Clobetasol Propionate Shampoo 0.05% in the Treatment of Seborrheic Dermatitis of the Scalp: Results of a Pilot Study

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Seborrheic dermatitis (SD), a common dermatosis associating hyperseborrhea, erythema, itching, and dandruff, has frequent scalp involvement. Malassezia furfur *infection seems to play an important role in the condition's etiopathology. Treatment of SD usually consists of corticosteroids or antifungals, such as ketoconazole. The aim of this multicenter, randomized, investigator-blinded, parallel-group pilot study was to evaluate the efficacy and safety of clobetasol propionate shampoo 0.05% after different short-contact application times compared with its vehicle and ketoconazole foaming gel 2% in the treatment of SD of the scalp. For 4 weeks, 55 subjects received one of the following treatments twice weekly: clobetasol propionate shampoo for 2.5, 5, or 10 minutes; clobetasol propionate vehicle for 10 minutes; or ketoconazole foaming gel for 5 minutes before rinsing off. Efficacy criteria included total severity score (TSS) and individual scores of signs such as itching and global improvement. Safety included reporting of burning, overall tolerance, and adverse events. Results showed that an application of clobetasol propionate for 5 and 10 minutes provided a similar mean percentage decrease of TSS, and the mean percentage decrease of TSS for all active groups was significantly superior to that of the vehicle (P≤.01). Overall and local safety were good for all treatment groups.*

The present pilot study demonstrated that a short-contact application of clobetasol propionate shampoo is effective and safe in the treatment of SD of the scalp.

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Seborrheic dermatitis (SD) is a common inflammation of the skin occurring most often on the face, scalp, and chest.[1,2] Symptoms of the disease include hyperseborrhea and erythema, as well as itching and dandruff, which affect the daily quality of life. In some patients, flexural areas also may be involved. SD tends to present around puberty, a time when skin lipids increase. SD is a common disorder, affecting about 3% to 5% of the adult population and up to 83% of patients with AIDS.[3-5] It tends to be more prevalent in adolescents and in patients older than 50 years and is reported more often in males than females. SD may be caused by an abnormal host response or an inflammatory response to toxins or mediators produced by *Malassezia* yeasts.[6,7] These organisms are part of the normal human cutaneous flora.[8] However, under the influence of predisposing factors, these organisms can become pathogenic and are associated with several diseases, including *Malassezia* folliculitis, some forms of atopic dermatitis, and SD.[9]

Different treatments are available for SD, including topical and systemic antimycotics (eg, terbinafine, ciclopirox, ketoconazole), coal tar, and metronidazole.[10-15] Terbinafine and ciclopirox alone or in combination with salicylic acid provide

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satisfying efficacy results,[16,17] and ketoconazole was shown to be effective in treating scalp and nonscalp SD.[18,19] Ketoconazole is currently available as a 1% or 2% rinse-off foaming gel formulation to treat scalp SD.[19]

Known for their excellent efficacy and anti-inflammatory profile, corticosteroids have been used for many years to treat SD. However, because of safety concerns, corticosteroids are being replaced by antifungals. Additionally, studies evaluating the efficacy and safety of corticosteroids such as betamethasone dipropionate lotion 0.05% versus ketoconazole foaming gel demonstrated that the antifungal was more effective than betamethasone dipropionate and at least as effective as hydrocortisone cream 1% when applied once daily.[20,21]

However, the investigated corticosteroids mentioned earlier are of lower potency than clobetasol propionate, and, therefore, it was thought that a superpotent corticosteroid applied as a short contact treatment, such as in a shampoo, would provide similar efficacy results to ketoconazole without showing side effects typically associated with the use of a superpotent corticosteroid (eg, skin atrophy, hypothalamic-pituitary-adrenal [HPA] axis suppression, telangiectasia). As a result, clobetasol propionate shampoo 0.05% was designed to treat moderate to severe inflammatory scalp dermatoses.

Methods

The present study received approval from the national ethics committee before any subjects were enrolled and was conducted in accordance with the Declaration of Helsinki and its amendments. All subjects provided written informed consent before entering the study.

Study Design and Population—For this multicenter, randomized, investigator-blinded, parallel-group pilot study, 55 adults of either sex were recruited. Individuals had to present with scalp SD defined as a total severity score (TSS; sum of erythema, loose desquamation, and adherent desquamation) of 2 or more. Subjects using topical or systemic anti-SD therapies were to respect treatment-specific washout periods (2 weeks for topical treatments [eg, antifungals, coal tar, salicylic acid preparations] and 3 weeks for systemic treatments [eg, psoralen plus UVA, corticosteroids, antifungals]).

Treatments—Subjects were randomized according to a computerized randomization schedule to receive a 4-week treatment with either clobetasol propionate shampoo 0.05% for 2.5, 5, or 10 minutes; clobetasol propionate vehicle for 10 minutes; or ketoconazole foaming gel 2% for 5 minutes. All treatments were to be applied twice weekly on wet hair and to be rinsed off after the specific application time. Because of the different appearance of the shampoo and foaming gel formulations, blinding of the treatments' identity to the subjects was not possible. Blinding for investigators was maintained by using independent study personnel to dispense medication and collect returned medication. Subjects were advised not to discuss the study medication with the investigator.

Efficacy and Safety Assessments—At each visit, efficacy assessments included evaluations of erythema and desquamation (loose and adherent) on each quarter of the scalp. Signs were evaluated using a 7-point scale from 0 to 3, with half points being permitted; TSS and a mean score for each sign were calculated for the whole scalp.

Other evaluations included itching, assessed at each visit by the subject on a 100-mm analog scale, and global improvement assessed by the investigator on a 7-point scale, (−1=worse than baseline; 5=clear) at each visit following baseline. Safety evaluations included burning assessed on a 7-point scale from 0 to 3 (half points being permitted) and overall tolerance, assessed throughout adverse event reporting.

Statistical Analysis—A previous clinical study indicated that the reduction in dandruff severity score after 4 weeks was 73% with ketoconazole compared with 44% with placebo.[22] Based on these results, 11 subjects per group (55 subjects total) were deemed sufficient to detect a similar effect with 80% power, using a 2-tailed test performed at a 5% level of significance and assuming an estimated 24% between-subject standard deviation.

The intent-to-treat population consisted of the entire population enrolled and randomized. No data was excluded from this population. The per-protocol population consisted of all enrolled and randomized subjects, except subjects or visits considered as not evaluable because of major deviations from the protocol. The safety population was the intent-to-treat population, excluding subjects having never applied the treatment with certainty.

Efficacy criteria and incidence of burning within each active treatment group were compared with the vehicle group using a 2-tailed Mann-Whitney test. A .05 probability level was used to declare significance. Safety was analyzed using the Fisher exact test.

Results

Subject Disposition at Baseline—A total of 55 subjects from 5 centers located in France were randomized

into the study. Each treatment group consisted of 11 subjects. During the study, 4 subjects withdrew: 1 subject in the clobetasol propionate 10-minute group and 1 subject in the clobetasol propionate 5-minute group (both for administrational reasons), as well as 2 subjects in the clobetasol propionate vehicle group (1 at subject's request and 1 because of lack of efficacy). Of the 55 randomized subjects, 54.5% (30) were men and 45.5% (25) were women. The proportion of men and women was similar in each treatment group, except in the clobetasol propionate 10-minute group, which was comprised of more than 80% (9/11) men. All treatment groups were comparable in race and age (Table).

At baseline, the mean±standard deviation scores for all subjects were TSS, 3.5±1.2; erythema, 1.1±0.5; itching, 45.1±22.8 mm; loose desquamation, 1.4±0.6; and adherent desquamation, 1.1±0.5. There were no significant differences between the treatment groups for any of the symptoms.

Efficacy—At the end of treatment, there was a statistically significant difference (all P values ≤.02) for the mean TSS between the active treatment groups with scores of 0.6, 0.7, and 0.8 for the clobetasol propionate 5-minute, 10-minute, and 2.5-minute groups, respectively; 0.7 for the ketoconazole group; and 2.6 for the vehicle group. Mean percentage decrease of the TSS from baseline to end point ranged from 75.6% (clobetasol propionate 2.5-minute group) to 82.3% (clobetasol propionate 5-minute group) in the clobetasol treatment groups and reached 76.9% for the ketoconazole group and 17.4% for the vehicle group (Figure 1). The difference between each of the active treatment groups and

Demographics and Baseline Characteristics (Intent-to-Treat Population)*

	Clobetasol Propionate 2.5 min (n=11)	Clobetasol Propionate 5 min (n=11)	Clobetasol Propionate 10 min (n=11)	Ketoconazole 5 min (n=11)	Clobetasol Propionate Vehicle 10 min (n=11)	Total (N=55)
Age, y						
Mean±SD	35.5±15.5	36.8±13.3	39.7±13.2	35.6±8.4	37.0±10.5	36.9±12.1
Minimum	20.0	18.0	20.0	25.0	23.0	18.0
Maximum	64.0	58.0	63.0	46.0	53.0	64.0
Sex, n (%)						
Male	5 (45.5)	5 (45.5)	9 (81.9)	5 (45.5)	6 (54.5)	30 (54.5)
Female	6 (54.5)	6 (54.5)	2 (18.2)	6 (54.5)	5 (45.5)	25 (45.5)
Fitzpatrick skin type, n (%)						
I	1 (9.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.8)
II	4 (36.4)	4 (36.4)	5 (45.5)	3 (27.3)	3 (27.3)	19 (34.5)
III	6 (54.5)	6 (54.5)	4 (36.4)	5 (45.5)	7 (63.6)	28 (50.9)
IV	0 (0)	1 (9.1)	2 (18.2)	3 (27.3)	1 (9.1)	7 (12.7)
Race, n (%)						
White/ Caucasian	11 (100)	11 (100)	11 (100)	10 (90.9)	11 (100)	54 (98.2)
Mixed race	0 (0)	0 (0)	0 (0)	1 (9.1)	0 (0)	1 (1.8)

*SD indicates standard deviation.

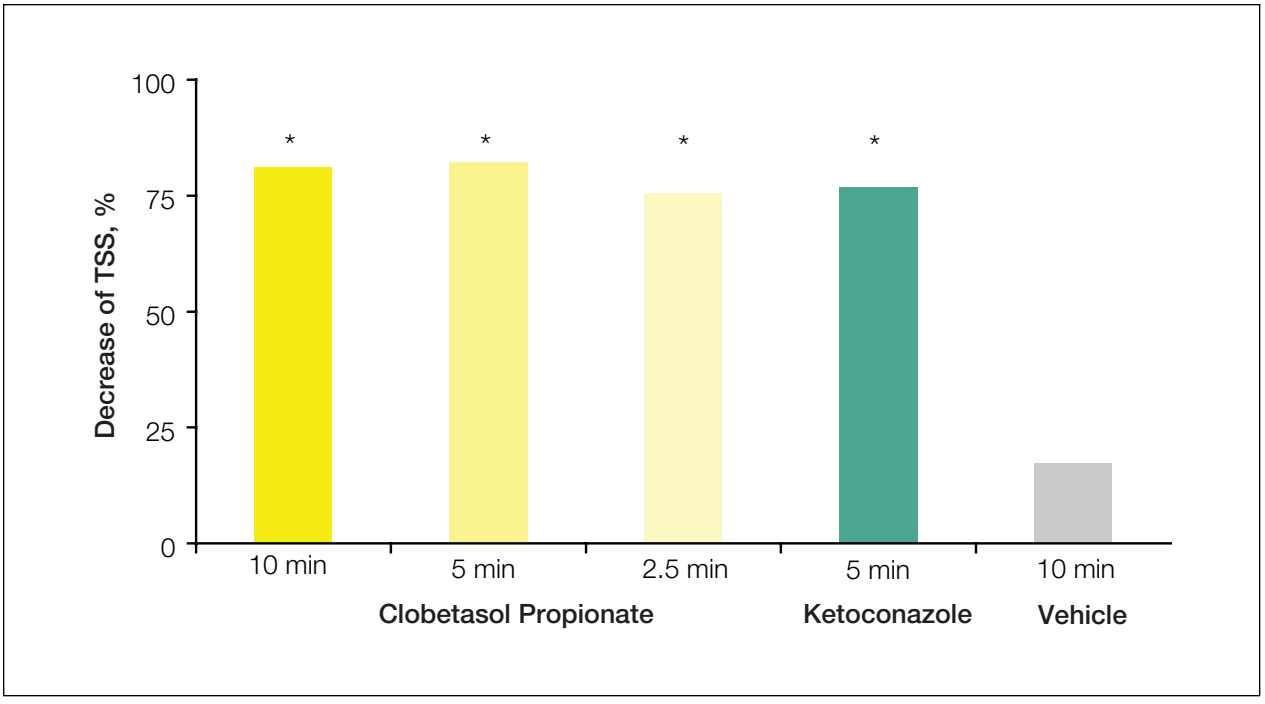

Figure 1. Mean percentage decrease of the total severity score (TSS) from baseline to week 4 (end point). Asterisk indicates $P \leq .01$ vs vehicle.

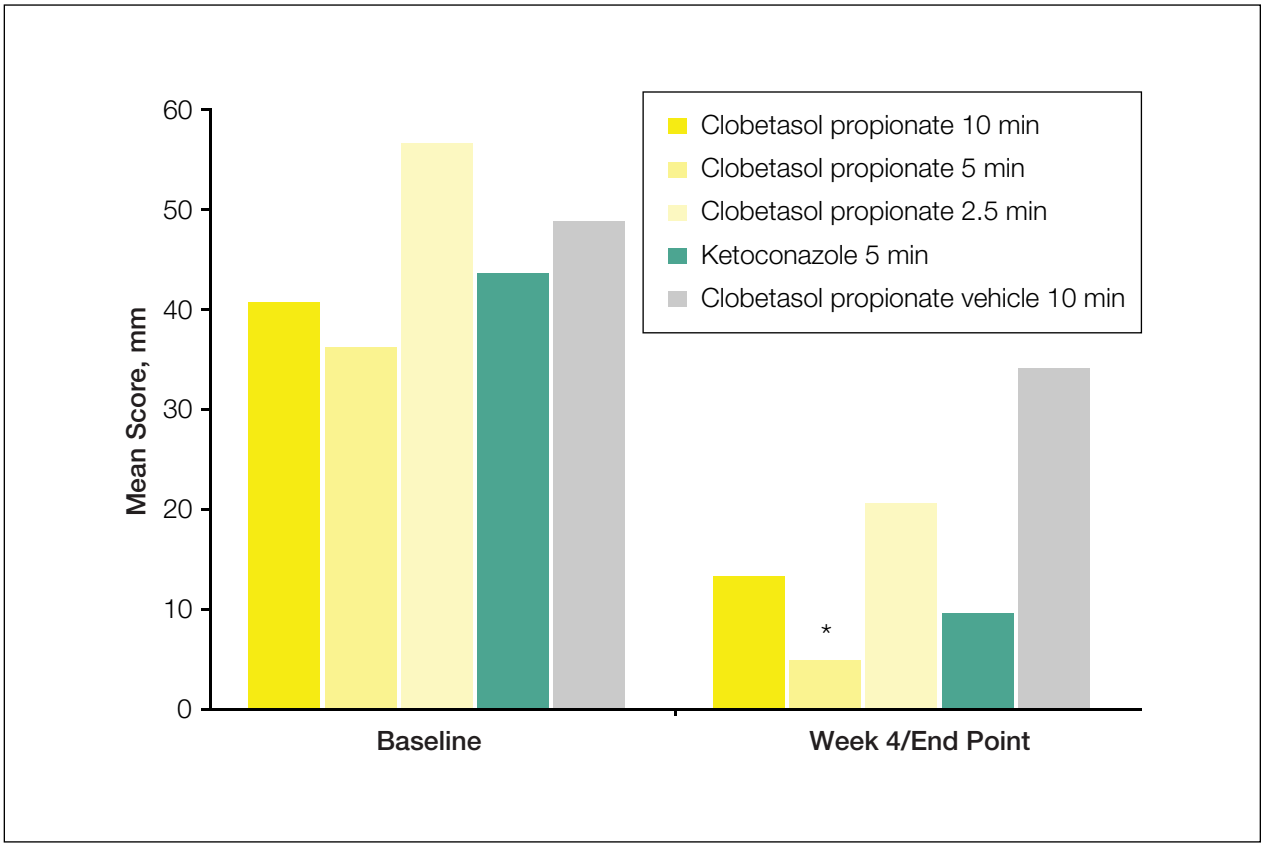

Figure 2. Mean score of itching at baseline and after 4 weeks of treatment. Asterisk indicates $P \leq .01$ vs vehicle.

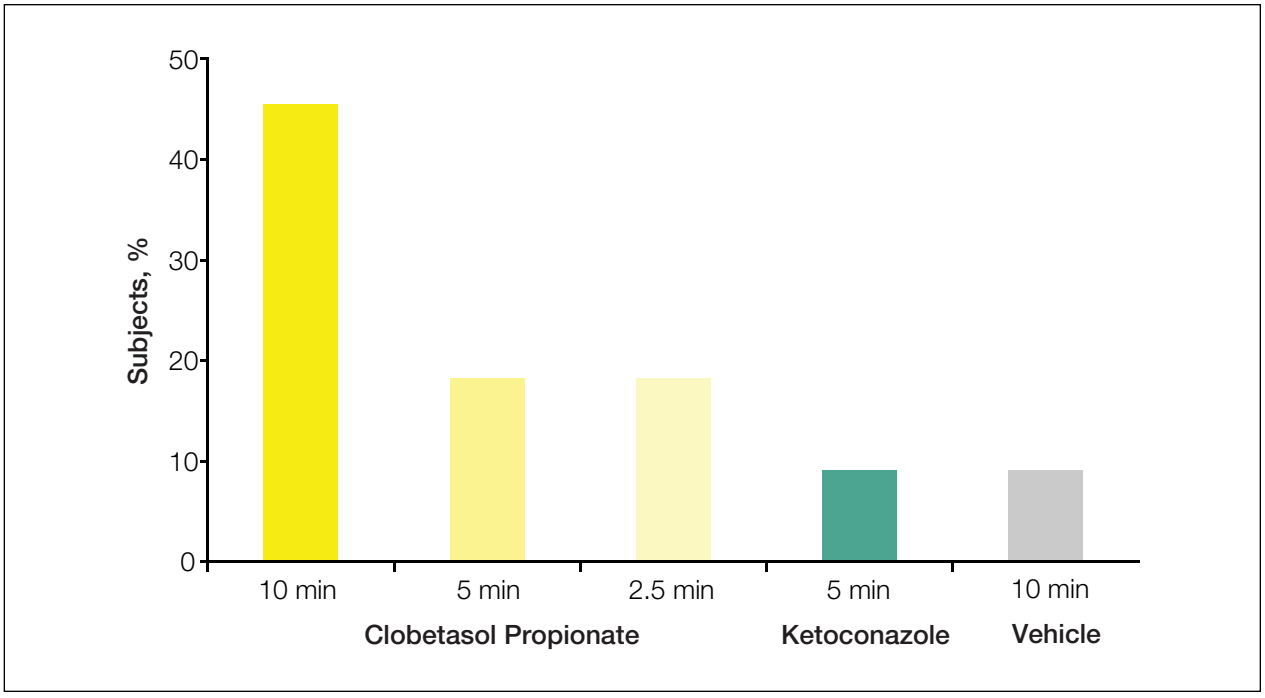

Figure 3. Percentage of subjects with complete clearance of seborrheic dermatitis after 4 weeks of treatment.

the vehicle was statistically significant, with *P* values not exceeding .01.

Differences for mean erythema scores between the vehicle (0.7) and active treatments were statistically significant for the clobetasol propionate 5-minute group (0.1; $P=.024$) and ketoconazole group (0.1; $P=.027$).

At end point, the mean score of itching had decreased from baseline in all treatment groups. The difference between the vehicle score (34 mm) and the active treatments was statistically significant for the clobetasol propionate 5-minute group only (4.8 mm; $P=.007$; Figure 2). The percentage of subjects with at least a marked global improvement at end point was higher in the active treatment groups (63.7% [7/11], 81.9% [9/11], 45.5% [5/11] in the clobetasol propionate 10-, 5-, and 2.5-minute groups, respectively, and 72.8% [8/11] in the ketoconazole group) than in the vehicle group (27.3% [3/11]). The difference between the vehicle and the 4 active treatment groups was statistically significant ($P\leq.05$).

For loose desquamation, the difference from vehicle (1.0) was statistically significant only for the clobetasol propionate 10-minute group (0.3; $P=.027$). A trend to significance was observed for the clobetasol propionate 5-minute group (0.4; $P=.051$). For adherent desquamation, a statistically significant difference from the vehicle (0.9) was shown for the clobetasol propionate 5-minute group (0.1; $P=.047$).

Complete clearance of SD was achieved in 45.5% [5/11] of clobetasol propionate 10-minute–treated subjects, being higher than with the other treatments (results ranging from 9.1% [1/11] for the ketoconazole and vehicle groups to 18.2% [2/11] for the clobetasol propionate 2.5- and 5-minute groups; Figure 3).

Safety—No serious adverse events were reported during the course of this study. A high percentage of patients in all 5 treatment groups (88.9% [8/9] for patients treated with the vehicle up to 90.9% [10/11]of the patients treated with clobetasol propionate) never experienced burning.

Treatment-related adverse events were reported by one subject in the clobetasol propionate 10-minute group (dry skin) and one subject in the clobetasol propionate 5-minute group (folliculitis). Treatment-related eczema was reported for one subject treated with the vehicle. The overall tolerance to all treatments was good, and no cases of skin atrophy, HPA axis suppression, or telangiectasia were reported.

Comment

Ketoconazole has successfully demonstrated its clinical efficacy in the treatment of dandruff and SD compared to nonsuperpotent corticosteroids, hence confirming its position as one of the preferred treatments of SD in Europe.[20,21] Clobetasol propionate shampoo 0.05% is a newly available formulation of a superpotent corticosteroid

thought to be an effective and safe option to ketoconazole in the treatment of SD. To assess the efficacy and safety profile of the new formulation, clobetasol propionate shampoo 0.05% was compared to the currently most used treatment in Europe, ketoconazole. The present multicenter investigator-blinded pilot study evaluated different short-time applications (2.5, 5, and 10 minutes) of clobetasol propionate shampoo 0.05%, a 5-minute application of ketoconazole foaming gel 2%, and a 10-minute application of clobetasol propionate vehicle.

The study illustrated that all active treatments showed a decrease in the mean TSS from baseline to week 4 significantly more than vehicle ($P \leq .02$).

Overall and local safety were good for all treatment groups. Corticosteroid-induced local and systemic side effects (skin atrophy, HPA axis suppression, and telangiectasia) that are currently described in the literature[23-27] were not reported with the shampoo formulation. An unpublished clinical study to evaluate HPA axis suppression of clobetasol propionate shampoo, performed in 26 subjects with SD of the scalp, confirmed this outcome—the shampoo formulation of this superpotent corticosteroid when applied twice weekly for 4 weeks did not induce any HPA axis suppression or skin atrophy.[28]

Conclusion

While *Malassezia* is thought to be the casual organism of SD and antifungal treatments are considered to be the most adequate treatments, the present results confirm that a short-contact application of clobetasol propionate shampoo may be an effective and safe alternative to ketoconazole in the treatment of SD of the scalp.

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