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Therapeutics

Efficacy of once-daily treatment regimens with calcipotriol/betamethasone dipropionate ointment and calcipotriol ointment in psoriasis vulgaris

K.KRAGBALLE, K.L.NOERRELUND,* H.LUI,† J.P.ORTONNE,‡ G.WOZEL,§ T.UURASMAA,¶ C.FLEMING,** J.L.LÓPEZ ESTEBARANZ,†† L.I.HANSSEN‡‡ AND L-M.PERSSON§§

Marselisborg Centret, Aarhus, Denmark
**LEO Pharma, Industriparken 55, 2750 Ballerup, Denmark*
†Division of Dermatology, University of British Columbia, Vancouver, Canada
‡Service de Dermatologie, Hôpital de L'Archet, Nice, France
§Universitätsklinikum Carl Gustav Carus Klinik und Poliklinik für Dermatologie, Dresden, Germany
¶Clinical Research Services Turku, Turku, Finland
***Perth Royal Infirmary Tayside University Hospital, Perth, U.K.*
††Servicio de Dermatología, Fundación Hospital Alcorcón, Alcorcón, Spain
‡‡Helse Sunnmøre HF, Aalesund Sjukehus, Aalesund, Norway
§§Kärnsjukhuset, Skövde, Sweden

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Summary

Background A two-compound ointment containing calcipotriol 50 μg g^{-1} and betamethasone dipropionate 0·5 mg g^{-1} has recently been shown to be an effective treatment for psoriasis.

Objectives This study was designed to investigate efficacy and safety of different treatment regimens with the two-compound product (Daivobet®/Dovobet®; LEO Pharma, Ballerup, Denmark) and calcipotriol 50 μg g^{-1} ointment (Daivonex®/Dovonex®; LEO Pharma).

Methods In total, 972 patients with psoriasis vulgaris were randomized to one of three treatment regimens: group 1, the two-compound product once daily for 8 weeks followed by calcipotriol ointment once daily for 4 weeks; group 2, the two-compound product once daily for 4 weeks followed by 8 weeks of treatment with calcipotriol ointment once daily on weekdays and the two-compound product once daily at weekends; and group 3, calcipotriol ointment twice daily for 12 weeks. The efficacy was evaluated by Psoriasis Area and Severity Index (PASI) and investigators' global assessments of disease severity. The primary response criteria were percentage reduction in PASI and proportion of patients with absent/very mild disease according to the investigators' global assessments after 8 weeks of treatment.

Results The mean reduction in PASI from baseline to the end of 8 weeks of treatment was 73·3% for group 1, 68·2% for group 2 and 64·1% for group 3. The proportion of patients with absent/very mild disease at the end of 8 weeks of treatment was 55·3% for group 1, 47·7% for group 2 and 40·7% for group 3. For both primary response criteria, group 1 was statistically superior to group 3 ($P < 0·001$), whereas group 2 did not differ significantly from group 3. The difference between group 1 and group 2 was statistically significant with regard to PASI but not regarding the proportion of patients with absent/very mild disease. Patients receiving initial therapy with the two-compound product achieved the fastest treatment response, and the maximum treatment effect for these patients was seen after 5 weeks. This effect was maintained with continued treatment with the two-compound product for up to 8 weeks. After 12 weeks of treatment, no significant

Correspondence: K.L.Noerrelund.
E-mail: kirsten.noerrelund@leo-pharma.com

differences were seen between the three groups with regard to reduction in PASI, whereas the proportion of patients with absent/very mild disease in group 2 was superior to that in group 3. Patients receiving therapy with the two-compound product experienced fewer lesional/perilesional adverse drug reactions than the calcipotriol-treated patients ($P < 0{\cdot}001$): 10·9% in group 1, 11·5% in group 2 and 22·3% in group 3.

Conclusions Two different short-term treatment regimens employing a recently developed two-compound product (calcipotriol/betamethasone dipropionate) provided rapid and marked clinical efficacy and were shown to be safe therapies for psoriasis vulgaris.

Key words: betamethasone dipropionate, calcipotriol, combination therapy, psoriasis

Psoriasis vulgaris is a common skin disease with a prevalence generally estimated to be in the range of 0·5–2·5%.[1,2] Calcipotriol and corticosteroids are both established topical treatments for psoriasis. Calcipotriol is a vitamin D analogue that has been shown through extensive, well-controlled studies to be safe and effective for the topical treatment of psoriasis vulgaris.[3–7] Topical corticosteroids have also been shown to be effective and safe in treatment of psoriasis vulgaris[8–10] and are extensively prescribed. Calcipotriol and topical corticosteroids have different modes of action in psoriasis vulgaris,[3,4] and by using the two compounds together, an improved efficacy and a rapid response may be achieved. Studies have shown that calcipotriol used in combination with a potent [World Health Organization (WHO) group III] corticosteroid, when applied at separate times of day, is more effective than calcipotriol alone or corticosteroid alone in the treatment of psoriasis vulgaris.[11–13] The products available on the market are usually incompatible.[14] Therefore, it is not recommended to apply both products simultaneously or to mix the two products in the same container. A two-compound product containing calcipotriol 50 μg g^{-1} and betamethasone dipropionate 0·5 mg g^{-1} (Daivobet®/Dovobet®; LEO Pharma, Ballerup, Denmark) has recently been developed in order to avoid separate applications and to improve patient compliance. The potent WHO group III steroid betamethasone dipropionate was chosen as corticosteroid because of its compatibility with calcipotriol in the new vehicle and its proven efficacy and tolerability when used to treat psoriasis vulgaris.[8–10]

Three large clinical studies have demonstrated that up to 4 weeks of once- or twice-daily use of the two-compound product in the treatment of psoriasis vulgaris has superior efficacy and similar or better tolerability than once- or twice-daily application of its individual active components.[15–17] A fourth study showed that up to 4 weeks of treatment with the two-compound product once daily had efficacy and safety similar to twice-daily use.[18]

The aim of this study was to evaluate the clinical efficacy and safety of two different treatment regimens involving the two-compound product and to compare them with twice-daily treatment with calcipotriol 50 μg g^{-1} ointment (Daivonex®/Dovonex®; LEO Pharma), following 8 and 12 weeks of treatment. Furthermore, continuous treatment with the two-compound product for up to 8 weeks was compared with a more 'steroid-sparing' regimen alternating between the two-compound product and calcipotriol ointment after up to 4 weeks of initial treatment with the two-compound product.

Patients and methods

The study was an international, multicentre, prospective, randomized, partly double-blind, three-arm parallel group study conducted in eight countries in Europe and in Canada. The study protocol was reviewed and approved by relevant Institutional Review Boards/Independent Ethics Committees, and all patients gave signed informed consent before enrolment in the trial.

Subjects

Patients aged 18 years or above with a clinical diagnosis of psoriasis vulgaris amenable to topical treatment, affecting at least 10% of one or more body regions (arms, trunk and legs) were entered. Investigators' global assessments of disease severity at inclusion had to be at least mild. Women of childbearing potential had to have a negative urine pregnancy test and agree to use an adequate method of contraception. The main exclusion criteria were unstable forms of psoriasis in the area to be treated, other inflammatory skin diseases confounding psoriasis assessment, systemic antipsoriatic treatment, psoralen plus

ultraviolet (UV) A treatment, UVB treatment, topical treatment of psoriasis of the trunk or limbs, known or suspected abnormality in calcium homeostasis, pregnancy or breast feeding.

Treatments

Patients were randomized to one of the three treatment groups shown in Table 1. Treatment assignment was preplanned according to a computer-generated randomization schedule in a 1 : 1 : 1 ratio. Patients whose psoriasis cleared before the end of 12 weeks' treatment continued in the study and restarted treatment, if needed, in the 12-week period following randomization. If treatment was re-instituted, it was with the investigational product packaged for that time period.

The packaging and labelling of the investigational products for group 1 and group 2 contained no evidence of their identity, and it was expected that patients and investigators remained unaware of the individual treatment assignments during the study. Group 3 used calcipotriol twice daily, and patients were therefore not blinded with respect to assignment to group 3. However, study medication was dispensed by a person other than the investigator performing the assessments, thus enabling the investigator to be blinded. Furthermore, a centralized telephone voice response system was used for the patient assignment and this removed the opportunity for investigator bias during randomization.

Assessments

Patients were assessed on inclusion and after 1, 2, 4, 5, 8 and 12 weeks of treatment. The extent and severity of psoriasis was evaluated using the Psoriasis Area and Severity Index (PASI) and the investigator's global assessment of disease severity on a six-point scale (absence of disease, very mild, mild, moderate, severe or very severe). All adverse events during the study were recorded.

The two primary response criteria were the percentage change in PASI from baseline to the end of 8 weeks' treatment and the proportion of patients with absent/very mild disease according to investigators' global assessment of disease severity at the end of 8 weeks' treatment.

Secondary response criteria included the change in PASI from baseline to each subsequent visit and to end of treatment at 12 weeks, and the proportion of patients with absent/very mild disease according to investigators' global assessment of disease severity at each visit and at end of treatment at 12 weeks.

Statistical methods

Continuous efficacy endpoints were compared between treatment groups using analysis of variance with centre effects included in the model. Binary efficacy endpoints were compared between treatment groups using the Cochran–Mantel–Haenszel test with centre effects in the model. The two primary endpoints were analysed at the 2·5% significance level. The adjustment method of Bonferroni was chosen to compensate for the pairwise comparisons. Estimated treatment differences were presented with 97·5% confidence intervals (CIs) and were adjusted for centre effects. For the comparisons at 8 and 12 weeks, last observation carried forward was used. Secondary endpoints were analysed at the 5% significance level. These included the percentage of patients experiencing adverse drug reactions. All hypothesis tests were two-sided.

The percentage of patients with adverse events was compared between treatment groups by χ^2 tests.

Results

In total, 974 patients were enrolled in the study, of whom 972 patients were randomized (322 in group 1, 323 in group 2 and 327 in group 3) (see Table 1). All randomized patients constitute the intention-to-treat

Table 1. The three treatment regimens

	Week 0–4	Week 5–8	Week 9–12
Group 1	Two-compound product*	Two-compound product*	Calcipotriol
	Once daily	Once daily	Once daily
Group 2	Two-compound product*	*Weekdays:* calcipotriol, once daily	*Weekdays:* calcipotriol, once daily
	Once daily	*Weekends:* two-compound product*, once daily	*Weekends:* two-compound product*, once daily
Group 3	Calcipotriol	Calcipotriol	Calcipotriol
	Twice daily	Twice daily	Twice daily

*The two-compound product is a combination ointment containing calcipotriol and betamethasone dipropionate.

analysis set. One patient was lost to follow-up after visit 1 and did not provide any safety data afterwards. The safety analysis thus includes 971 patients (322 in group 1, 322 in group 2 and 327 in group 3). In total, 90·4% of all randomized patients attended the final visit (week 12), and the proportion of patients withdrawing during the study was 9·3% for group 1, 6·5% for group 2 and 14·4% for group 3. The main reason for withdrawal was lost to follow-up. At each on-treatment visit, patients were asked if they had used the trial medication as prescribed. Compliance with the prescribed trial medication for the total treatment period was reported by 63·4% of the patients in group 1, 65·8% in group 2 and 55·2% in group 3.

At baseline, the three treatment groups were well balanced for age, sex, ethnic origin, mean PASI, investigator's overall assessment of disease severity and mean duration of psoriasis (Table 2).

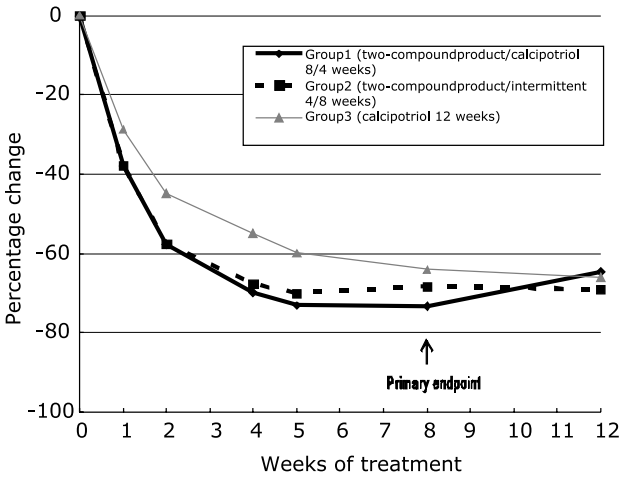

Figure 1. Percentage change in Psoriasis Area and Severity Index from baseline using last observation carried forward at each visit.

Efficacy

At the time of the primary comparison (8 weeks), group 1 had received 8 weeks' once-daily treatment with the two-compound product, group 2 had received 4 weeks' once-daily treatment with the two-compound product followed by 4 weeks' once-daily intermittent therapy (weekday calcipotriol/weekend two-compound product), while group 3 had received 8 weeks' twice-daily treatment with calcipotriol. The mean percentage reduction in PASI from baseline to end of 8 weeks' treatment was 73·3% in group 1, 68·2% in group 2 and 64·1% in group 3 (Fig. 1). The estimated treatment difference between group 1 and group 3 was −9·2%; between group 2 and group 3 it was −4·4% and between group 1 and group 2 it was −4·8%. Group 1 was statistically significantly superior to group 3 (97·5% CI −13·7 to −4·7, $P < 0·001$) and group 2 (97·5% CI −9·3 to −0·3, $P = 0·016$), whereas group 2 was not statistically significantly different from group 3 (97·5% CI −8·9 to 0·1, $P = 0·029$).

The number of patients with absent/very mild disease at the end of 8 weeks' treatment was 178 of 322 (55·3%) in group 1, 154 of 323 (47·7%) in group 2 and 133 of 327 (40·7%) in group 3. The estimated odds ratio between group 1 and group 3 was 1·94; between group 2 and group 3 it was 1·37, and between group 1 and group 2 it was 1·37. Group 1 was statistically significantly superior to group 3 (97·5% CI 1·33–2·83, $P < 0·001$), whereas group 2 did not differ statistically from group 3 (97·5% CI 0·94–1·99, $P = 0·063$) and group 1 (97·5% CI 0·95–1·99, $P = 0·057$).

The percentage reduction in PASI and the proportion of patients with absent/very mild disease in groups 1 and 2 were statistically superior to group 3 when evaluating the change from baseline to each of the following weeks of treatment: 1, 2, 4 and 5 (week 1, $P < 0·02$; weeks 2, 4 and 5, $P < 0·001$).

After 12 weeks of treatment, no significant differences were seen between the three groups with regard to reduction in PASI, whereas for proportion of patients with absent/very mild disease according to investigators' global assessment of disease severity, group 2 was found to be statistically superior to group 3 [odds ratio 1·45 (95% CI 1·04–2·01), $P = 0·026$].

Table 2. Demographics and baseline characteristics of patients with psoriasis vulgaris

	Group 1 ($n = 322$)	Group 2 ($n = 323$)	Group 3 ($n = 327$)
Age (years)			
Mean	47·8	47·8	47·5
Range	18–97	18–88	18–86
Males (%)	62·4	63·8	65·1
Caucasians (%)	96·6	95·7	97·9
Duration of psoriasis (years)			
Mean	18·3	19·0	18·3
Range	0–70	0–60	0–60
PASI score			
Mean	10·3	10·4	10·9
Range	2–49	2–42	2–41
Patients with moderate disease (%)	64·6	62·8	65·4

PASI, Psoriasis Area and Severity Index.

Tolerability and safety

During the study, adverse events were reported by 43·5% of the patients in group 1, 45·7% in group 2 and 53·2% in group 3. Adverse events identified as lesional/perilesional adverse drug reactions were cutaneous adverse events occurring on the treatment area, for which the investigator considered the relation to trial medication to be either not classifiable, possible or probable.

Lesional/perilesional adverse drug reactions were reported by 35 of 322 patients (10·9%) in group 1, 37 of 322 (11·5%) in group 2 and 73 of 327 (22·3%) in group 3. There was a significant difference between group 1 and group 3 ($P < 0·001$) and between group 2 and group 3 ($P < 0·001$). For all three treatment groups, the most frequently reported lesional/perilesional adverse drug reaction was pruritus. This was most frequent in group 3, with the lowest frequency in group 1 (Table 3).

Table 3. Lesional/perilesional adverse drug reactions recorded during the study period

Adverse drug reaction	Group 1 ($n = 322$)	Group 2 ($n = 322$)	Group 3 ($n = 327$)
Pain NOS	0	1	2
Folliculitis	2	1	0
Rash, pustular	0	0	1
Blister	0	1	0
Burning sensation NOS	3	4	9
Paraesthesia	0	0	2
Dermatitis NOS	2	0	2
Dermatitis, contact	0	0	2
Dermatitis, exfoliative NOS	1	0	0
Dry skin	0	0	1
Erythema	5	2	6
Pigmentation disorder NOS	0	0	1
Postinflammatory pigmentation change	0	1	0
Pruritus NOS	9	14	25
Psoriasis	0	1	2
Psoriasis, aggravated	4	0	5
Rash NOS	0	0	2
Rash, papular	1	0	1
Rash, scaly	8	13	17
Skin atrophy	1	0	0
Skin hyperpigmentation	1	3	1
Skin hypopigmentation	1	0	1
Skin inflammation NOS	0	0	1
Skin irritation	3	1	8
Telangiectasia	1	0	0
Flushing	0	1	0
Total number of lesional/perilesional adverse drug reactions*	42	43	89
Total number of patients (%)	35 (10·9)	37 (11·5)	73 (22·3)

*Different adverse drug reactions with the same preferred term in the same patient have been counted as one. NOS, not otherwise specified.

Once-daily use of the combination product for up to 8 weeks revealed no additional safety risk compared with the previously studied 4-week treatment. In the first 4 weeks of treatment, 6·8% of patients receiving the two-compound product alone reported adverse drug reactions. In the subsequent 4-week period, only 4·7% of patients receiving the two-compound product alone reported adverse drug reactions.

One single case of reversible skin atrophy was reported during the treatment with the two-compound product in group 1, occurring at visit 5. The investigator characterized this event as perilesional/lesional in nature and the severity was rated as mild. There were no serious adverse events deemed to be related to use of any study medication during the study.

Discussion

Once- or twice-daily therapy with the two-compound product has been shown to be effective and safe in the treatment of psoriasis vulgaris for up to 4 weeks.[15–18] Furthermore, patients may safely be transferred to calcipotriol ointment after discontinuation of the two-compound product without signs of rebound phenomena.[16] However, as psoriasis vulgaris is a chronic condition, an extended therapy using different treatment regimens may be required in order to meet individual patient needs.

The aim of the present study was to identify different treatment alternatives after the initial treatment with the two-compound product. The study was designed to investigate efficacy as well as safety of different regimens with the two-compound product and calcipotriol ointment. Two treatment regimens including the two-compound product were compared with the standard treatment with calcipotriol. Furthermore, continuous treatment with the two-compound product for up to 8 weeks was compared with the more 'steroid-sparing' regimen alternating between the two-compound product and calcipotriol ointment.

From the study, it can be concluded that 8 weeks' treatment with the two-compound product was effective and safe. The optimal effect was reached after 5 weeks of treatment and was maintained during the following 3 weeks. Eight weeks of continuous treatment with the two-compound product once daily was superior in effect to 8 weeks of treatment with calcipotriol ointment twice daily. Likewise, at week 8 continuous treatment with the two-compound product was superior to the intermittent treatment regimen with regard to PASI. In terms of short-term safety, both regimens

including the two-compound product were better than calcipotriol monotherapy, as lesional/perilesional adverse drug reactions were less frequently reported in the steroid-containing therapies. One single case of reversible skin atrophy of mild severity was reported during treatment with the two-compound product.

After 12 weeks of treatment, the effect of all three regimens was comparable. The treatment regimen involving calcipotriol once daily on weekdays and the two-compound product once daily at weekends was able to maintain stabilization of treatment efficacy during the 8- to 12-week period. This patient group benefited from rapid reduction of symptoms during the initial treatment phase. Symptom reduction was then maintained at a stable level for the rest of the trial.

When patients were switched to calcipotriol treatment once daily after 8 weeks of continuous treatment with the two-compound product, a slight increase in PASI was observed. Previously, evidence has shown that in the treatment of psoriasis vulgaris, twice-daily calcipotriol is more effective than once-daily application.[19] It could thus be conceived that calcipotriol twice daily in this treatment phase would produce better maintenance of treatment results. In addition, it is possible that due to the more irritating nature of calcipotriol compared with the two-compound product, irritation-related eythema was induced. This could be readily judged as psoriasis-related redness and thus increase the PASI score.

The study results indicate that: (i) all three treatment regimens are effective and safe; (ii) the two-compound product can efficiently and safely be used for up to 8 weeks; and (iii) symptom reduction reached after initial treatment with the two-compound product can be maintained with either continuous or intermittent therapy with the two-compound product.

As this was a short-term study (up to 12 weeks), additional studies may be needed to describe long-term efficacy and safety and to identify the optimal transition from the initial treatment with the two-compound product to a follow-up maintenance therapy.

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