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The effect of addition of calcipotriol ointment (50 μg/g) to acitretin therapy in psoriasis

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Summary Our purpose was to find out whether the addition of calcipotriol ointment (50 μg/g) to systemic treatment with acitretin produces additional therapeutic effects and thereby an acitretin-sparing effect, and further to investigate the safety and tolerability of this combination. A multicentre, randomized, double-blind placebo-controlled study was designed. Patients were randomized to receive calcipotriol or placebo. All patients were treated with a starting dose of 20 mg acitretin per day and doses were adjusted at 2-weekly intervals with increments of 10 mg per day up to a maximum of 70 mg per day. The dose requirement for acitretin, clinical signs and adverse events were recorded. Seventy-six patients were randomized to treatment with calcipotriol 50 μg/g ointment twice daily and 59 patients to treatment with the vehicle only twice daily. Clearance or marked improvement was achieved by 67% of the patients in the calcipotriol group and by 41% of the patients in the placebo group ($P = 0{\cdot}006$). Calcipotriol treatment proved to have a statistically significant additional effect to acitretin on the Psoriasis Area and Severity Index, redness, thickness and scaliness as compared with placebo. Clearance or marked improvement was achieved with a statistically significantly lower cumulative dose of acitretin by the patients in the calcipotriol group as compared with the placebo group. The number of patients reporting adverse events was pronounced and largely related to acitretin. No significant differences were observed between the two treatment groups with respect to adverse events. Laboratory assessments were essentially normal. The addition of calcipotriol ointment to acitretin treatment contributes to the efficacy, reduces the cumulative dose of acitretin to reach marked improvement or clearance, and is well-tolerated and safe.

Systemic treatment with acitretin is efficacious in about 50–60% of patients with plaque-type psoriasis.[1–3] Because of side-effects on the skin and mucous membranes, it is often not possible to raise the dose to improve efficacy. Therefore, acitretin is mainly used in combination with other therapies such as topical steroids, dithranol, UVB phototherapy and PUVA. By using acitretin in combination with other treatments it is often possible not only to improve efficacy, but also to lower the dose, thereby reducing the dose-dependent side-effects. Indeed, the combination of acitretin or etretinate with PUVA or UVB is a well-established highly effective principle in the management of difficult psoriasis.[4,5] There has hitherto been no information on the efficacy and side-effects of a combination of systemic retinoids and vitamin D_3 analogues.

Over the last decade, topical treatment of psoriasis has been improved by vitamin D_3 analogues, in

particular calcipotriol. Preclinical studies have demonstrated calcipotriol to have a high binding affinity to the cellular receptor for calcitriol (1α,25-dihydroxyvitamin D_3), the biologically active form of vitamin D_3, and calcipotriol has been shown to be both a potent regulator of cell differentiation and an inhibitor of cell proliferation in human keratinocytes.[6,7] Its systemic effect on calcium metabolism in rats is 100–200 times less than that of calcitriol.[7] Placebo-controlled dose-finding studies revealed that calcipotriol 50 μg/g in ointment is the optimal concentration.[8,9] In comparative studies, calcipotriol proved to be as effective as or superior to betamethasone ointment and dithranol ambulatory treatment.[10–12] Combining calcipotriol with cyclosporin[13] and with PUVA[14] proved to be highly effective and well-tolerated. Long-term safety and efficacy studies revealed that calcipotriol remains effective and safe after 12 months of treatment.[15]

The objectives of the present study were to determine whether the addition of calcipotriol ointment (50 μg/g) to systemic treatment with acitretin produces an additional therapeutic effect and thereby, possibly, an acitretin-sparing effect, and to investigate the safety and tolerability of combined treatment with calcipotriol ointment and acitretin.

Patients and methods

Design

The study was a multicentre, parallel group, randomized, double-blind placebo-controlled study on the efficacy and safety of the combination of acitretin and calcipotriol vs. acitretin and placebo treatment. After a washout and qualification phase lasting 2 weeks, a double-blind phase of combined treatment followed for 12 weeks. During the washout/qualification phase the patients used only an emollient and protocol inclusion and exclusion criteria were assessed.

Subjects

In-patients or out-patients, of either sex, aged more than 18 years, with a clinical diagnosis of severe/extensive psoriasis vulgaris which was not deemed responsive to topical treatment alone, were included in the study. Patients had to have psoriatic lesions on one or more of the following regions: arms, trunk or legs. Excluded were patients with acute guttate or pustular psoriasis, premenopausal females who had not been sterilized, patients who had used systemic antipsoriatic treatment or photo(chemo)therapy within 2 weeks prior to study entry (12 weeks for etretinate or acitretin), patients taking ≥ 400 U vitamin D daily, calcium tablets, or ≥ 5000 U vitamin A daily. Patients with hyperlipidaemia, insulin-dependent diabetes mellitus, hypercalcaemia, or impaired renal or hepatic function were excluded from the study. All patients had to give informed consent before inclusion. The trial was approved by medical ethical committees of the participating hospitals.

Treatments

A maximum of 120 g calcipotriol ointment (Dovonex/Daivonex, Leo Pharmaceutical Products, Ballerup, Denmark) was provided per patient per week. Calcipotriol ointment (50 μg/g) or its vehicle only was to be applied twice daily at ≈ 12-hourly intervals without occlusion. Lesions on all body areas except for the scalp, face and flexures were to be treated with topical trial medication. Patients with psoriasis on the scalp, face or flexures were allowed to use low or medium potency steroids on those areas. The ointments were applied, as far as possible, to lesional skin only. Patients had to wash their hands after applying the ointment to avoid inadvertent spread of the medication to other body areas. Acitretin (Neotigason, Hoffmann-La Roche, Denmark) was provided in capsules of 10 mg. The starting dose was 20 mg once daily. The dose was increased every 2 weeks in steps of 10 mg as required until the maximum dose was reached, clearance was recorded by the investigator, or unacceptable adverse events attributable to acitretin occurred. The maximum dose was set at 70 mg/day or, in patients weighing below 60 kg, 1 mg/kg per day. An emollient cream (Danatek, Danapharm, Denmark) was provided for use during the entire study period.

Patients were not permitted to take other medication, either topically or systemically, that could affect the course of their psoriasis or interact with acitretin. Concurrent medication, except for agents mentioned in the exclusion criteria, that was not being used to treat psoriasis and would not affect the condition, could be continued throughout the study, without any change in dosage wherever possible. Patients already taking beta-blockers or non-steroidal anti-inflammatory drugs were allowed to continue their treatment throughout the study.

Assessments

At each post-randomization visit the investigator and

the patient gave their assessment of the overall response to treatment, considering both the extent and the severity of the psoriasis using a six-category scale: 1, worse; 2, no change; 3, slight improvement; 4, moderate improvement; 5, marked improvement; 6, clearance. At every visit the investigator assessed the extent and severity of the patient's psoriasis, using the PASI (Psoriasis Area and Severity Index) scoring system.[16] In each patient the cumulative dose of acitretin was recorded. The proportion of patients who achieved marked improvement or clearance of their psoriasis according to the investigator's overall assessment at the end of treatment, was designated as the primary response criterion. Adverse events were recorded at all assessments, and adverse events related to skin and mucous membranes were additionally checked from a positive check-list. Routine laboratory parameters, including serum calcium and serum lipids were measured.

Statistical evaluation

The analyses of efficacy were based on intra-individual differences between responses to calcipotriol and placebo treatment. The comparison was carried out on data collected at the end of treatment and at each assessment (visits 3, 4, 5 and 6). The binomial test was applied to test homogeneity of positive and negative differences of clinical scores. In respect of safety, changes in laboratory parameters were tested for statistical significance using the one-sample *t*-test.

Results

The double-blind phase of the study was completed over a period of 18 months. Recruitment was stopped between April and September to avoid patients receiving therapeutic benefits from sunlight. In total, 154 patients were recruited as out-patients by 64 investigators at 34 centres in four countries. Out of 154 patients who were recruited, 19 patients were not randomized. Seventy-six patients were randomized to treatment with calcipotriol ointment and 59 to treatment with placebo.

Table 1 summarizes the demographic details of the calcipotriol and placebo groups. The composition of the calcipotriol group and placebo group was similar with respect to age, sex, race, duration of psoriasis, PASI, erythema, induration and desquamation. During the 2-week wash-out period the severity of the patients' psoriasis was evaluated using the PASI. Among patients assigned to treatment with calcipotriol, the mean PASI increased by 0·45 ($P = 0·13$) from the start of the wash-out/qualification phase to the end of this phase. For patients randomized to treatment with placebo, the mean change during this phase was 1·04 ($P = 0·008$). Of the 135 patients randomized in the study, 37 (27%) were withdrawn from the double-blind treatment. The reasons for withdrawal are given in Table 2. Of the 76 patients randomized to treatment with calcipotriol ointment, 56 (74%) attended the final visit at the end of the treatment period or at clearing. During the study, 16 patients withdrew and four patients cleared and left the study for this reason. Of the 59 patients randomized to treatment with placebo, 40 patients (68%) attended the final visit. In total, 21 patients were withdrawn in this group and no patient left for reason of clearance.

Table 1. Comparability of treatment groups (mean ± SD)

	Calcipotriol ($n = 76$)		Placebo ($n = 59$)	
	No.	%	No.	%
Age (years)	48·1 ± 13·4		47·1 ± 142	
Male	57	75	43	73
Female	19	25	16	27
Duration of psoriasis (years)	18·3 ± 11·2		18·8 ± 12·8	
PASI	17·8 ± 8·9		17·4 ± 8·6	

The proportion of patients achieving clearance or marked improvement is shown in Table 3. There is a highly significant difference between the treatment groups at the end of treatment, favouring calcipotriol treatment ($P = 0·006$). In the calcipotriol group, the mean change in PASI from baseline to the end of the double-blind treatment was −13·2 (Fig. 1). The decrease is statistically significant ($P \leq 0·001$). In the placebo group, the mean change in PASI from baseline to the end of the double-blind treatment was − 8·8. This decrease is statistically significant ($P < 0·001$). Comparing the two treatment groups at the end of the treatment, there was a statistically significant difference, favouring calcipotriol treatment ($P = 0·007$). Comparing the mean whole-body scores for redness, thickness and scaliness at the end of the double-blind treatment, there was a statistically significant difference between the two treatment groups, favouring calcipotriol treatment ($P = 0·0001$, $P = 0·002$ and $P = 0·03$, respectively). The patients' overall assessments revealed that comparing the two treatment groups at the end of the treatment, there was a trend which appeared to favour calcipotriol therapy ($P = 0·05$) (Table 3).

In total, 40 patients in the calcipotriol group and 25 patients in the placebo group returned complete sets of

Table 2. Reasons for withdrawal from double-blind treatment

Reason	Calcipotriol ($n = 76$)	Placebo ($n = 59$)
Adverse event	9	13
Unacceptable treatment response	2	3
Exclusion criteria*	0	3
Lost to follow-up	2	1
Voluntary	1	0
Other	2	1
Total no. of patients withdrawn	16	21

*Exclusion criteria appeared during the study.

tubes to the investigators. Within this group, the median total dose of ointment to reach clearance or marked improvement was 660·8 g calcipotriol ointment in the calcipotriol group and 1195·4 g placebo ointment in the placebo group ($P = 0{\cdot}01$, log-rank test). The median total dose of acitretin to reach clearing or marked improvement was 1680 mg in the calcipotriol group and 2100 mg in the placebo group ($P = 0{\cdot}01$).

Skin and appendage adverse events were the most reported adverse events in 43% and 45% of the patients in the calcipotriol group and placebo group, respectively. The most frequently reported adverse events in both groups were non-fatal dryness of the skin and scaling of healthy skin, in particular of palms and soles. Mucous membrane disorders (e.g. cheilitis and dry nose) and visual disorders (e.g. conjunctivitis) were also frequently reported. The calcipotriol group and placebo group did not differ with respect to the occurrence of side-effects that are well-known with acitretin treatment. In total, 12% of the patients in the calcipotriol group and 22% of the patients in the placebo group were withdrawn due to adverse events ($P = 0{\cdot}18$).

There were no statistically significant changes between the two treatment groups with respect to any laboratory parameter investigated. Concerning serum triglycerides, however, there were 13 patients with raised levels in the calcipotriol group vs. five patients in the placebo group. Results of laboratory tests related to calcium metabolism demonstrated no consistent or clinically important difference between the treatment groups.

Discussion

During the 12-week study, 135 of 154 patients were randomized for treatment with either acitretin and calcipotriol ointment or acitretin and placebo ointment. Analysis of demographic data and previous history and severity of psoriasis indicated that both study groups were comparable.

It was shown that the addition of calcipotriol ointment (50 μg/g) to systemic treatment with acitretin produced a statistically significantly better treatment response compared with ointment vehicle with respect to clinical signs and to the investigators' overall assessments of treatment efficacy in patients with severe and extensive psoriasis vulgaris. The cumulative dose of acitretin to achieve target response was statistically significantly lower in the calcipotriol group. Therefore, it can be concluded that combination therapy with acitretin can be extended to calcipotriol. Although the data on ointment consumption are incomplete, the patients using calcipotriol ointment used significantly less ointment as compared with the patients using the vehicle.

Table 3. Overall assessments of the treatment response at end of treatment by investigators/patients

	Calcipotriol ($n = 76$)		Placebo ($n = 59$)		
	No.	%	No.	%	P^a
Cleared/marked improvement	51/50	67/66	24/28	41/47	0·005
Moderate/slight improvement/ unchanged/worse	25/26	33/34	33/29	56/49	
Missing	0	0	2/2	3/3	

[a]Log-linear regression analysis.

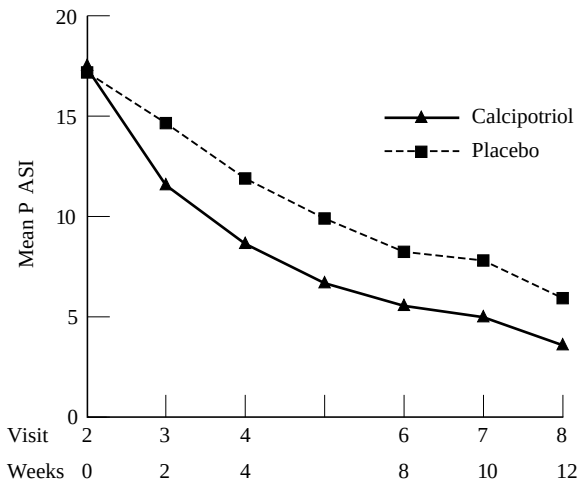

Figure 1. Psoriasis Area and Severity Index (PASI) at successive visits during double-blind treatment (mean values).

Several molecular interactions between retinoids and vitamin D_3 analogues have been described. Some retinoids bind to the retinoid X receptor (RXR), and the ligand-activated vitamin D_3 receptor (VDR) interacts via heterodimer formation with the ligand-activated RXR receptors.[17,18] In osteoblasts it has been shown that all-*trans*-retinoic acid upregulates VDR expression.[19] So far, however, no *in vitro* studies have demonstrated that the combination of acitretin and calcipotriol is additive or synergistic with respect to interference with epidermal proliferation, keratinization or inflammation. The additional effect of calcipotriol over acitretin was expressed with respect to reduction of redness, induration and scaling ($P = 0{\cdot}0001$, $P = 0{\cdot}002$ and $P = 0{\cdot}03$, respectively). From a mechanistic point of view, it might be relevant that calcipotriol enhances the normal keratinization process (increasing cornified envelope formation and transglutaminase activity), whereas retinoids inhibit this process (reducing cornified envelope formation and inhibiting transglutaminase expression).[20] The opposing effects on keratinization might reduce the additional effect of the combination on scaling.

In total, 622 adverse events were reported. In the calcipotriol group 97% and in the placebo group 95% of the patients reported one or more adverse events. However, the investigators had to fill in a check-list containing nine potential adverse effects of acitretin at every visit and it is possible that this prompted the investigators to report all possible adverse events. Most adverse events were acitretin-associated (cheilitis, dry mouth, dry nose and conjunctivitis). Remarkably, between the calcipotriol group and placebo group no difference was observed with respect to the occurrence of signs or symptoms of skin irritation: only one patient had to discontinue treatment due to irritation on application areas. One explanation might be that acitretin inhibits the occurrence of calcipotriol-induced irritation. Another explanation might be that the acitretin-induced tenderness of the skin is of more substantial discomfort, masking any subjective sensation of irritancy from vitamin D_3.

Laboratory parameters of calcium metabolism demonstrated no consistent or clinically relevant differences between the two treatment groups. Therefore, there is no clinical substantiation for the supposition that acitretin might have facilitated transcutaneous absorption of calcipotriol to a sufficient extent to influence systemic calcium metabolism.

In conclusion, the present study demonstrates that the addition of calcipotriol ointment (50 μg/g) to systemic treatment with acitretin produces an additional therapeutic effect and thereby an acitretin-sparing effect. The combination therapy did not interfere significantly with systemic calcium metabolism, and did not aggravate the mucocutaneous side-effects of acitretin.

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