Noncorticosteroid Combination Shampoo versus 1% Ketoconazole Shampoo for the Management of Mild-to-Moderate Seborrheic Dermatitis of the Scalp: Results from a Randomized, Investigator-Single-Blind Trial Using Clinical and Trichoscopic Evaluation

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Introduction

Seborrheic dermatitis (SD) is a common chronic, recurrent, inflammatory skin condition that most commonly affects the scalp and face of adolescent and adult patients [1–7]. Scalp SD may range from loosely adherent, small white flakes (dandruff) to yellowish, oily scales. They may accumulate in localized patches or may be distributed diffusely on the scalp surface. Erythema and pruritus are generally present [8, 9].

The pathogenesis of SD is still unclear, but it seems to be multifactorial, involving sebaceous gland function,
the presence on the skin of yeasts belonging to *Malassezia* spp. (formerly called *Pityrosporum ovale*), and the individual immunological response [5–6, 10]. In particular, *Malassezia* yeasts act by digesting sebaceous triglycerides and producing free fatty acids which in turn promote inflammation in susceptible individuals [2, 8]. Additional precipitating factors include neurological and degenerative disorders (Parkinson’s disease), immune suppression (HIV and non-HIV related), genetic disorders (trisomy 21), as well as physical and psychological stress [1, 11].

Available treatments for scalp SD are intended to eradicate *Malassezia* spp. and to reduce inflammation and scaling [9, 12, 13]. Topical therapies are the mainstay of treatment as the condition is recurrent and responds well to these agents [2].

According to two recent Cochrane reviews, some topical drugs, including corticosteroids (0.1–1% hydrocortisone, 0.05–0.1% betamethasone, 0.05% clobetasol, 0.1% amcinonide, 0.1% mometasone, 0.01% fluocinolone acetonide) and antifungals (1–2% ketoconazole, 1% ciclopirox), are effective in scalp SD by reducing inflammation, scaling, and itch when compared to placebo [14, 15]. However, their prolonged application is associated with some disadvantages, including skin atrophy, folliculitis, and tachyphylaxis for corticosteroids, and irritant contact dermatitis for antifungals such as ketoconazole [16]. Therapeutic options such as topical noncorticosteroid antiinflammatory/antifungal combinations may represent a promising therapeutic approach as evidenced by some clinical trials [11–13, 17–20].

One of the Cochrane reviews also highlighted that better outcome measures are needed to improve the evidence base for SD treatment [15]. So far, the most common therapeutic monitoring for SD is based on clinical assessment, although the identification of minimal changes may sometimes be difficult. Scalp dermoscopy or trichoscopy, which allows a magnified view of the scalp with image capture/storage facility, is a noninvasive tool for the diagnosis and treatment monitoring that has shown to be useful in some inflammatory scalp disorders [21–23].

The aim of this 1:1 sequentially randomized, controlled, investigator-single-blind clinical trial was to assess, by clinical and trichoscopic examination, the efficacy and tolerability of a combination noncorticosteroid, antiinflammatory/antifungal shampoo compared to 1% ketoconazole shampoo in the treatment of adult patients with mild-to-moderate scalp SD.

### Materials and Methods

#### Study Design and Methodology

This clinical investigation was performed in accordance with Good Clinical Practices and the Declaration of Helsinki 1996.

Twenty patients attending the Dermatology Clinic of the University of Catania from November 2013 to April 2014 and affected by mild-to-moderate scalp SD were enrolled. Inclusion criteria were age >16 years, 2-week wash-out from topical antifungals/corticosteroids, and 4-week wash-out from oral antifungals/corticosteroids and hormonal therapy. Exclusion criteria were recent sun exposure and pregnancy. A written informed consent was obtained from each subject before the study procedures were conducted.

The patients were randomized into two groups (A and B). Patients of group A (10 cases) used a combination shampoo containing piroctone olamine, *Vitis vinifera* lactis acid, lactoferrin, dipotassium glycyrrhizate, and telmesteine (Sebclair® shampoo, Sinclair Pharmaceuticals Ltd., Godalming, UK), while patients of group B (10 cases) used 1% ketoconazole shampoo (Triatop® 1% shampoo, Janssen Cilag SpA). All patients applied the shampoo 3 times a week every other day for 8 weeks. A 1-month follow-up after the end of treatment was carried out for both groups of patients. To reduce potential confounding issues, all subjects were assessed by the same physician investigator (dermatologist).

#### Subject Demographics

Subject demographic information and anamnestic data are shown in table 1.

<table>
<thead>
<tr>
<th>Table 1. Demographic characteristics and anamnestic data</th>
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<tr>
<td><strong>Group A</strong></td>
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<td>Sex</td>
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<td>SD clinical severity (baseline)</td>
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<td>Duration of current episode, months</td>
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<td>Pattern of disease</td>
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<tr>
<td>Persistent</td>
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<td>Intermittent</td>
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#### Clinical Evaluation

Efficacy was assessed by measuring the degree of scaling and pruritus at baseline, weeks 4 and 8. Scaling was evaluated by ×20 magnification using a dermatoscope (VitaScope®), and pruritus was measured by a 0–10 visual analog scale. Clinical responses were defined as: *Improvement* (score reduction ≥1 point), *no change* (score reduction 0), or *worsening* (score increase ≥1 point).

#### Clinical Endpoints

Clinical endpoints were validated by a dermatologist investigator (dermatologist) at baseline and after 8 weeks.

#### Statistical Analysis

Statistical analysis was done using the SPSS 17.0 software package (IBM Corp., Armonk, NY, USA). Normally distributed data were compared by using Student’s t test, and categorical variables were compared using the chi-square test. A p value of 0.05 or less was considered significant.
trichoscopy (Hi-Scope KH-2200, Hirox Co. Ltd., Tokyo, Japan) using a 4-point scale: 0 = none (no desquamation); 1 = mild (few small loose white flakes); 2 = moderate (several small to large loose white flakes), and 3 = severe (many large adherent white flakes). The measurement of pruritus was carried out by a subject-completed Visual Analogue Scale: 0 = no pruritus; 100 mm = severe pruritus.

Additionally, a Physician Global Assessment (PGA) was conducted at the end of the study using a 6-point scale: complete response (>90% improvement); excellent response (70–90% improvement); moderate response (40–69% improvement); mild response (<40% improvement); no response (no change), and worsening.

An investigator evaluation of product tolerability was carried out with the help of a 4-point scale: 0 = very poor; 1 = poor; 2 = good, and 3 = excellent. In addition, subjective cosmetic acceptability was evaluated at week 4 by a 3-point scale: 0 = poor; 1 = good, and 2 = excellent.

**Study Endpoints**
The primary endpoint was the efficacy evaluation of the tested products at weeks 4 and 8. The secondary endpoint was the evaluation of tolerability and cosmetic acceptability.

**Statistical Analysis**
Data were analyzed using the Kruskal-Wallis nonparametric analysis of variance (ANOVA) test. Analyses were conducted using the SPSS statistical software package (p < 0.05).

**Results**
All participants completed the study. At 4 weeks, there was a significant reduction of scaling from baseline for both groups (group A: median from 2.5 to 1.5; p < 0.01; group B: median from 2.5 to 1.5; p < 0.01; table 2). Pruritus showed a significant reduction only for group A (median from 70 to 30; p < 0.01; fig. 1, 2) and of pruritus (group A: median from 70 to 20; p < 0.01; group B: median from 70 to 30; p < 0.01) for both groups (table 2).

PGA showed a complete response in 90% of the cases for both groups. Overall, tolerability was rated as excellent (no sign of irritation) in 95% of the patients in group A and in 80% of the patients in group B (table 3). The cosmetic acceptability was rated as excellent in 90% of the subjects in group A and 70% of the subjects in group B (table 3).

The efficacy seen at the end of treatment was maintained for both groups at the 1-month follow-up.

**Discussion**
Scalp conditions with visible flaking, such as SD, have a negative impact on the patient’s quality of life and should be properly treated [8]. In our study, the noncorticosteroid combination shampoo has shown to be a safe and effective treatment approach for 90% of the patients with mild-to-moderate SD and, in particular, was noninferior to 1% ketoconazole shampoo. Ketoconazole shampoo in concentrations ranging from 1 to 2% is considered one of the most effective treatments for scalp SD as confirmed by several randomized controlled trials [15].
Although both tested products proved to be safe and efficacious for SD after 8 weeks, the combination shampoo was assessed as better than ketoconazole to control pruritus at 4 weeks. Moreover, the efficacy for both groups was maintained at the 1-month follow-up after therapy discontinuation.

The effect of the combination shampoo in SD may be related to multiple mechanisms of action of the active ingredients. Piroctone olamine is a well-known antifungal agent that may act on Malassezia spp. by chelation of iron and other elements. V. vinifera (grapevine) is able to block endothelial oxidative damage, and lactic acid is an effective keratolytic enhancing the desquamation of upper layer corneocytes. Finally, lactoferrin is a glycoprotein with recognized antimicrobial activity (bactericide and fungicide), dipotassium glycyrrhizate (extracted from liquorice root) has antiinflammatory, antioxidative, and antiirritant properties, and telmesteine exhibits anti-inflammatory, soothing, and antipruritic effects [12, 24]. The product is fragrance free, and its vehicle is formulated with some ingredients, such as olive oil and glycerin, for an additional moisturizing effect.

In our study, treatment outcome has been evaluated by trichoscopy, a technique that has demonstrated to allow for a simple, more accurate evaluation of scaling severity in patients with scalp psoriasis [25]. So far, no published studies using trichoscopic evaluation of SD treatment outcome are available.

In conclusion, the results of our study demonstrate that the combination noncorticosteroid, antiinflammatory/antifungal shampoo represents an alternative to standard topical treatment in the management of scalp SD. Moreover, trichoscopy proves to be an accurate and reliable therapeutic monitoring method for acquisition of quantifiable data during treatments of scalp SD. Further studies on a higher number of patients and with a long-term follow-up are needed in order to consolidate the approach proposed by our research.

**Statement of Ethics**

This clinical investigation was performed in accordance with Good Clinical Practices and the Declaration of Helsinki 1996.

**Disclosure Statement**

The authors declare no conflicts of interest.
References