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Therapeutics

Efficacy and safety of a new combination of calcipotriol and betamethasone dipropionate (once or twice daily) compared to calcipotriol (twice daily) in the treatment of psoriasis vulgaris: a randomized, double-blind, vehicle-controlled clinical trial

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Summary

Background Calcipotriol and betamethasone dipropionate are both widely used, effective treatments for psoriasis. Vitamin D analogues and topical corticosteroids have different mechanisms of action in the treatment of psoriasis. A new vehicle has been developed in order to contain both calcipotriol (50 μg g⁻¹) and betamethasone dipropionate (0.5 mg g⁻¹) in an ointment form. By using calcipotriol and a corticosteroid together, greater efficacy may be achieved than by using either compound alone.

Objectives The present study was conducted in order to compare the clinical efficacy and safety of the combined ointment formulation used once daily with the vehicle ointment used twice daily, calcipotriol ointment used twice daily and the combined formulation used twice daily in psoriasis vulgaris.

Methods This was an international, multicentre, prospective, randomized, double-blind, vehicle-controlled, parallel group, 4-week study in patients with psoriasis vulgaris amenable to topical treatment. Patients were randomized to one of four treatment groups: combined formulation once daily, combined formulation twice daily, calcipotriol twice daily or vehicle twice daily. Efficacy and safety were assessed.

Results There was no statistically significant difference in the mean percentage change in the Psoriasis Area and Severity Index (PASI) from baseline to end of treatment between the two combined formulation groups, but the difference in PASI reduction was significantly higher in the combined formulation groups (68.6% once daily, 73.8% twice daily) than in both the twice daily calcipotriol group (58.8%) and the vehicle group (26.6%). Safety data showed the frequency of adverse events to be less in the combined formulation groups than in both the calcipotriol group and the vehicle group. The proportion of patients with lesional/perilesional adverse reactions was less in the combined formulation groups and vehicle group than in the calcipotriol group (9.9% combined formulation once daily, 10.6% combined formulation twice daily, 19.8% calcipotriol, 12.5% vehicle).

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Conclusions  No statistically significant nor clinically relevant difference in efficacy was seen between the combined formulation used once daily and twice daily. When compared to vehicle ointment or calcipotriol ointment alone, the combined formulation was shown to be clearly more efficacious.

Key words: betamethasone, calcipotriol, combination, once daily, psoriasis vulgaris, randomized controlled trial

Psoriasis is one of the most common chronic dermatoses in the world, with an estimated 0.3–2.6% of the population affected. The histopathology is characterized by a greatly increased rate of epidermal proliferation with impaired differentiation of keratinocytes. Dermal blood vessels are dilated and there is infiltration of the skin with immunologically active cells.

Several short-term studies have been conducted with topical calcipotriol ointment applied twice daily for psoriasis. Calcipotriol ointment has been shown to be at least as effective as betamethasone 17-valerate 0.1% ointment. Calcipotriol was quite well tolerated, with adverse events being mainly mild, application-related lesional/perilesional irritation occurring in about 20% of patients, and which tended to subside despite continuation of treatment.

Betamethasone dipropionate is a synthetic fluorinated corticosteroid classified as a potent WHO Group III steroid and is used topically to treat psoriasis vulgaris on a short-term basis. It has been available on prescription worldwide for many years for once or twice daily treatment of psoriasis.

Previous studies have shown that a potent corticosteroid used in conjunction with calcipotriol, when applied at different times of the day, is more effective than corticosteroid alone or calcipotriol alone in the treatment of psoriasis vulgaris. Vitamin D analogues and topical corticosteroids have different modes of action in psoriasis vulgaris. Vitamin D analogues bind to the vitamin D receptor, which acts as a heterodimer with the retinoid receptor RXR. Keratinocytes and lymphocytes have vitamin D receptors. Vitamin D analogues regulate the epidermal hyperproliferation and abnormal keratinization associated with psoriasis, induce apoptosis in inflammatory cells, inhibit T helper (Th) 1 cytokine production, induce a Th1 to Th2 switch and have an antiangiogenic effect. Corticosteroids bind to cytoplasmic glucocorticoid receptors then rapidly translocate to the nucleus to either stimulate or inhibit genes regulating inflammation. Protein to protein corticosteroid inhibition also occurs. Corticosteroids reduce mediators of inflammation (e.g. prostaglandins, leukotrienes and nitric oxide) and inhibit production of cytokines by inflammatory cells (e.g. interleukin (IL)-1, IL-8, tumour necrosis factor alpha, gamma interferon). By using the two compounds together, greater efficacy and a rapid response may be achieved.

Nonetheless, due to incompatibility between existing marketed formulations, it is not recommended to apply both products simultaneously. For ease of application, calcipotriol and betamethasone dipropionate have been combined in an ointment containing the same concentration of calcipotriol (50 μg g⁻¹) and betamethasone dipropionate (0.5 mg g⁻¹) as the individual products already granted marketing authorization in Europe and North America.

Two large studies (data on file, Leo Pharmaceuticals) with the combined formulation used twice daily in the treatment of psoriasis vulgaris have shown better efficacy and similar or better tolerability than its active components alone.

In addition to determining if the combined formulation used once daily was more effective than calcipotriol ointment or vehicle ointment used twice daily, the present study was conducted in order to estimate the difference in efficacy between the combined formulation used once daily and twice daily.

Patients and methods

This was an international, multicentre, prospective, randomized, double-blind, vehicle-controlled, parallel group, four-arm study conducted in seven European countries and in Canada. The study was reviewed and approved by all relevant ethics committees and health authorities. All patients gave signed consent to participate in the trial.

Subjects

Volunteers aged 18–86 years were recruited on the basis of a clinical diagnosis of psoriasis vulgaris which involved at least 10% of one or more body regions (arms, legs and trunk). Any patients who had received systemic antipsoriatic treatment within the previous...
6 weeks or topical antipsoriatic treatment within the previous 2 weeks were excluded. Other exclusion criteria included the need for concurrent use of type III or IV topical corticosteroids, recent exposure to sun or ultraviolet treatments, a current diagnosis of unstable psoriasis, atopic dermatitis, seborrhoeic dermatitis or other inflammatory skin disease, pregnancy or breast-feeding and the use of any other medications that could affect the course of the psoriasis.

Treatments

Patients were randomized in the ratio 2 : 2 : 2 : 1 to the following treatment groups:

- Combined formulation (Dovobet® ointment) once daily: calcipotriol 50 μg g⁻¹ (as hydrate) plus betamethasone 0·5 mg g⁻¹ (as dipropionate) in a new ointment vehicle used once daily (evening) and, to allow for the double-blind, the new ointment vehicle used once daily (morning); or
- combined formulation (Dovobet® ointment) twice daily: calcipotriol 50 μg g⁻¹ (as hydrate) plus betamethasone 0·5 mg g⁻¹ (as dipropionate) in a new ointment vehicle used twice daily; or
- calcipotriol (Dovonex® ointment): 50 μg g⁻¹ (as anhydrate) in the currently marketed ointment vehicle used twice daily; or
- vehicle: new ointment vehicle used twice daily.

Patients were randomized to a treatment group by a computer-generated random numbers table. Patients were each given a treatment kit identified by a randomization code number, and the treatment kits were assigned to patients in sequence of ascending randomization code number at each centre.

All treatments were in identical tubes and the three different investigational products (combined formulation, calcipotriol, vehicle) were ointments of almost identical appearance. Each tube was labelled either ‘morning’ or ‘evening’. All study personnel and participants were thus blinded to treatment assignment for the duration of the study.

Treatment was applied twice daily to the affected areas. Scalp and facial psoriasis were not treated with trial medication nor assessed.

Assessments

The extent and severity of psoriasis were recorded at each visit (week 0, 1, 2 and 4) using the Psoriasis Area and Severity Index (PASI). A target lesion was selected at visit 1 and assessed for thickness, redness and scaliness at each visit. An overall efficacy assessment was made by the investigator and the patient at each visit after baseline using a defined six-point scale of worse, unchanged, slight improvement, moderate improvement, marked improvement, and clearance. Blood samples were taken at visit 1 and at the end of treatment to check albumin corrected serum calcium. Adverse events were recorded at each visit.

The primary efficacy criterion was the percentage change in PASI from baseline to end of treatment. Secondary response criteria included the following: percentage change in thickness score of the target psoriatic lesion from baseline to each subsequent assessment and to the end of treatment, speed of response as assessed by the percentage change in PASI from baseline to visit 2, and the investigator’s overall assessment of the treatment efficacy from baseline to end of treatment.

Sample size and statistics

A sample size of 160 patients in the combined formulation used once and twice daily groups and 80 patients in the vehicle group was calculated to give each comparison between the combined formulation and vehicle 95% power to detect a difference of 15% in percentage change of PASI. This assumes that the common standard deviation (SD) is 30 and uses a two-group t-test with a 0·05 two-sided significance level.

A sample size of 160 patients in the combined formulation used once and twice daily groups and the calcipotriol used twice daily group would give a power near 85% to detect a 10% difference in mean percentage change of PASI between the combined formulation used once daily and calcipotriol used twice daily, and between the combined formulation used once daily and the combined formulation used twice daily. Again, this calculation assumes that the common SD is 30 using a two-group t-test with a 0·05 two-sided significance level.

All efficacy analyses were performed on the intention-to-treat population.

The sample size of the study population was increased in an amendment because of an error in the initial packaging procedure. The study medication was packaged in two batches: in the first batch a ratio of 1 : 2 : 2 : 2 was erroneously followed, whereas in the second batch, the correct ratio of 2 : 2 : 2 : 1 was followed. To compensate for this deviation the sample size was increased to 828.
Results

Demographics

Patients were recruited from 57 centres: 51 centres in seven European countries (Denmark, Finland, France, the Netherlands, Spain, Sweden, U.K.) and six centres in Canada. Recruitment per centre ranged from three to 62 patients.

Overall, patients in all four groups were well-matched at baseline for age, gender, PASI, duration of psoriasis and target lesion thickness (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>Combined formulation once daily</th>
<th>Combined formulation twice daily</th>
<th>Calcipotriol twice daily</th>
<th>Vehicle twice daily</th>
<th>All</th>
</tr>
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<tr>
<td>Randomized</td>
<td>n = 152</td>
<td>n = 237</td>
<td>n = 231</td>
<td>n = 208</td>
<td>n = 828</td>
</tr>
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<td>Mean age (years)</td>
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<td>49.3</td>
<td>49.0</td>
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<td>48.5</td>
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<td>Gender (percentage males)</td>
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<td>69.6</td>
<td>61.9</td>
<td>63.5</td>
<td>64.0</td>
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<tr>
<td>Mean PASI</td>
<td>9.9</td>
<td>10.6</td>
<td>10.8</td>
<td>10.4</td>
<td>10.5</td>
</tr>
<tr>
<td>Mean duration of psoriasis (years)</td>
<td>18.3</td>
<td>18.3</td>
<td>18.5</td>
<td>17.9</td>
<td>18.3</td>
</tr>
</tbody>
</table>

PASI, Psoriasis Area and Severity Index.

Patients

In total, 828 patients were included in the study. Of these, 818 comprised the efficacy population (150 combined formulation once daily, 234 combined formulation twice daily, 227 calcipotriol, 207 vehicle) and 821 comprised the safety population (151 combined formulation once daily, 235 combined formulation twice daily, 227 calcipotriol, 208 vehicle).

In total, 77 (9%) patients contributed efficacy data but withdrew during the study, including nine (6%) in the combined formulation once daily group, 16 (7%) in the combined formulation twice daily group, 19 (8%) in the calcipotriol group, and 33 (16%) in the vehicle group. The main reasons for withdrawal included unacceptable adverse events, occurring in two patients in the vehicle group and four patients in the calcipotriol twice daily group, and unacceptable treatment efficacy, occurring in 19 patients in the vehicle group, two patients in the calcipotriol group and a single patient in the combined formulation twice daily group. The most common reason for withdrawal was ‘emergence of various exclusion criteria’, which affected all treatment groups similarly. Attendance at study visits was good.

Efficacy

The difference of 5.4% in the mean percentage change in PASI from baseline to end of treatment was not statistically different between the combined formulation used once or twice daily (P = 0.052). The mean percentage change at the end of treatment was greater in the once daily combined formulation group (68.6%) compared with both the calcipotriol group (58.8%, P < 0.001), and the vehicle group (26.6%, P < 0.001). Similarly, the twice daily combination group had a greater mean percentage PASI reduction (73.8%) than both the calcipotriol and vehicle groups (P < 0.001) (Fig. 1, Table 2).

The speed of response was assessed using the percentage change in PASI from baseline to visit 2 (week 1). After 1 week of treatment the percentage change in PASI was greater in the combined formulation groups (45.5% once daily, 47.6% twice daily) than in the calcipotriol groups (33.6%, P < 0.001) and the vehicle group (20.4%, P < 0.001). There was no significant difference seen in the speed of response between the once or twice daily dosing of the combined formulation (P = 0.30).

In terms of the percentage change in thickness of the target lesion from baseline to the end of treatment, no statistically significant difference was seen between the combined formulation once daily and calcipotriol. Similarly, the combined formulation used once vs.
twice daily showed no significant difference in the percentage change in the thickness of the target lesion. However, a statistically significant difference in the thickness of the target lesion was seen between both of the combined formulation groups and the vehicle group ($P < 0.001$) at the end of treatment.

Patients who achieved ‘marked improvement’ or ‘clearance’ according to the investigators’ or patients’ overall assessment were classified as ‘responders’. At the end of treatment there was a higher percentage of ‘responders’ in the combined formulation groups (once daily: investigators 63·3%, patients 65·3%, $n = 150$; twice daily: investigators 73·5%, patients 70·1%, $n = 234$) than in the calcipotriol group (investigators 50·7%, patients 51·5%, $n = 227$) and vehicle group (investigators 9·2%, patients 12·6%, $n = 206$) (Fig. 2).

With respect to the investigators’ overall assessment of efficacy at the end of treatment, clearance was achieved in 14% of patients (21 patients) who had received the combined formulation once daily and in 20·1% of patients (47 patients) who had received the combined formulation twice daily, compared with clearance in 9·7% (22 patients) of the calcipotriol group and 0% of the vehicle group. No rebound flare was seen in any of the patients.

The amount of study medication used during the total treatment period (from visit 1 to end of treatment) varied between the treatment groups. Approximately twice as much medication (not including the vehicle) was used in the groups using the combined formulation or calcipotriol twice daily compared with the group using the combined formulation once daily [combined formulation once daily: 76·2 g combined formulation plus 72·1 g vehicle; combined formulation twice daily: 156·0 g; calcipotriol: 166·8 g; vehicle: 152·8 g (mean 4 week values)].

**Safety**

Safety data were contributed by 821 of 828 patients. All adverse drug reactions were of a lesional or perilesional nature. The proportion of patients who experienced adverse reactions was less in the combined formulation group (once and twice daily) than in the calcipotriol group [odds ratio (OR) = 0·45 ($P = 0·01$) and OR = 0·48 ($P < 0·01$), respectively]. Overall, the percentage of patients with lesional/perilesional adverse reactions was less in the combined formulation groups and the vehicle group than in the calcipotriol group (9·9% combined formulation once daily, 10·6% combined formulation twice daily, 19·8% calcipotriol, 12·5% vehicle). The most common adverse reaction was pruritus (2·6% combined formulation once daily, 5·1% combined formulation twice daily, 12·3% calcipotriol, 10·6% vehicle). None of the patients randomized to the combined formulation once and twice daily groups withdrew due to an unacceptable adverse event compared with 1·8% in the calcipotriol group and 1% in the vehicle group.

No changes in any of the groups were seen during the study for the laboratory parameters S-albumin, S-calcium and albumin adjusted S-calcium.

In this study three cases of mild to moderate skin atrophy were reported as adverse events after 2 weeks.
of treatment. One event (mild intensity) followed treatment with the combined formulation used once daily, another event (moderate intensity) followed treatment with calcipotriol and the third event (mild intensity) followed treatment with the vehicle. The events of atrophy were lesional/perilesional in the combined formulation and calcipotriol treated patients, while in the vehicle group the atrophy occurred on the finger which applied the ointment.

**Discussion**

This was a large, double-blind, randomized clinical trial studying the treatment response to different treatment agents and treatment regimen.

The prestudy sample size calculations, based on a predicted SD of 30, showed a need for 160 patients in each active treatment arm, and 80 in the vehicle group. The actual SD was 31.3, and the number of patients enrolled into each treatment group was deemed adequate to provide a reliable assessment of treatment efficacy. The once daily group only had 151 patients enrolled into it, due to the packaging error noted earlier in the paper. Blinding was ensured during the study, as described in the Methods section, and no treatment was revealed prematurely by opening the randomization code envelopes. PASI was employed as the primary measure of efficacy. PASI is a widely used validated scale that takes into account the relevant features of psoriasis, and thus changes in PASI reflect the clinical response of the whole body.

The rationale for the design of the trial should be reviewed. A 4-week treatment regimen was chosen to measure the initial response to the therapy, as both the degree of efficacy and the speed of efficacy of the treatment are meaningful. A previous study showed that the combined formulation used twice daily was effective within a short period of time, and thus provided the basis for a 4-week treatment plan in this trial including a once daily treatment group. The study was not intended to examine the combined formulation as maintenance therapy.

To respect the double-blind design, in the combined formulation once daily treatment arm a vehicle was given in addition to the combined formulation to have two applications per day as in the other arms. Patients in this group received the vehicle ointment in the morning and the combined formulation in the evening. The active treatment was given in the evening because patients were thought to be most compliant with their evening treatment.

The results from the present study are in agreement with previous studies which have shown that the combined formulation is superior in efficacy to each of its active ingredients (calcipotriol and betamethasone dipropionate) when used alone in a twice daily dosing regimen (data on file, Leo Pharmaceuticals). In addition, this is the first study that estimates the difference in efficacy between once and twice daily treatment with the combined formulation.

The difference in efficacy demonstrated between the combined formulation used once and twice daily based on the mean percentage change in PASI from baseline to the end of treatment narrowly missed statistical significance ($P = 0.052$). Data from other measures of efficacy (speed of response, percentage change in thickness of lesion) also showed non-statistical differences between the once and twice daily combined formulation groups. These outcomes taken together suggest that treatment with the combined formulation once daily is as clinically effective as treatment with the same formulation twice daily.

It is important to put the statistical comparison between the combined formulation used once and twice daily based on the mean percentage change in PASI from baseline to the end of treatment ($P = 0.052$) into clinical perspective when comparing the two dosing regimens. Initially, patients had a mean PASI of 10.5, which is generally considered to correspond to moderate to severe psoriasis. However, 4 weeks after therapy with the combined formulation (once or twice daily) the mean PASI had decreased to approximately 3, which is indicative of a mild condition. With a PASI near 3 (change in PASI in the 70% range), reductions in the area affected with psoriasis are usually not associated with improvements in PASI, as the percentage of each segment affected with psoriasis is usually less than 10%. Therefore PASI may be a less precise tool to measure the psoriasis condition when scores are low.

Clinical relevance of the therapy must also be evaluated by accounting for patient satisfaction. A 70–75% improvement in PASI is often satisfactory to the patient. From a clinical standpoint, the 3–5% differences in PASI improvement between the combined formulation used once and twice daily translate to a non-significant clinical difference and thus favour a once daily dosing regimen. A once daily dosing schedule would offer some potential benefits in the management of this chronic disease. Once daily dosing would halve the amount of ointment used by the patient, and thus reduce the cost of treatment and the
patient’s risk of experiencing steroid-related adverse events. Furthermore, the convenience of a once daily treatment regimen is valued by patients.

Potent topical corticosteroid preparations used for long periods, or in excessive quantities, can detrimentally affect the skin in various ways, with skin atrophy being a well-recognized risk. Corticosteroid-induced skin atrophy is thought to be principally due to the inhibition of the synthesis of collagen in connective tissue. Optimal use of corticosteroids (i.e. using the lowest potency possible for the shortest period of time) or discontinuous application may decrease or eliminate the chance of permanent atrophy.

In this study, three cases of mild to moderate skin atrophy were observed: one case in each of the once-daily combined formulation, calcipotriol and vehicle groups. Interestingly, as opposed to the skin-thinning effects of corticosteroids, calcipotriol alone has been noted to cause skin thickening, and thus an event of skin atrophy would not be expected to occur with its use. There are reports of ultrasound-detected (but not clinically detected) skin atrophy following application of the vehicle, but the mechanism is not clear. With these factors in mind, the three reports of skin atrophy in three different treatment groups, at least one of which has a mode of action contrary to producing atrophy, do not correlate to a notable risk of skin atrophy with any of the compounds when used for 4 weeks. The resolution of psoriasis, involving reduction in skin thickness and pre-existing atrophy may contribute to the difficulty in assessing the condition.

The overall proportion of patients reporting lesional/perilesional adverse reactions to the combined formulation was significantly less than the proportion reporting adverse reactions to calcipotriol. No statistical difference existed between the combined formulation once and twice daily groups. These results support data from previous studies (data on file, Leo Pharmaceuticals), which concluded that the risk–benefit ratio for the combined formulation is favourable compared to treatment with each of the components as monotherapy. Future studies are needed to evaluate the long-term safety potential of the combined formulation.

The combination in an ointment formulation of calcipotriol 50 μg g⁻¹ and betamethasone dipropionate 0·5 mg g⁻¹ used once or twice daily is a highly effective and well-tolerated treatment for psoriasis vulgaris, which offers an improved risk–benefit ratio over treatment with calcipotriol ointment or vehicle alone. The observed difference in efficacy between the once and twice daily dosing regimens was both statistically and clinically non-significant. The insignificant statistical and clinical differences between treatment with the combined formulation once and twice daily, together with the desire to reduce the dose of corticosteroids and to increase patient compliance, support the recommendation that the combined formulation should be used in psoriasis therapy as a once daily treatment.

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