

CLINICAL REPORT

A New Calcipotriol/Betamethasone Formulation with Rapid Onset of Action was Superior to Monotherapy with Betamethasone Dipropionate or Calcipotriol in Psoriasis Vulgaris

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In this study, we compared a new combination ointment containing both calcipotriol and betamethasone dipropionate with betamethasone dipropionate ointment (Diprosone®) and calcipotriol ointment (Daivonex®) in patients with psoriasis vulgaris; 1106 patients were randomized to twice daily double-blind treatment with combination, betamethasone dipropionate or calcipotriol for 4 weeks. Patients then received twice daily calcipotriol, unblinded, for a further 4 weeks. Mean percentage change in PASI at end of the double-blind phase was –74.4 (combination group), –61.3 (betamethasone group) and –55.3 (calcipotriol group). Mean difference (95% CI) combination-betamethasone was –13.1 (–16.9 to –9.3, $p < 0.001$) and for combination-calcipotriol –19.0 (–22.8 to –15.2, $p < 0.001$). The differences in PASI were also statistically significant after 1 week. In the double-blind phase, 8.1% of patients (combination) reported lesional/perilesional adverse reactions compared to 4.7% (betamethasone) and 12.0% (calcipotriol). In the combination group, mean PASI at the end of the double-blind phase was 2.5, and at end of the unblinded phase 3.6, compared with 3.9 and 4.1 (betamethasone) and 4.4 and 3.7 (calcipotriol). Calcipotriol/betamethasone combination is more effective and has a more rapid onset of action than either active constituent used alone, and is well tolerated. It is safe to transfer patients from combination to calcipotriol, with maintenance of clinical effect. **Key words:** *randomized controlled trial; PASI; maintenance.*

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Psoriasis vulgaris is one of the most common chronic skin diseases, with a prevalence generally estimated at 1.4% to 2.9% of the population. Calcipotriol ointment has been widely available for the treatment of psoriasis since introduction in 1991. It has been shown to be

more effective than vehicle (1), short contact dithranol (2), coal tar (3) and at least as effective as betamethasone 17-valerate (4, 5). Long-term efficacy and safety have been confirmed in studies using calcipotriol for up to 1 year (6–8).

Topical corticosteroids are also extensively prescribed for the treatment of psoriasis. Since calcipotriol and corticosteroids work by different mechanisms (4, 5), superior efficacy may be achieved by combined use. In addition, the local irritation reported with calcipotriol may be alleviated by the anti-inflammatory action of the corticosteroid. Several studies have shown that calcipotriol applied in the morning and corticosteroid in the evening is more effective than either calcipotriol twice daily or corticosteroid twice daily (9–11). However, currently available formulations cannot be applied simultaneously, as they are incompatible.

In view of this, a combination treatment has been formulated in which both calcipotriol and a corticosteroid are stable. The corticosteroid chosen was betamethasone dipropionate, as this is widely used in the treatment of psoriasis and its efficacy and safety are well documented (12–14). The combination treatment contains the same concentration of calcipotriol and betamethasone dipropionate as the individual licensed formulations in Europe and North America.

The purpose of the double-blind phase of the present study was to compare the combination treatment with its active components used alone as licensed formulations. The results of this study will therefore be relevant to the efficacy of these treatments in routine clinical practice.

In the double-blind phase, a parallel group comparison of combination treatment with its individual active components lasted 4 weeks, at the end of which patients entered the maintenance phase and received calcipotriol. The purpose of the maintenance phase was to demonstrate that patients can be safely transferred from combination treatment to a non-steroid-containing treatment with maintenance of efficacy.

The primary efficacy criterion was the percentage

change in psoriasis area and severity index (PASI) from baseline to end of the double-blind phase.

MATERIALS AND METHODS

Patient selection

Prior to inclusion of patients, relevant Institutional Review Boards/Independent Ethics Committees gave favourable opinion/approval of the study, and patients gave signed informed consent. Patients aged 18 years or above, with a clinical diagnosis of psoriasis vulgaris, were entered. Females of child-bearing potential were required to use adequate contraception. Patients with guttate, erythrodermic, exfoliative or pustular psoriasis, other inflammatory skin diseases, abnormality of calcium metabolism or hypercalcaemia were excluded, together with patients who were pregnant, breast-feeding or previously randomized in this study. Also excluded was the use of systemic antipsoriatic treatment or phototherapy 6 weeks before or during the study, topical treatment of psoriasis of trunk or limbs 2 weeks before or during the study, treatment of any lesion where topical corticosteroid was contra-indicated, or current participation in another clinical trial.

Treatment assignment

In the double-blind phase, patients were randomized to one of 3 groups, and received up to 4 weeks' treatment with calcipotriol 50 µg/g plus betamethasone dipropionate 0.5 mg/g combination ointment, or betamethasone dipropionate 0.5 mg/g ointment (Diprosone®) or calcipotriol 50 µg/g ointment (Daivonex®). Randomization was pre-planned in accordance with a computer-generated randomization schedule in a 1:1:1 ratio. The three treatments were ointments of almost identical appearance, and the packaging of each was identical.

After the double-blind phase, all patients entered the maintenance phase and received 4 weeks open treatment with calcipotriol 50 µg/g ointment as required. Patients whose psoriasis cleared in the double-blind phase before 4 weeks entered the maintenance phase at this time and were supplied with calcipotriol to use as required. All medications in both phases were used twice daily to treat psoriasis of the trunk and/or limbs.

Assessments

Patients were assessed at baseline, after 1, 2 and 4 weeks in the double-blind phase and after 1 and 4 weeks in the maintenance phase. Assessments made were PASI, target lesion assessment (redness, thickness and scaliness each assessed on a 9-point scale) and investigators' and patients' assessment of treatment response compared to baseline (worse, unchanged, slight improvement, moderate improvement, marked improvement, cleared). A modified PASI was used which excludes assessment of the head, since this area was not treated with study medication; its possible range was 0 to 64.8. At baseline and the end of the double-blind phase, a blood sample was taken for analysis of serum albumin and serum total calcium, and calculation of albumin-corrected serum calcium.

Statistical methods

The primary efficacy criterion was the percentage change in PASI from baseline to end of the double-blind phase. A sample size of 270 in each treatment group would give each comparison of the combination treatment with its active components

90% power to detect a difference in mean change of 8.4 percentage points, assuming a common standard deviation of 30% (9, 13) and using a two group *t*-test with a 0.05 two-sided significance level.

For all analyses, the combination treatment group was compared with the betamethasone dipropionate and with the calcipotriol groups. The efficacy of the combination treatment group was not based on detecting a significant treatment effect for either of the two comparisons considered, but rather both comparisons had to show a statistically significant effect in favour of the combination treatment. Therefore no adjustment of significance levels to account for multiple testing was deemed necessary.

The percentage change in PASI and in thickness of the target lesion were compared between treatment groups using analysis of variance including treatment and country in the model as design variables. The difference, its 95% CI and a *p*-value were calculated from the analysis of variance.

In accordance with the protocol for both investigator and patient assessments, patients who achieved "marked improvement" or "clearance" at the end of the double-blind phase were classified as responders. The proportions of responders were compared between the treatment groups using logistic regression with country in the model as a design variable.

All the double-blind phase efficacy analyses were performed on the intention-to-treat (ITT) population. The results of the maintenance phase are based on all the patients who entered this phase.

RESULTS

Of 1113 patients entered at 79 centres in 10 countries, 1106 were randomized: 372 to combination, 365 to betamethasone and 369 to calcipotriol. The proportions of patients withdrawing in the double-blind phase were 7.5%, 5.8% and 10%, respectively. Of the patients entering the maintenance phase, 6.7%, 8.1% and 6%, respectively, withdrew prematurely. Five patients were excluded from the safety population and nine from the ITT population as they provided no data after visit one. The randomization code was prematurely broken for four patients prior to unblinding of the study. Table I gives the demographics and baseline characteristics of randomized patients. Six patients of more than 80 years of age were included. Six patients had a duration of psoriasis of zero years, but this was only measured to the nearest whole year.

Compliance with using medication as prescribed

Table I. *Demographics and baseline characteristics*

	Combination (<i>n</i> = 372)	Betamethasone (<i>n</i> = 365)	Calcipotriol (<i>n</i> = 369)
Mean age (years)	47.6	46.0	47.6
Range	18–89	18–89	18–88
Males (%)	58.1	60.8	60.4
Caucasian (%)	99.2	96.4	99.5
Mean baseline PASI	10.8	10.5	10.9
Range	2.1–38.0	2.4–39.6	2.4–38.8
Mean duration of psoriasis (years)	19.0	17.7	18.6
Range	0–62	0–63	0–65

during the double-blind phase was 68% for the combination and calcipotriol groups and 69% for the betamethasone group. The mean weight of medication used in this phase was 143.1 g (combination group), 144.5 g (betamethasone group) and 163.0 g (calcipotriol group). Patients in the maintenance phase were given calcipotriol to use as required; 990 (97%) used calcipotriol.

Efficacy

Mean percentage change in PASI from baseline to end of the double-blind phase (primary efficacy criterion) was -74.4 in the combination group compared to -61.3 in the betamethasone group and -55.3 in the calcipotriol group. The mean difference for combination-betamethasone was -13.1 (95% CI: -16.9 to -9.3 , $p < 0.001$) and for combination-calcipotriol -19.0 (95% CI: -22.8 to -15.2 , $p < 0.001$). The mean percentage decrease in PASI in the combination group was also greater than that in the other two groups when just young (< 35 years of age) or just old (> 60 years of age) patients were considered.

Speed of response assessed by the mean percentage change in PASI at week 1 was -47.4 in the combination group, -39.8 in the betamethasone group and -31.0 in the calcipotriol group (Fig. 1). The mean difference for combination-betamethasone was -7.7 (95% CI: -10.8 to -4.5 , $p < 0.001$) and for combination-calcipotriol -16.3 (95% CI: -19.4 to -13.2 , $p < 0.001$).

Mean percentage decrease in grading of thickness of the target lesion from baseline to end of the double-blind phase was 79.4 in the combination group, 61.7 in the betamethasone group and 63.0 in the calcipotriol group (Fig. 2). The mean difference for combination-betamethasone was 17.8 (95% CI: 13.0 to 22.5, $p < 0.001$) and for combination-calcipotriol 16.3 (95% CI: 11.5 to 21.0, $p < 0.001$).

The numbers of patients classified as responders by the investigators' assessment at the end of the double-blind phase were 251 (68.0%) in the combination group,

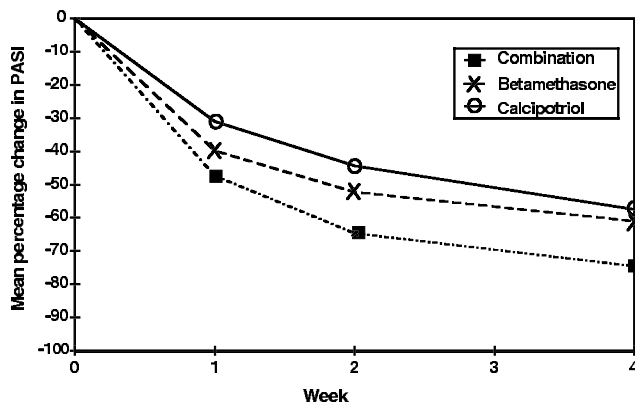


Fig. 1. Percentage change in PASI from baseline to each visit during the double-blind phase.

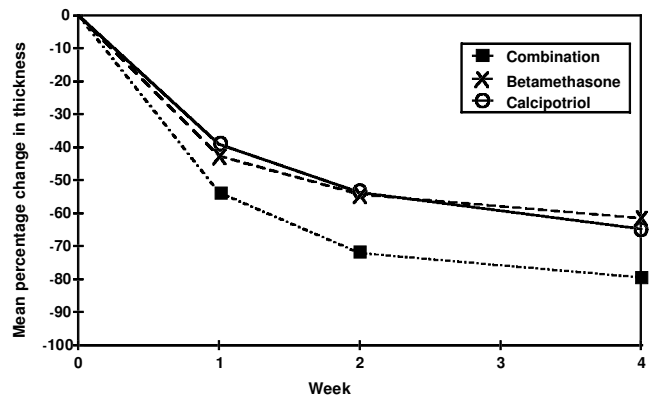


Fig. 2. Percentage change in thickness of target lesion from baseline to each visit during the double-blind phase.

169 (46.6%) in the betamethasone group and 142 (38.9%) in the calcipotriol group. The odds of responder in the combination group relative to those in the betamethasone group were 2.53 (95% CI: 1.86 to 3.44, $p < 0.001$) and in the combination group relative to those in the calcipotriol group 3.45 (95% CI: 2.54 to 4.72, $p < 0.001$). The proportions of responders by the patients' assessment at the end of the double-blind phase were similar (67.2% combination, 50.4% betamethasone, 38.4% calcipotriol).

For the patients who entered the maintenance phase, the mean PASI in the combination to calcipotriol group was 2.5 at the end of the double-blind phase and 3.6 at the end of the maintenance phase. The corresponding figures for the betamethasone to calcipotriol group were 3.9 and 4.1 and for the calcipotriol to calcipotriol group 4.4 and 3.7.

Safety

In the double-blind phase, 99 (26.8%) patients in the combination group, 117 (32.1%) in the betamethasone group and 130 (35.5%) in the calcipotriol group reported adverse events. The proportions of patients reporting lesional/perilesional adverse reactions were 8.1%, 4.7% and 12.0%, respectively. In the maintenance phase, 107 (31.1%) patients in the combination to calcipotriol group, 125 (36.3%) in the betamethasone to calcipotriol group and 113 (34.0%) in the calcipotriol to calcipotriol group reported adverse events.

There was only one serious adverse event where a possible relationship to study treatment was not excluded. This was a patient in the combination group who presented at baseline with widespread, infiltrated, oozing and crusting psoriasis. After 2 weeks' treatment, a facial oedema was described. Serum cortisol and plasma ACTH were within the normal range. The patient was withdrawn after 3 weeks' treatment in the double-blind phase, and the facial oedema resolved over the next 2 weeks.

The geometric mean of the ratio at end of the

double-blind phase to baseline for each of the laboratory parameters was close to one for each treatment group, indicating that mean values at the end of the double-blind phase were similar to those at baseline.

DISCUSSION

The primary objective of this study was to compare the clinical efficacy, in terms of the percentage change in PASI, of the calcipotriol/betamethasone dipropionate combination treatment (Daivobet®) with betamethasone dipropionate treatment alone and with calcipotriol treatment alone in marketed formulations (Diprosone® and Daivonex®, respectively) in patients with psoriasis vulgaris after 4 weeks. PASI is a widely used, validated scale, and change in PASI measures the whole body clinical response of the patient. The three treatment groups were well matched at baseline for age, sex, mean PASI and mean duration of psoriasis.

In this study, the primary efficacy criterion clearly demonstrates that the combination treatment is more effective than marketed formulations of the individual active components. The mean decrease in PASI from baseline to the end of the double-blind phase was statistically significantly greater in the combination group compared to both the betamethasone and calcipotriol groups. The mean percentage decrease in PASI after 1 week was again statistically significantly greater in the combination group compared to both the betamethasone and calcipotriol groups. The calcipotriol/betamethasone dipropionate combination treatment therefore has a more rapid onset of action than either active constituent used alone. The other analyses of response criteria in the double-blind phase, the comparative treatment phase, which included assessments of thickness of a target lesion, and the investigators' and patients' overall assessment of treatment response all showed that the efficacy of the combination treatment was statistically significantly better than that for both betamethasone and calcipotriol treatment.

Combination treatment is well tolerated. There was a lower proportion of patients reporting adverse events in the double-blind phase on combination treatment relative to calcipotriol treatment, probably due to the anti-inflammatory effect of the steroid. There was one serious adverse event where a causal relation with study treatment was not excluded, which was facial oedema, after 2 weeks combination treatment. Redness and oedema in the facial regions could be an effect of the steroid due to increased subcutaneous flow. However, the course seems short for a steroid-induced moon face with changed fat distribution. The systemic effect of glucocorticoid on the hypophysis adrenal axis can only be decided finally with stimulation and suppression tests, which were not performed in this case. However, the normal level of ACTH indicates that there was no major systemic glucocorticoid exposure. Facial redness could

also be due to the calcipotriol component, due to inadvertent transfer of ointment to the face, which has previously been reported (15).

No change in mean albumin-corrected serum calcium was seen. There were no clinically important changes in any albumin-corrected serum calcium values during the study in individual patients in the combination group.

In this study, the results of the defined response criteria are consistent with each other, and the double-blind phase shows that the combination treatment is more effective than its individual active components in the treatment of psoriasis vulgaris.

Ninety-two percent of randomized patients entered the maintenance phase of the study, in which no formal statistical analyses were planned. However, since over 330 patients in each treatment group entered this phase, it is considered that general conclusions can be drawn from the information they provide on the transfer of patients from combination to calcipotriol treatment. Although this phase was open, investigators and patients were still blinded to what treatment had been used before.

The mean PASI at the end of double-blind treatment in the combination group was 2.5. At the end of the maintenance phase, after a further 4 weeks treatment with calcipotriol, the mean PASI was 3.6. The corresponding figures for the betamethasone to calcipotriol group were 3.9 and 4.1 and for the calcipotriol to calcipotriol group 4.4 and 3.7. Psoriasis was maintained under control following transfer to calcipotriol without any signs of rebound flare.

The study supports the conclusion that the benefit/risk ratio of the combination product is clearly superior both to betamethasone dipropionate monotherapy and to calcipotriol monotherapy in their marketed formulation of ointment base. The study has further demonstrated that, after short-term treatment with combination ointment, it is safe to transfer patients to calcipotriol treatment and clinical control of psoriasis can be maintained.

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REFERENCES

1. Dubertret L, Wallach D, Souteyrand P, Perussel M, Kalis B, Meynadier J. Efficacy and safety of calcipotriol (MC 903) ointment in psoriasis vulgaris. *J Am Acad Dermatol* 1992; 27: 983–988.
2. Berth-Jones J, Chu AC, Dodd WAH, Ganpule M, Griffiths W, Haydey R, et al. A multi-centre, parallel-group comparison of calcipotriol ointment and short-contact dithranol therapy in chronic plaque psoriasis. *Br J Dermatol* 1992; 127: 266–271.
3. Tham SN, Lun KC, Cheong WK. A comparative study of calcipotriol ointment and tar in chronic plaque psoriasis. *Br J Dermatol* 1994; 131: 673–677.
4. Cunliffe WJ, Berth-Jones J, Claudy A, Fairiss G, Goldin D, Gratton D, et al. Comparative study of calcipotriol (MC 903) ointment and betamethasone 17-valerate ointment in patients with psoriasis vulgaris. *J Am Acad Dermatol* 1992; 26: 736–743.
5. Kragballe K, Gjertsen B, de Hoop D, Karlsmark T, Van de Kerkehof P, Larko O, et al. Double-blind, right/left comparison of calcipotriol and betamethasone valerate in treatment of psoriasis vulgaris. *Lancet* 1991; 337: 193–196.
6. Ramsay CA, Berth-Jones J, Brundin G, Cunliffe W, Dubertret L, Van de Kerkehof PC, et al. Long-term use of topical calcipotriol in chronic plaque psoriasis. *Dermatology* 1994; 189: 260–264.
7. Poyner T, Hughes IW, Dass BK, Adnitt P. Long-term treatment of chronic plaque psoriasis with calcipotriol. *J Dermatol Treat* 1993; 4: 173–177.
8. Ellis JP, Griffiths WAD, Klaber MR. Long-term treatment of chronic plaque psoriasis with calcipotriol ointment in patients unresponsive to short-contact dithranol. *Eur J Clin Res* 1995; 7: 247–257.
9. Kragballe K, Barnes L, Hamberg KJ, Hutchinson P, Murphy F, Moller S, et al. Calcipotriol cream with or without concurrent topical corticosteroid in psoriasis: tolerability and efficacy. *Br J Dermatol* 1998; 139: 649–654.
10. Lebwohl M, Siskin SB, Epinette W, Breneman D, Funicella T, Kalb R, et al. A multicenter trial of calcipotriene ointment and halobetasol ointment compared with either agent alone for the treatment of psoriasis. *J Am Acad Dermatol* 1996; 35: 268–269.
11. Ruzicka T, Lorenz B. Comparison of calcipotriol monotherapy and a combination of calcipotriol and betamethasone valerate after 2 weeks' treatment with calcipotriol in the topical therapy of psoriasis vulgaris: a multicentre, double-blind, randomized study. *Br J Dermatol* 1998; 138: 254–258.
12. Roberts DT. Comparison of fluticasone propionate ointment, 0.005%, and betamethasone 17,21-dipropionate ointment, 0.05%, in the treatment of psoriasis. *Cutis* 1996; 57: 27–31.
13. Shupack JL, Jondreau L, Kenny C, Stiller MJ. Diflorasone diacetate ointment 0.05% versus betamethasone dipropionate ointment 0.05% in moderate-severe plaque-type psoriasis. *Dermatology* 1993; 186: 129–132.
14. Chuang TY, Samson CR. Clinical efficacy and safety of augmented betamethasone dipropionate ointment and diflorasone diacetate ointment for psoriasis – a multicentre, randomized, double-blinded study. *J Dermatol Treat* 1991; 2: 63–66.
15. Serup J. Calcipotriol irritation: mechanism, diagnosis and clinical implication. *Acta Derm Venereol* 1994; Suppl. 186: 42.