Evaluation of a Topical Anti-inflammatory/Antifungal Combination Cream in Mild-to-moderate Facial Seborrheic Dermatitis

An Intra-subject Controlled Trial Examining Treated vs. Untreated Skin Utilizing Clinical Features and Erythema-directed Digital Photography

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ABSTRACT

Objective: To evaluate if nonprescription topical agents may provide positive outcomes in the management of mild-to-moderate facial seborrheic dermatitis by reducing inflammation and scale production through clinical evaluation and erythema-directed digital photography. **Setting:** Open-label, prospective, not-blinded, intra-patient, controlled, clinical trial (target area). **Participants:** Twenty adult subjects affected by mild-to-moderate facial seborrheic dermatitis were enrolled and instructed to apply the study cream two times daily, initially on a selected target area only for seven days. If the subject developed visible improvement, it was advised to extend the application to all facial affected area for 21 additional days. **Measurement:** Efficacy was evaluated by measuring the grade of erythema (by clinical examination and by erythema-directed digital photography), desquamation (by clinical examination), and pruritus (by subject-completed visual analog scale). Additionally, at the end of the protocol, a Physician Global Assessment was carried out. **Results:** Eighteen subjects completed the study, whereas two subjects were lost to follow-up for nonadherence and personal reasons, respectively. Day 7 data from target areas showed a significant reduction in erythema. At the end of study, a significant improvement was recorded for erythema, desquamation, and pruritus compared to baseline. Physician Global Assessment showed improvement in 89 percent of patients, with a complete response in 56 percent of cases. **Conclusion:** These preliminary results indicate that the study cream may be a viable nonprescription therapeutic option for patients affected by facial seborrheic dermatitis able to determine early and significant improvement. This study also emphasizes the advantages of using an erythema-directed digital photography system for assisting in a simple, more accurate erythema severity grading and therapeutic monitoring in patients affected by seborrheic dermatitis. (*J Clin Aesthet Dermatol.* 2015;8(9):33–38.)

Seborrheic dermatitis (SD) is a common chronic, recurrent, inflammatory skin disorder that most commonly affects adults.[1–8] Evidence suggests that topical drugs are effective in the management of facial SD by reducing inflammation and scale production.[9–14] These principally include corticosteroids (1% hydrocortisone cream)[15] and antifungals (2% ketoconazole cream/gel, 1% ciclopiroxolamine cream, 1% terbinafine cream).[15–20] Further to these conventional approaches to management, various other drugs have been reported to have therapeutic benefit, including 0.75 to 1% metronidazole gel,[21–23] 5% benzoyl peroxide gel,[24] 8% lithium succinate/8% lithium gluconate ointment,[25–27] 1% pimecrolimus cream,[28–34] and 0.1% tacrolimus ointment[35–37] (Table 1).

Various nonprescription agents may provide positive outcomes in the management of mild-to-moderate SD, as

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TABLE 1. Anti-inflammatory/antifungal combination cream in the treatment of mild to moderate facial seborrheic dermatitis: laboratory and *in vivo* studies

LABORATORY STUDY			
AUTHOR	**STUDY DESIGN**	**DATA ASSESSMENT**	**RESULTS**
Nalamothu 2009	Promiseb cream vs. 0.77% ciclopirox olamine cream vs. no treatment (once daily for 7 days on guinea pig skin)	Microbiologic: evaluation of *Malassezia Spp.* CFUs/g	Reduction of CFUs/g from 5.03 (baseline) to <1.45 (Promiseb) vs. <1.45 (ciclopirox olamine) vs. 3.61 (no treatment)

IN VIVO STUDIES				
AUTHOR	**STUDY DESIGN**	**PTS (#)**	**DATA ASSESSMENT**	**RESULTS**
Veraldi 2008	Double-blind, placebo-controlled RCT: Sebclair cream vs. placebo (twice daily for 28 days)	60	Clinical: evaluation of erythema, desquamation by IGA, and measurement of itch by VAS	68% (Sebclair) vs. 11% (placebo) improvement of erythema, desquamation, and statistical reduction of itch
			Self-assessment: evaluation of efficacy by questionnaires	57% better response (Sebclair cream) vs. 10% (placebo)
Kircik 2009	Open controlled CT: Promiseb cream vs. no treatment (twice daily for 7 days)	10	Microbiologic: evaluation of *Malassezia Spp.* CFUs/g	94% (Promiseb) vs. 49% (no treatment) reduction of CFUs/g from baseline
Elewski 2009	Multicenter, single-blind, comparative RCT: Promiseb cream vs. 0.05% desonide cream (twice daily for 28 days)	77	Clinical: evaluation of erythema, desquamation by IGA, and measurement of itch by VAS	85% (Promiseb) vs. 92% (desonide cream) improvement of erythema, desquamation, and itch at 14 days; 71% (Promiseb) vs. 14% (desonide) at 28 days

CFUs/g=Colony Forming Units per gram; IGA=Investigator's Global Assessment; VAS=Visual Analog Scale (0–100mm)

supported by laboratory and *in vivo* studies (Table 1).[39–43] The efficacy of these agents for SD has historically been evaluated by clinical assessment alone, often by Physician Global Assessment (PGA) scoring system. On clinical ground, however, changes in erythema during treatment are sometimes difficult to identify.

More definitive and modern methods that may be used to supplement PGA include advanced digital photography techniques that provide quantifiable data for assessment of conditions such as SD. Of particular interest is VISIA-CR™ imaging system (Canfield Scientific, Inc.), which enables separation of the unique color signatures of red skin components,[10] and is a useful tool for evaluation of intensity of erythema before and after treatment in patients affected by inflammatory dermatoses, including SD.[44,45]

The aim of this trial was to assess the efficacy and tolerability of a combination nonsteroid, anti-inflammatory/antifungal cream in the treatment of adult patients with mild-to-moderate facial SD by scoring clinical parameters, including grade of erythema, desquamation, and itch.

MATERIALS AND METHODS

This clinical investigation was performed in accordance with Good Clinical Practices and the Declaration of Helsinki 1996. A written informed consent was obtained from each subject before study procedures were started.

Study design and methodology. From October 2013 to February 2014, the authors conducted an open-label, prospective, non-blinded, intra-patient, controlled clinical trial (target area), on efficacy and safety of a topical product principally containing 1.2% bisabolol, 1% piroctone olamine, 1% alglycera, and 0.01% telmesteine. (Sebclair® cream; Sinclair Pharmaceuticals Ltd, Godalming, Surrey, UK: EU class II medical device; known as Promiseb in the U.S.; Promiseb, Promius Pharma, LLC, Bridgewater, New Jersey). To reduce potential confounding issues, all subjects were assessed by the same investigator.

Enrolled subjects were instructed at baseline (T0) to apply the study cream twice daily to the selected target area (up to 10cm^2) located on the glabella (10 subjects) or on the nasofacial folds (10 subjects) for seven days (T1).

If the subject developed visible improvement at T1, then the subject was instructed to extend the application to all facial affected SD areas for three additional weeks, with assessments at Day 14±2 days (T2) and at Day 28±2 days (T3). Follow-up to two months from the time treatment ended was carried out for all patients.

Inclusion/exclusion criteria. Enrolled subjects were adults, of either sex, affected by mild-to-moderate facial SD with visible erythema, who underwent a wash-out period of two weeks minimum for topical antifungal and corticosteroid agents, and of at least one month for oral antifungals, corticosteroids, and hormonal therapy. Exclusion criteria included concurrent exposure to sunlight and/or artificial ultraviolet sources and pregnancy. Topical cosmetic agents, such as mild cleansers, sunscreens, and decorative make-up, were allowed.

Subject demographic. Subject demographic information and anamnestic data are shown in Table 2.

Clinical evaluation. Grading of erythema was quantitatively evaluated by an imaging system (cross-polarized images obtained by RBX™ via the VISIA-CR™ system that is able to identify and highlight intensity of erythema as well as detail of vascular structures). Grading of erythema was accomplished by rating on a 4-point scale: 0=none (not red); 1=slight (mild red); 2=moderate (clearly red); 3=severe (red violet).

Desquamation was rated by clinical observation using a 4-point scale: 0=none (no desquamation); 1=slight (few small loose white flakes); 2=mild (several small to large loose white flakes); 3=severe (many large adherent white flakes).

Measurement of pruritus was carried out by subject-completed Visual Analog Scale (VAS): 0=no pruritus; 100mm=severe pruritus.

To assess efficacy at four weeks, the PGA was determined using a 6-point scale: 0=complete response (>90% improvement); 1=excellent response (70–90% improvement); 2=moderate response (40–70% improvement); 3=mild response (<40% improvement); 4=no response (no change); 5=worsening.

Investigator evaluation of product tolerability was carried out by a 4-point scale: 0=very poor; 1=poor; 2=good; 3=excellent. In addition, subjective cosmetic acceptability was evaluated at Week 4 by a 3-point scale: 0=poor; 1=good; 2=excellent.

Study endpoints. Primary endpoints for efficacy were at one week (T1) the evaluation of all clinic parameter scores (erythema, desquamation, pruritus) recorded for the targeted area of facial SD compared to untreated areas in the same subjects, and at four weeks (T3) the evaluation of the same scores on the entire affected areas compared to baseline. The secondary endpoint was the evaluation of tolerability and cosmetic acceptability.

Statistical analysis. Data were evaluated using Kruskal-Wallis, nonparametric analysis of variance (ANOVA) test. All analyses were performed using Analyze-it for Microsoft Excel (version 3.0, Analyze-it Software, Ltd.).

TABLE 2. Demographic characteristics and anamnestic data

Sex	
Female	6
Male	14
Age (years)	
mean	44.1
range	21–70
SD clinical severity (baseline)	
Mild	7
Moderate	13
SD duration (years)	
≤5	7
6–10	9
≥10	4
Duration of current episode (months)	
Mean	5
Range	4–9
Pattern of disease	
Persistent	8
Intermittent	12

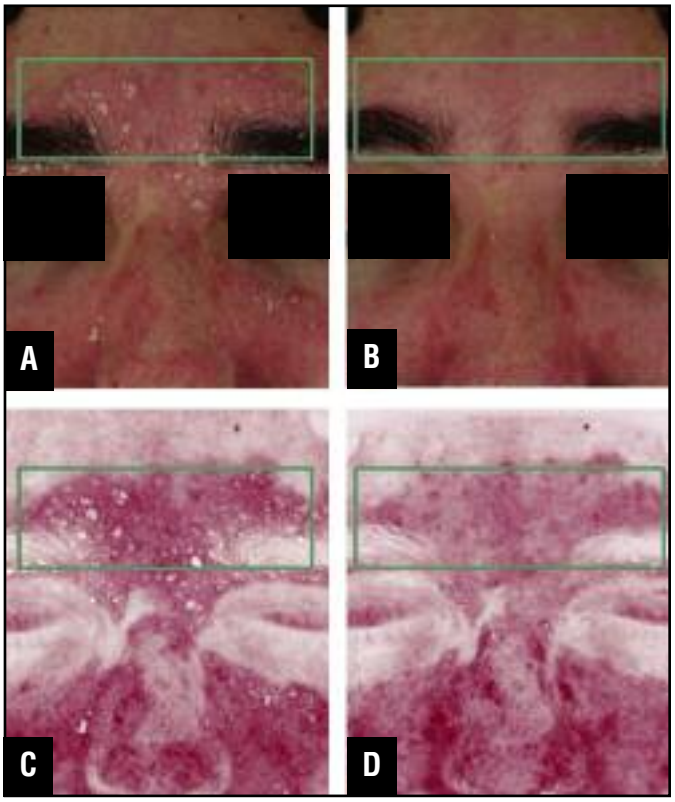

Figure 1. Standard and erythema-directed digital photography of a target area of a patient affected by moderate seborrheic dermatitis before (A and C) and after 7 days of treatment (B and D) showing significant reduction of erythema compared to untreated areas

TABLE 3. Study results

		MEDIAN*	1ST TO 3RD QUARTILE	*P*-VALUE
Erythema	T0 T1 T2 T3	2 1.5 1 1	2–3 1–2 1–2 0–1	 *p*=0.0020** *p*=0.0010** *p*=0.0001**
Desquamation	T0 T1 T2 T3	2 1 0.5 0	1–2 1–2 0–1.1 0–1	 n.s.*** *p*=0.0035** *p*=0.0002**
Itch	T0 T1 T2 T3	25 20 8.5 0	20–51.3 10–25.4 0–20.1 0–0	 n.s.*** *p*=0.0027** *p*=0.0001**

*median values = numerical values separating the higher half of a data sample, a population, or a probability distribution, from the lower half
***p*-values for significant differences toward T0
***n.s. = no significant difference

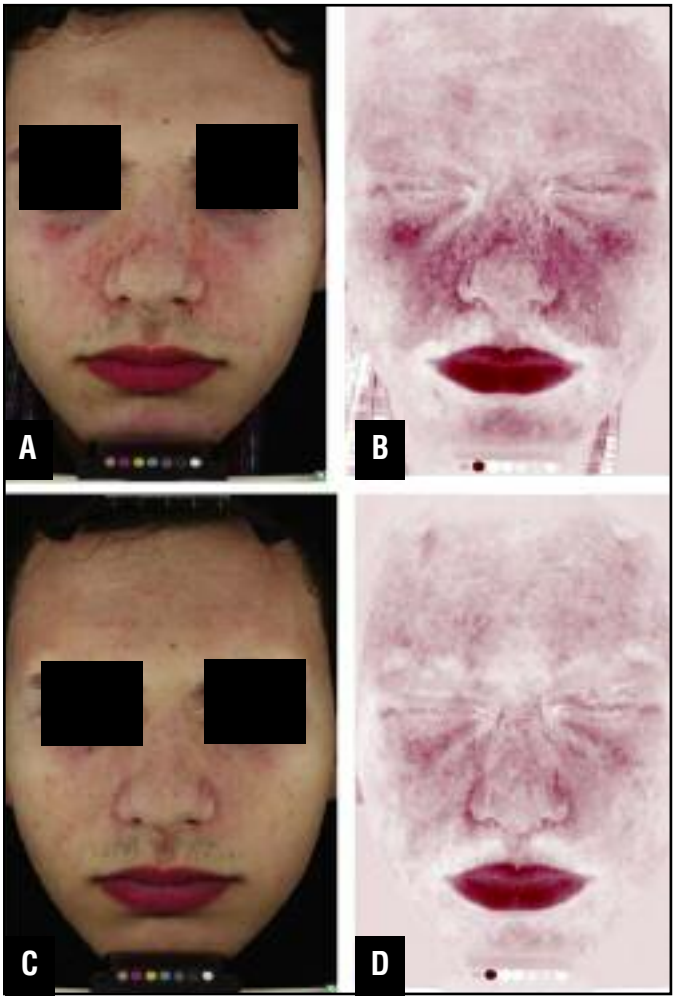

Figure 2. Standard and erythema-directed digital photography of a patient affected by mild seborrheic dermatitis before (A and B) and after 28 days of treatment (C and D) showing complete response

RESULTS

Twenty subjects (14 males, 6 females), mean age 30.7 years (range 21–70), affected by mild (n=7) or moderate (n=13) SD were enrolled (Table 2).

Eighteen subjects (90 percent) (mild: n=7; moderate: n=11) completed T1, whereas two subjects (both moderate SD) were lost to follow-up for nonadherence and personal reasons, respectively.

T1 data in all 18 subjects showed in the target area a statistically significant reduction of erythema from baseline compared to no change in the untreated adjacent area (median from 2 to 1.5; p=0.002), a non-significant reduction in desquamation (median from 2 to 1; p=0.1630), and a non-significant reduction in pruritus (median from 25 to 20; p=0.1919) (Figure 1). At T3, a statistically significant reduction was found for erythema from baseline (median from 2 to 1; p=0.0001), for desquamation (median from 2 to 0; p=0.0002), and for pruritus (median from 25 to 0; p=0.0001). Results are summarized in Table 3.

At the end of study period, PGA showed complete response in nine subjects (50%) (Figures 2 and 3), excellent response in two subjects (11%), moderate response in three subjects (17%), mild response in two (11%), and no change in two (11%). No signs of local intolerance were observed for any subject. Cosmetic acceptability was rated as "excellent" in 15 subjects and as "good" in the remaining three subjects.

DISCUSSION

This pilot, open label, intra-subject, controlled trial using clinical and advanced digital photography evaluation of facial SD indicates that the nonsteroidal formulation of combined ingredients is an efficacious treatment approach for 50 percent of patients with mild-to-moderate SD. No serious side effects were recorded for the 18 subjects who completed the study. Of note, a complete response was maintained at a two-month follow-up, suggesting a potential for some duration of action that may delay relapse that commonly occurs after SD therapy is discontinued. Also, the erythema in the selected target area significantly improved compared to the adjacent unaffected area after only one week of treatment.

The effect of the study cream in SD may be related to combined multiple mechanisms of action of the active ingredients, including 8% isohexadecane, 6% shea butter, 1.2% bisabolol, 1% vitamin E, 1% piroctone olamine, 1% alglycera, 0.35% allantoin, 0.1% *Vitis vinifera,* and 0.01% telmesteine. Isohexadecane and shea butter (extracted from *Butyrospermum parkii* rich in linoleic acid, phytosterols and tocopherols) have emollient properties, whereas bisabolol and vitamin E, show antioxidant/anti-inflammatory effects; the former has demonstrated *in vitro* of downregulating human polymorphonuclear neutrophil (PMN) release of reactive oxygen species (ROS),[46] and the latter to reduce the production of lipid peroxyl radicals.[47] Piroctone olamine is a well-known antifungal agent that may act on *Malassezia spp* by chelation of iron and other

elements. Alglycera, or allantoin glycyrrhetinic acid, combines the anti-inflammatory properties typical of the related compound glycyrrhetinic acid, with those of allantoin. The latter is an effective moisturizer that increases the water content of the extracellular matrix and has a mild keratolytic effect by enhancing the desquamation of upper layer corneocytes; in addition, it has soothing action and minimizes pruritus.[48] Finally, *Vitis vinifera* (grapevine) has shown to block endothelial oxidative damage, and telmesteine exhibits anti-inflammatory, soothing, and antipruritic effects.[43,48] The study cream is also formulated with vehicle ingredients (ethylhexylpalmitate, cera alba, butylen glycol, propyl gallate), which further improve the moisturizing action of the product, and is fragrance-free to reduce the risk of irritant and allergic contact dermatitis.

In conclusion, the results of this study are in agreement with those from other similar trials using these combined agents.[39–41] It also emphasizes the advantage of using an erythema-directed digital photography system for assisting in a simple, more accurate erythema severity grading and therapeutic monitoring of patients affected by seborrheic dermatitis.

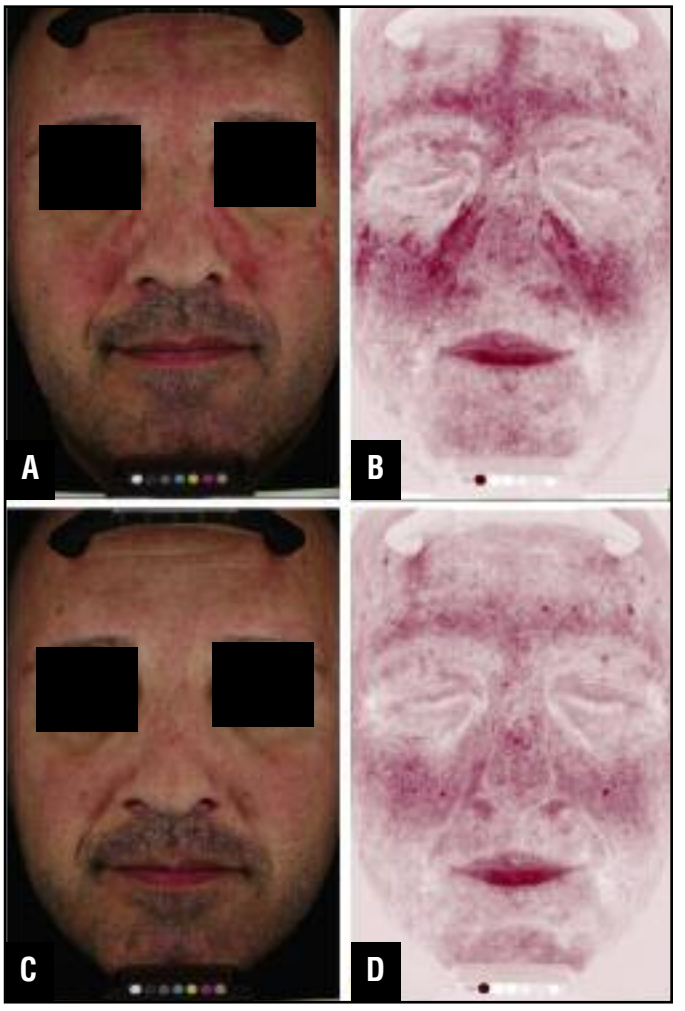

Figure 3. Standard and erythema-directed digital photography of a patient affected by moderate SD before (A-B) and after 28 days of treatment (C-D) showing complete response

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