in pale-skinned, light-sensitive individuals of Celtic origin (skin types I and II according to Fitzpatrick) and less common in dark skinned individuals (skin type ≥ 3). Over 16 million Americans suffer from rosacea according to the National Rosacea Society[3]; its prevalence in Caucasian population is estimated in Europe to be between 5% (Southern Europe) and 10% (Northern Europe).[1,4] Patients are most often diagnosed during their 30s to 50s[5]; overall, around 57% of cases are diagnosed in the under-50s.[3] The first signs of the condition can occur in the form of flushing reactions before the age of 20. Rosacea starts in the vessels and the connective tissue of facial skin; it is characterized by a transient and persistent erythema and telangiectasia are regularly seen. Seborrhea is occasionally found and does not correlate with the severity of the condition.[6]

Diversity exists with regard to the classification of rosacea. It is clinically divided into a preliminary stage (pre-rosacea), three main stages of progression (stages I to III) and special forms.[2,7,8] Based on this classification, standard treatment options have been proposed for the different subtypes. Rosacea does not only have a detrimental effect cosmetically, but due to its localization on the face, problems of disfigurement can arise leading to a distinct decrease in quality of life.[9]

Additionally, rosacea is incurable and requires long-term management. Key treatment goals are to alleviate symptoms and improve appearance, delay or prevent development of the more advanced stages of the condition and to sustain remission. Care must be taken to ensure against psychosomatic co-morbidities, such as anxiety and personality disorders, social phobias or depression.[9,10] Recently, ROSacea International Expert (ROSIE) consensus group proposed an algorithm for the choice of treatment based on the use of signs and symptoms rather than on rosacea stage or subtype.[1]

The diversity in rosacea is also reflected in its pathophysiology. Potential pathogenetic roles have been postulated, for example for vascular abnormalities, dermal matrix degeneration, and implication of microorganisms, such as Demodex folliculorum and Helicobacter pylori, and environmental factors. A number of predisposing factors and stimuli, the so-called "trigger factors", are recognized which result in initial manifestations or exacerbations of symptoms including heat, cold, alcohol, sunlight, stress, spicy foods, some cosmetic products, etc.[1,11]

Most experts believe that an infectious cause is unlikely and that the disease is primarily inflammatory in etiology. It is believed that pro-inflammatory substances and degradative enzymes from inflammatory cells in the facial skin lead to the angiogenesis and dermal destruction associated with rosacea.[12] Recent research demonstrates an up-regulation of local inflammatory cytokines in patients with rosacea, and these mediators may play key roles in the pathophysiology of this disease.[1,12] A further novel approach is the link of rosacea to a dysfunction in the innate immune system elicited by elevated levels of abnormally processed cathelicidin antimicrobial peptides.[1,12,13]

Rosacea therapy pursues three goals: resolve current flare-ups, avoid "trigger factors" and maintain remission and the triad of rosacea care in treatment, education and skin care.[1]

Rosacea management may seem standardized; topical treatments should be the mainstay of treatment for many patients. Metronidazole is the most frequently used and internationally common rosacea medicine. It is therefore a benchmark in topical rosacea therapy. But many patients are moderately satisfied with their treatment.[1,2,9]The aim of treatment for rosacea is multi-factorial: to reduce symptoms such as facial flushing and telangiectasias and eruption of papules and pustules, to prevent or delay worsening from milder to more severe manifestations of the condition as well as to maintain remission.

Furthermore, in a National Rosacea Society survey of 1066 patients, 41% reported that some skincare products aggravated their condition and 27% said some cosmetics also caused rosacea flare-ups.[3] Therefore, it is important that products are noted as appropriate for sensitive skin or skin with rosacea, and avoid any products that sting, burn or cause irritation. So tolerance of cosmetics is key.

We therefore set out to design a product specifically adapted for patients with erythro-couperosic and rosacea sensitive skin. Ambophenol, Neurosensine, and La Roche-Posay thermal spring water were chosen for this formula for their anti-inflammatory and soothing properties. To reduce the number of additives, a hermetic packaging was designed to protect the product.

1. Ambophenol is a purified extract of Tambourissa trichophylla leaves (used in Madagascar as soothing and pain relief infusion), titrated in polyphenols and containing condensed tannins and flavonoids. In particular, rutin and nicotiflorin have powerful anti-oxidant properties. Furthermore, rutin is also known for anti-inflammatory potential whereas nicotiflorin is considered as anti-hemorrhagic.[14-16] Ambophenol combines extensive properties to minimize skin reactivity and skin redness ie, normalization of the overexpression of cathelicidins and the related enzymes (SCTE or Stratum Corneum Tryptic Enzyme, also called kallikrein-5 and SCCE: or Stratum Corneum Chemotryptic Enzyme, also called kallikrein-7)[12] leading to an improvement of the skin immune protection balance; a global anti-inflammatory activity with the modulation of key inflammatory pathways (cyclooxygenase or COX and lipooxygenase or LOX)[17] and the neoangiogenesis regulation with effect on both pro-angiogenic and anti-angiogenic factors and microcirculation improvement.[18] These properties are confirmed by a clinical study on skin redness / rosacea, with visible results from a one month treatment.[18]

2. We previously noticed a significant reduction in the number of patients with rosacea prone skin affected by functional or physical signs of skin reactivity at the end of a 4-week treatment with a simple formula (aqueous emulsion with more than 80% of water and 5% glycerin) containing Neurosensine or [N-acetyl-Tyr-Arg-hexadecylester][19] at the same concentration as in the tested formula. We also noted a reduction in the number of patients sensitive to some "trigger factors" and of the average intensity of the skin reactivity to these "trigger factors" ie cold weather, spicy food ingestion, cosmetic product use, etc.

3. Lastly, La Roche-Posay thermal spring water with a high concentration of Selenium, is a powerful anti-oxidant, has antiradical, immunomodulatory, and anti-inflammatory properties. At the thermal care center of La Roche-Posay, these clinical therapeutic properties have been demonstrated in chronic inflammatory diseases such as atopic dermatitis (eczema), psoriasis and also, wound healing, burn scars, pruritus, and other dermatosis like rosacea or ichthyosis.[20]

Three studies were performed to investigate whether this formula would be valuable in the management of rosacea-prone skin.

MATERIALS AND METHODS

Three studies were performed to evaluate the efficacy of the test formula in different therapeutic regimes: the first as monotherapy, the second either as monotherapy or as adjunctive therapy and the third as maintenance treatment.

Test Materials

The test formula contained Ambophenol, Neurosensine, and La Roche-Posay thermal spring water in a vehicle base. This base was also used as the control. The formula contained no preservatives, parabens, alcohol, fragrances or colorants. The hermetic packaging was designed to protect the product from microbial contamination.

Subjects

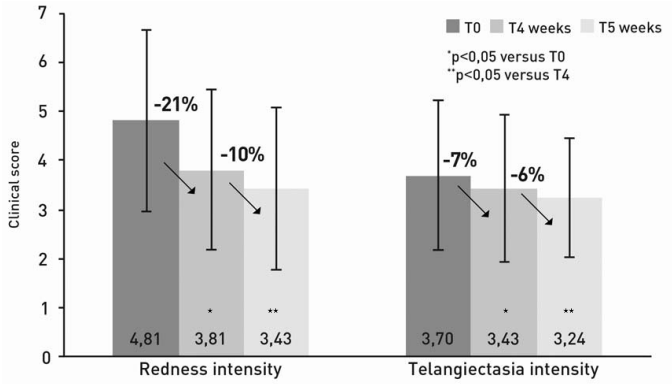
Each study protocol complied with the ethical guidelines of the 1975 Declaration of Helsinki, was approved by an ethical committee and was conducted according to ICH guidelines for Good Clinical Practice. Informed consent and photography consent were obtained from each subject before enrollment.

Study 1: Healthy, female volunteers between 18 and 45 years of age with diagnosed added stage 2 erythro-couperosis were included in this open controlled study. Patients applied the test formula on their full face twice a day for 4 weeks (after cleaning). The investigating dermatologist clinically evaluated redness and telangiectasia at baseline, 4 weeks, and then 1 week after stopping the treatment. Redness intensity and telangiectasia were evaluated using a visual analog scale (VAS) ranging from 0 (no symptoms) to 9 (intense symptoms).

Study 2: Adult volunteers with stage I or II rosacea were included into this open controlled study. At baseline, a dermatologist questioned the patients on their skin condition. This information was collected using a questionnaire containing questions about patient characteristics, tolerance, clinical signs, symptoms and skin reactivity to "trigger factors".The test formula was prescribed to each patient as either monotherapy for 117 patients with stage I rosacea or as adjunctive therapy for 433 patients with stage I or II rosacea. After 2 months treatment, the dermatologist administered the same questionnaire and each patient completed a self-questionnaire about physical (8 questions), social (10 questions) and psychological (11 questions) impairments.

Study 3: This single center, randomized, double-blind, vehicle controlled study included 65 patients finishing an 8-week Metronidazole treatment applied once daily (evening) (67 were enrolled before the beginning of treatment). Patients applied test formula or vehicle twice a day for 8 weeks.The investigating dermatologist clinically evaluated the tolerance and the evolution of rosacea.

FIGURE 1. Evaluation of the skin redness and telangiectasia intensity after 1 month's use of the test formula and 1 week later.



Statistical Analysis

Statistical evaluation of data was performed with SPSS software. Student test was used for normal distribution data and Wilcoxon test for non-normal distribution (Shapiro-Wilk test) data. A *P* value <0.05 was considered statistically significant.

RESULTS

Evaluation of Efficacy on Redness in Monotherapy

37 healthy women volunteers with erythro-couperosis aged between 18 and 45 years were enrolled in this study. Figure 1 shows the significant efficacy of the test formula on redness and telangiectasia intensity following 1 month's use on erythro-couperosic skin. Efficacy was prolonged 1 week after the end of treatment (T5 weeks). An excellent tolerance and an efficacy confirmed by patients who appreciated the product (for example 82% thought the texture was pleasant and 98% noted that the product was easily applied).

Impact on Clinical Signs, Symptoms and Triggering Factors

117 patients (20% M and 80% F), mean age 50 ± 13 years (20-80), mainly skin type II (61%) and III (23.5%) with a stage 1 rosacea completed the study. At the first visit the main clinical signs recorded were erythema, telangiectasia, flushes, dryness and feeling of tightness (Figure 2). At the 2nd visit, 2 months later, dermatologists noticed a significant improvement in all clinical signs and symptoms (reduction of -38%, *P*<0.0001) (Table 1), particularly skin dryness and feeling of tightness (Figure 2). Additionally, at the first visit the main "trigger factors" recorded were sun, intense physical exercise, heat and wind. At the 2nd visit, dermatologists noticed a significant reduction of the skin reactivity to trigger factors (-38%, *P*<0.0001) (Table 1 and Figure 3). The social impact of the disease was not as important as the physical and psychosocial impacts. Nevertheless, all these impairments significantly improved between the 2 visits (*P*<0.05) (data not shown).

FIGURE 2. Percentage of patients with clinical signs and symptoms at the 2 visits V1 and V2 (n=117).

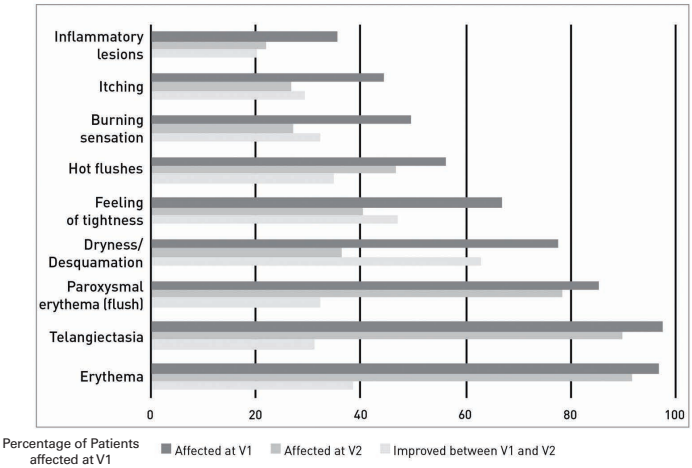


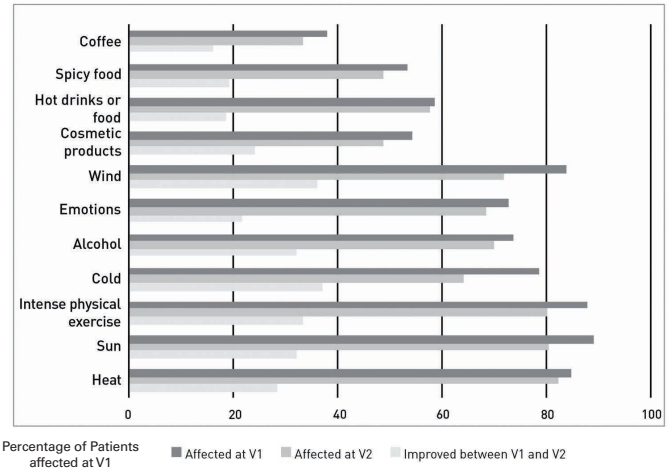
TABLE 1.

Evolution of Clinical Signs and Symptoms and Skin Reactivity to "Trigger Factors" Between the 2 Visits (V1 and V2)

	V1	V1	
Score of sign and symptoms	9,83 ± 4,04	6,21 ± 3,67*	-38%
Score of trigger factors	13,38 ± 6,21	10,77 ± 6,10*	-38%

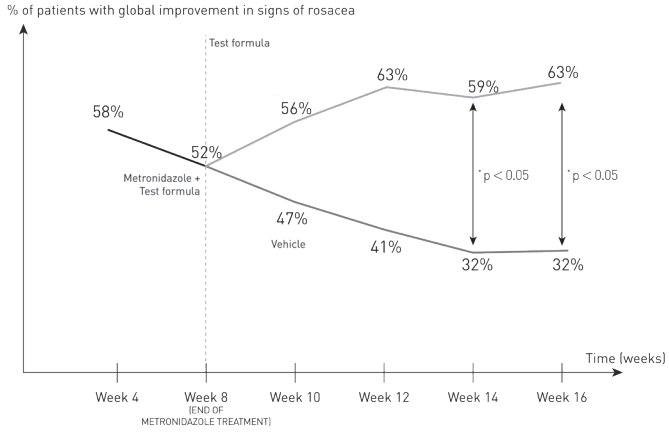
*p<0,05 versus V1

FIGURE 3. Percentage of patients with skin reactivity to "trigger factors" between the 2 visits V1 and V2 (n=117).



In addition, the tolerance and the satisfaction with the test formula were good to excellent in 85% and 74% of cases respectively and in 77% of cases, patients noticed a positive impact on their skin quality.

FIGURE 4. Evolution of rosacea after the end of an 8-week Metronidazole treatment with the use of test formula versus vehicle during 8 more weeks.



Evaluation of Tolerance as Adjunctive Therapy

Test formula has been also used by patients with stage 1 or stage 2 rosacea as adjunctive therapy with Metronidazole (n=181); Azelaic acid (n=23); Erythromycin (n=14); Doxycycline (n=31); Minocyclin (n=7); Isotretinoin (n=11); Ichtyol (n=107); Vascular laser (n=16); IPL (n=43) with a "good to excellent" tolerance and satisfaction in more than 80% of cases (data not shown).

Evaluation of the Efficacy Post-Prescription Treatment

Lastly, test formula was used in association with a leading rosacea prescription medicine (Metronidazole) for 8 weeks and for an additional 8 weeks following treatment withdrawal. After 16 weeks, the percentage of patients with global improvement in the signs of rosacea stayed significantly higher in the group treated with the test formula compared to the one treated with the vehicle (Figure 4). The formula containing Ambophenol, Neurosensine, and La Roche-Posay thermal spring water helped prolong the efficacy of the Metronidazole treatment.

DISCUSSION

Topical agents provide the mainstay of treatment for many patients with rosacea. The three primary drugs approved for the topical treatment of rosacea are azelaic acid, metronidazole and sodium sulfacetamide-sulphur.[1] Their efficacy has been validated by multiple studies. A number of other topical therapies are used in rosacea but are not approved for the indication.[1] This also includes adapted skincare and cosmetics. We have evaluated the test formula in association to various topical therapies with good tolerance and satisfaction.

We have also shown that the test formula in erythro-couperosis patients can significantly reduce redness and telangiectasia intensity after a 1 month treatment and that this effect was prolonged even 1 week after the end of treatment.

Rosacea does not only have a detrimental effect cosmetically, but also leads to a distinct decrease in quality of life which, according to the latest studies, is nonetheless less conspicuous than in the case of atopic eczema, psoriasis or acne.[2,9,10] Care must be taken to avoid psychosomatic co-morbidities, such as anxiety and personality disorders. In addition to the visible aspects of this disease, it can have a psychosocial impact that must be evaluated when considering the treatment options. By improving the physical appearance of the skin by reducing erythema, the disabling psychological and social consequences of the condition can be relieved, and patients' quality of life and confidence improved. In this case the test formula improved not only clinical signs and symptoms and skin reactivity to "trigger factors" but also social, physical, and psychosocial impacts of the disease.

The chronic nature of rosacea and the need for lifelong treatment requires chosen therapies to be effective, safe and well tolerated. Patient education and skincare counseling need to be highlighted as having a major role in the management of this complex and chronic disease. Provision of instructions on skin care and cosmetics to female acne patients influenced quality of life positively compared with a group of patients in which no instructions about make-up were given.[21,22] It is likely that these results can be extrapolated to rosacea, in which fewer studies investigating quality of life have been performed. A recent study showed that patient quality of life is improved by make-up in disfiguring skin diseases, including rosacea.[23] As ultraviolet light is a recognized trigger for rosacea, patients should use regular applications of a high-factor sunscreen embracing protection against UVB and UVA light wavelengths.

CONCLUSION

These studies highlight the value of a specifically designed and packaged skincare product containing Ambophenol, Neurosensine, and La Roche-Posay thermal spring water in monotherapy or in combination with or after therapeutic treatment in the global management of patients suffering from rosacea.

DISCLOSURES

These studies were funded by La Roche-Posay Pharmaceutical Laboratories France. All the authors excepted M. Sakalikova, L. Gibejova and H. Zelenkova, are employees of L'Oréal.

ACKNOWLEDGEMENTS

Amy Whereat provided proofreading services.

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