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CLINICAL REPORT

Scalp Psoriasis: Synergy Between the *Malassezia* Yeasts and Skin Irritation due to Calcipotriol

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To investigate if there is a synergy between the presence of the *Malassezia* yeasts and the adverse reaction during treatment of scalp psoriasis with calcipotriol scalp solution, patients were treated with itraconazole to reduce the number of *Malassezia* yeasts. This study was a double-blind, placebo-controlled parallel group study between oral itraconazole or placebo for 8 weeks in patients with scalp psoriasis. After 2 weeks, calcipotriol scalp solution was applied twice daily for 6 weeks. Altogether 137 patients, 67 in the itraconazole group and 70 in the placebo group, comprised the intention-to-treat population. There were 13 (19.4%) patients with local skin irritation in the itraconazole group compared to 33 (47.1%) in the placebo group ($p < 0.001$). The skin irritation was significantly lower in patients with a low number of cultured *Malassezia* yeasts ($p = 0.017$). Thus, when *Malasessia* was eliminated or the numbers reduced, the irritation produced by calcipotriol was significantly diminished. *Key words: itraconazole; side effects; topical vitamin D.*

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Calcipotriol, a vitamin D analogue manufactured by Leo Pharmaceutical Products (1), is now an established treatment for psoriasis (2, 3). Preclinical studies have demonstrated calcipotriol to have a high binding affinity to the cellular receptor for the biologically active form of vitamin D3 (1). Furthermore, calcipotriol has been shown to be both a potent regulator of cell differentiation and an inhibitor of cell proliferation in human keratinocytes (4). Its systemic effect on calcium metabolism in rats is 100 to 200 times less than of calcitriol (1). However, with respect to psoriasis of the face and scalp, calcipotriol in different formulations appears less successful (5, 6). The efficacy and safety of calcipotriol scalp solution (50 μg/ml) applied twice daily for 4 weeks have been compared with placebo in 2 double-blind studies (5, 6). The solution was significantly more effective than placebo (5) but inferior to betamethasone 17-valerate (6). Calcipotriol is usually a safe drug, but it may produce local irritation with redness, especially on the face and scalp. The adverse effect is often mild with only stinging or burning sensations, but frequencies of local adverse events up to 30% have been reported on the scalp or face during calcipotriol treatment (5, 6).

The lipophilic yeasts *Malassezia* (formerly *Pityrosporum* and the species name *Pityrosporum ovale*) are members of the normal human cutaneous flora and can be cultured from almost all body areas (7–10). The *Malassezia* yeasts are lipophilic and requires the addition of lipids to the culture medium for growth (7, 8). Under the influence of predisposing factors it becomes pathogenic and are associated with several diseases such as pityriasis versicolor, *Malassezia* (*Pityrosporum*) folliculitis, seborrhoeic dermatitis, some forms of atopic dermatitis, some forms of confluent and reticulate papillomatosis and systemic infections (7, 9).

The role of micro-organisms in psoriasis, especially the post-streptococcal guttate variety, is well known. Rivolta's description of round, double-contoured budding cells, which he called *Cryptococcus* psoriasis, in scales of psoriasis was the first association of lipophilic yeasts with this disease (11). There have also been other reports indicating a role of the *Malassezia* yeasts in psoriasis, especially psoriasis involving the scalp, eyebrows, ears and seborrhoeic areas of the trunk (12–15).

A high number of *Malassezia* yeasts are found in the same skin areas where skin irritation with calcipotriol is most commonly seen. The question is whether this is a coincidence or could *Malassezia* interfere with calcipotriol when calcipotriol is used to treat patients with psoriasis?

Itraconazole is an orally active triazole derivative developed by Janssen Pharmaceutica (Beerse, Belgium) (16). Its mechanism of action is a selective effect on fungal cytochrome P-450 leading to a disturbance of the sterol biosynthesis in fungal membranes and

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ultimate cell death. Itraconazole is active *in vitro* against dermatophytes, various moulds and yeasts including *Malassezia* (16). Clinically, it is effective in the treatment of various fungal infections including *Malassezia*-related diseases (16). Itraconazole is lipophilic and found in high concentrations in sebum and in stratum corneum.

The aim of the present study was to investigate the difference in local skin irritation effect with topically calcipotriol scalp solution, used to treat scalp psoriasis, between patients with high numbers of *Malassezia* in the scalp and those with low numbers. Orally administered itraconazole was used to reduce the numbers of *Malassezia*.

MATERIAL AND METHODS

Patients

Characteristics of patients. 149 patients with mild to moderate scalp psoriasis, 73 randomized to itraconazole and 76 to placebo were included. The mean age in the itraconazole group was 45 years (range 18 to 79 years), and 44 years in the placebo group (range 19 to 77 years). The sex distribution was 43 males and 30 females in the itraconazole group and 35 males and 41 females in the placebo group.

Exclusion criteria. These were severe scalp psoriasis, seborrhoeic dermatitis, any established bacterial or fungal infections (other than *Malassezia* related) affecting the scalp, pregnancy or breast-feeding, significant renal disease, known history of liver reactions to drugs and cardiovascular or other systemic disease such as HIV or immunosuppression. Systemic antipsoriatic treatment, oral antifungal drugs (other than investigatory), topical antifungal drugs, >400 IU vitamin D daily or calcium tablets.

Study design

In order to assess the contributing effect of *Malassezia* on irritations caused by calcipotriol solution, two groups of patients were formed, both assumed to have a normal flora of *Malassezia*. One group was given itraconazole 200 mg per day in order to completely eradicate *Malassezia*, the other was given placebo in order to maintain a normal level of the yeasts in the scalp. After 2 weeks of oral treatment with itraconazole or placebo, all patients were also treated with calcipotriol solution for an additional 6 weeks and all irritations carefully recorded. After 3 weeks of calcipotriol scalp treatment an extra application of calcipotriol solution behind the ear was added on an unaffected area. The area behind the ear was considered as an extremely sensitive area for external irritant agents and this area was chosen in order to increase the possibility to show any contributing effect of *Malassezia*.

The study was a prospective, randomized, double-blind, placebo-controlled parallel group study in patients with mild to moderate scalp psoriasis (the combination score of redness, thickness and scaliness between 2 and 9 on a scale from 0 to 12). It was a multicentre study involving 4 centres with 2 investigators at each centre. The study was divided into two phases.

Phase 1. The duration of phase 1 was 2 weeks. Itraconazole 100 mg capsules once daily or placebo capsules once daily was given randomized and double-blind. One capsule was to be swallowed whole once daily immediately after a meal. The patients were instructed not to use any other drugs up to 2 h before or after the intake of the capsule. Female patients were included provided a pregnancy test was negative. The scalp psoriasis was only treated with a non-medical shampoo.

Phase 2. Treatment with calcipotriol scalp solution twice daily for 6 weeks was given to all patients in phase 2. The patients continued with calcipotriol scalp solution for the whole period even if the psoriasis was cleared. Oral treatment with itraconazole or placebo from phase 1 was continued during this 6 weeks period. Visits in phase 2 were after 3 and 6 weeks of treatment with calcipotriol scalp solution.

Concurrent treatment. Only a non-medical shampoo, provided by the investigator, was allowed on the scalp during the entire study. Treatment with dithranol and/or tar preparation and/or a strong corticosteroid (maximum group III) was allowed on psoriatic lesions on the body. Higher potency topical corticosteroids (group IV) or calcipotriol were not allowed. A mild to medium (group II) potency corticosteroid was allowed for the face, but was restricted to the facial lesions only. Systemic concurrent medication for conditions other than psoriasis could be continued throughout the study.

Assessment of lesions

Investigators' assessments. Whenever possible, the same investigator was to see the patient at all visits during the study. The overall assessment, considering both the extent and severity of the patient's scalp psoriasis since the first visit, was assessed using a 0 to 4 scale, with 0 meaning worse and 4 cleared. Signs of cutaneous irritation (i.e. erythema, infiltration, papules and vesicles) were recorded by the investigator.

Patient assessments. The patients also made an assessment of their scalp psoriasis, considering both the extent and severity, from the start of active therapy (visit 2), and using a 0 to 4 scale with 0 meaning worse and 4 meaning cleared. The patient noticed signs of cutaneous irritation such as itching, redness and a burning sensation of the skin.

Culture of Malassezia

Semi-quantitative culture for *Malassezia* was performed using a contact plate with a modified Leeming's agar medium as described earlier (17, 18). Cultures were taken from the surface of the skin by pressing the plate against the skin for 15 sec. A follicular culture was taken using a modification of the technique described by Mills & Kligman (19). One drop of a cyanoacrylate adhesive (Loctide) was spread uniformly on a 1 cm^2 area on a glass slide. The glass slide was then pressed against the skin and the adhesive allowed to polymerize for 90 sec. The slide was then peeled away with a gentle motion. The microcomedones adhered to the adhesive. The glass slide containing the microcomedones was then pressed against a contact plate with the modified Leeming's agar medium for 30 sec. The contact plates were incubated in plastic bags at 37°C for 6 days and the number of colonies (colony forming units) were counted. The maximum number possible to count on one plate was 100. Both surface and follicular cultures were taken from normal looking skin behind one ear. Follicular cultures were included in order to obtain *Malassezia* yeasts present in the follicle where they could be more difficult to eradicate. Cultures were taken from behind the ear because this was the area that was selected to study the irritating effect of calcipotriol.

Laboratory examinations

A urine pregnancy test was performed on all females of child-bearing potential prior to randomization at visit 1. All subjects had tests performed on blood samples taken on the first and last days of the study. The following analyses were done: S-Alanine aminotransferase (ALAT), S-aspartate aminotransferase (ASAT), S-alkaline phosphatase, S-bilirubin, S-creatinine, S-calcium and S-albumin.

Statistical analysis

The proportion of patients with local irritation on the skin was compared between the treatment groups using logistic regression with treatment and centre in the model (20). The cumulative logits model was used to compare the two treatment groups with respect to investigators' overall assessment of treatment response and patients' overall assessment. The model included the effect of centre. All tests and confidence intervals were two-sided and the 5% level of significance was applied throughout.

RESULTS

Of the 149 patients included in the study 120 attended the last visit; 59 randomized to itraconazole and 61 to placebo. The intention-to-treat population comprised 137 patients; 67 randomized to itraconazole and 70 to placebo. Twelve patients provided no efficacy data. With few exceptions, each patient was followed by the same investigator throughout the study.

Thirteen patients (19.4%) in the itraconazole group developed cutaneous adverse events located on the face or scalp compared to 33 patients (47.1%) in the placebo group ($p<0.001$).

No difference was seen in the investigators' overall assessments of therapeutic response in the two groups ($p=0.86$, Table I). Likewise no difference was found in the patients' overall assessment of treatment response ($p=0.77$).

The result of culture of *Malassezia* at each visit from the skin and hair follicles is given in Table II. Patients were assigned to either a "low" *Malassezia* group or a "high" *Malassezia* group irrespective of randomized treatment group. A "low" *Malassezia* number was defined as a mean count from the period visit 2 to visit 4 of less than 15 (18). A "high" *Malassezia* number was defined as a mean count for the period visit 2 to visit 4 of at least 15. There were 62 patients in the low group and 75 in the high group. The number of patients with local irritation on the skin was 13 (21.0%) in the low *Malassezia* group compared to 33 (44.0%) in the high *Malassezia* group. The difference between the groups was statistically significant ($p=0.017$).

Table II. *Culture of Malassezia from the skin and hair follicles*

	Median no. of colonies			
	Itraconazole ($n=67$)		Placebo ($n=70$)	
Visit no.	Skin	Hair follicles	Skin	Hair follicles
1	38	5	54	13
2	9	3	34	7
3	9	2	49	11
4	9	3	22	10

Adverse events, other than sign of skin irritation, were seen in 8 patients (11%) in the itraconazole-treated group compared to 5 (6.8%) in the placebo group. The most common of these adverse events was gastro-intestinal disorders reported in 4 patients in the itraconazole group and 3 in the placebo group. No patients left the study due to these non-cutaneous adverse events. There was no statistically significant difference between the treatment groups from initiation to end of treatment for any of the laboratory parameters measured.

DISCUSSION

There are now several studies proving the efficacy of topically applied calcipotriol in the treatment of psoriasis (2, 3, 5). However, although calcipotriol is a safe drug it may produce a local irritation, especially on the face and scalp. The mechanisms involved in production of this skin irritation are unknown. The lipophilic yeast *Malassezia* may play a role in deterioration of psoriasis, especially psoriasis located to the scalp or face (12–15). The effect of *Malassezia* in

Table I. *Investigator's overall assessment of treatment result*

Investigator's overall assessment	Itraconazole ($n=67$)		Placebo ($n=70$)		Difference between groups Odds ratio* (95% CI) p-value
	No	%	No	%	
Worse	3	4.5	5	7.1	
No change	4	6.0	5	7.1	
Slight improvement	13	19,4	16	22.9	
Marked improvement	39	58.2	28	40.0	
Cleared	8	11.9	16	22.9	0.95 (0.51 to 1.77) p=0.86
Total	67	100.0	70	100.0	

*Adjusted for centre effect by logistic regression.

psoriasis may be an aggravation through a Koebner phenomenon.

The *Malassezia* yeasts are located in the highest numbers in the same skin areas that are most frequently involved in skin irritation produced by calcipotriol. Is this a coincidence or do *Malassezia* or *Malassezia* products interact with calcipotriol to produce substances that may be skin irritating? This was our question when we designed this study.

We found that high numbers of *Malassezia* in areas treated with calcipotriol increase the risk of skin irritation. The skin irritation was significantly lower in patients with a low number of cultured *Malassezia* compared to those patients with a high number. There was a clear parallel between this result and that seen in patients treated with itraconazole versus placebo-treated controls. The number of patients with local skin irritation was 19.4% in the itraconazole-treated group compared to 47.1% in the placebo-treated group. Itraconazole is a broad spectrum oral triazole derivative with a high activity against *Malassezia* and *Malassezia*-related diseases (16). We used itraconazole in this study as a requisite to prove our hypothesis. The azoles do not only have an antimycotic activity but also an anti-inflammatory effect. However, the anti-inflammatory effect of itraconazole is low compared to other azoles and the drug concentration in the skin after oral medication is much lower compared to topical applied drug.

The addition of itraconazole to topical calcipotriol did not increase the efficacy of the anti-psoriatic treatment. However, calcipotriol scalp solution may be so highly effective (66% cleared or markedly improved in both groups) that the effect of adding itraconazole will be masked.

In conclusion, reduction in numbers of *Malassezia* with oral itraconazole gave a statistically significant and clinical relevant reduction in the skin irritation seen on the face and scalp with topically applied calcipotriol solution from 47.1% to 19.4%. Further studies with a combination of a topically applied antifungal drugs, e.g. in a shampoo, and topically applied calcipotriol for the treatment of scalp psoriasis would be interesting. Investigations of the mechanisms involved in the interaction between calcipotriol and *Malassezia* should be started.

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