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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

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Summary A clinical study was conducted to determine whether, in the topical treatment of psoriasis, a combination of calcipotriol and betamethasone valerate after previous treatment with calcipotriol alone was more effective than the continuation of the monotherapy with calcipotriol, especially in 'low responders'. Patients ($n = 169$) with the clinical diagnosis 'chronic plaque-type psoriasis' were treated twice daily for 2 weeks with calcipotriol, followed by a 4-week treatment with calcipotriol monotherapy in 87 patients or combined calcipotriol/betamethasone valerate in 82 patients; all patients were followed for 8 weeks. The psoriasis area and severity index (PASI) was used to compare the two treatment groups. The overall therapeutic result was also assessed by the investigators and patients. The combination therapy was more effective, as assessed by all evaluated variables; moreover, patients showing insufficient response to calcipotriol alone after 2 weeks showed a regression of psoriatic lesions using the combination regimen. Thus, the combination of calcipotriol and topical steroids is recommended as the therapy of first choice for patients who do not respond well to treatment with 2 weeks of calcipotriol alone. Furthermore, this combination reduces the hazards associated with the long-term use of topical corticosteroids (atrophy and rebound) as well as the irritation associated with calcipotriol.

Several drugs are currently available for the treatment of psoriasis. Substances like tar, dithranol (anthralin), steroids, retinoids, methotrexate and cyclosporin A, as well as ultraviolet (UV) radiation and their combinations, have been effective treatments for many years. Calcipotriol, the first vitamin D_3 analogue, was introduced into antipsoriatic therapy in the early 1990s and since then it has been used for mild and moderate plaque-type psoriasis. Many clinical studies report the favourable effect of calcipotriol or other calcitriols on the various clinical features of psoriasis.[1–6] Further clinical studies showed that calcipotriol is as clinically effective as topical steroids and short-contact therapy with dithranol.[7–15] Clinical experience and a re-analysis of the clinical comparisons of calcipotriol with topical steroids have shown that about two-thirds of patients respond with a marked improvement in psoriatic lesions.[16] Further experience has been gained with calcipotriol in combination with UVB, PUVA and cyclosporin A. The combinations were more effective and the response showed a more rapid onset than the monotherapy; fewer calcipotriol-induced side-effects were also reported.[17–24]

The present study is the first to determine whether a combination of topical calcipotriol and betamethasone valerate after a 2-week course of treatment with calcipotriol is better than continued monotherapy alone.

Patients and methods

The study was conducted as a multicentre, double-blind, randomized comparison between monotherapy with 0·005% calcipotriol ointment (Psorcutan® Salbe, Schering AG, Berlin, Germany) and a combination of calcipotriol and 0·1% betamethasone valerate ointment (GlaxoWellcome, Hamburg) after 2 weeks of treatment with calcipotriol alone. The study was carried out according to good clinical practice (GCP) guidelines.

Included were men and women patients older than 18 years having chronic plaque-type psoriasis with

lesions on the lower and/or upper extremities and/or trunk, with an affected area not exceeding 30% of the total body surface. No systemic antipsoriatic treatment or UV therapy had been administered during the previous 2 months. The serum calcium levels, renal and liver function were in the normal range; the patients were neither pregnant nor nursing.

Treatment schedule

The study treatment was carried out in four consecutive phases: (i) a 2-week wash-out in which the patients were only allowed to apply an ointment base; (ii) a 2-week monotherapy when calcipotriol was applied twice daily; (iii) a 4-week treatment continuation with either calcipotriol twice daily (monotherapy group) or calcipotriol once daily (morning) and betamethasone valerate once daily (evening) comprising the combination therapy group; and (iv) an 8-week follow-up when the patients applied only the ointment base. Patients with exacerbated disease during the first 2-week treatment phase were excluded from the study. Complete remission before the end of therapy led to the early termination of treatment.

Clinical assessment

Patients were examined 2 weeks before the start of the treatment, after the wash-out period and at 2, 6 and 14 weeks after the start of treatment. At these intervals the severity of the psoriasis was evaluated according to the psoriasis area and severity index (PASI).[25] Additionally, at 2 and 6 weeks the investigators and patients rated the global response according to six- and five-point scales, respectively. The investigator's scale was used to classify patients into high (those graded as 'complete healing' or 'distinct improvement') and low (graded as 'moderate' or 'slight improvement', 'no change' or 'deterioration') responders. A safety evaluation was performed before the start of the wash-out period and after 2 and 6 weeks of treatment, which included serum measurements of creatinine, urea, total calcium, inorganic phosphate, total protein and albumin. All adverse events, whether subjective or objective, were recorded at each visit and particular attention given to any increase in calcium levels above the normal range.

Statistical analysis

The primary end-point was the reduction of the PASI at the end of the therapy. The evaluation of the primary variable was performed as an intention to treat (ITT) analysis. The two treatments were compared using the *t*-test or the non-parametric Mann–Whitney *U*-test at $\alpha = 0{\cdot}025$. The number of patients who remained low responders after the end of the therapy was compared using the one-sided Fisher's exact test at $\alpha = 0{\cdot}025$, so an overall α of 0·05 was maintained. For additional variables, descriptive *P*-values were calculated with the *U*-test or Fisher's test.

Results

Of the 178 patients recruited into the trial, the data for 169 patients from 20 centres in Germany were analysed (94 men and 75 women, mean age 42 years, range 18–80); 87 patients were treated with calcipotriol monotherapy and 82 with the combination therapy. Eleven patients discontinued therapy (five monotherapy and six combination therapy); the reasons for the premature discontinuation were: pathological laboratory values at the beginning, insufficient healing, adverse events, healing of psoriasis or non-medical reasons. Nearly all patients had previously used antipsoriatic medication, with topical glucocorticoid steroids the most frequent. An ITT analysis was carried out of all patient data available after the beginning of treatment.

Psoriasis area and severity index

In the monotherapy group, the mean PASI decreased from 6·2 at the beginning of therapy to 3·5 after 2 weeks, and to 1·9 after 6 weeks; 8 weeks after the end of therapy the PASI increased to 2·6. In the combination

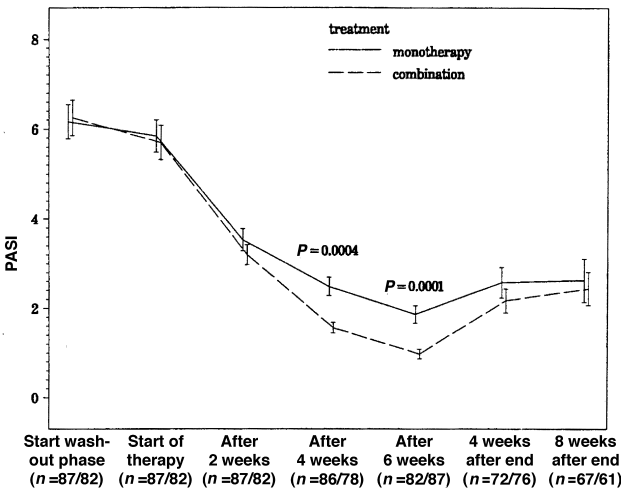

Figure 1. The mean (± SD) changes in the PASI, by 'intention to treat' analysis.

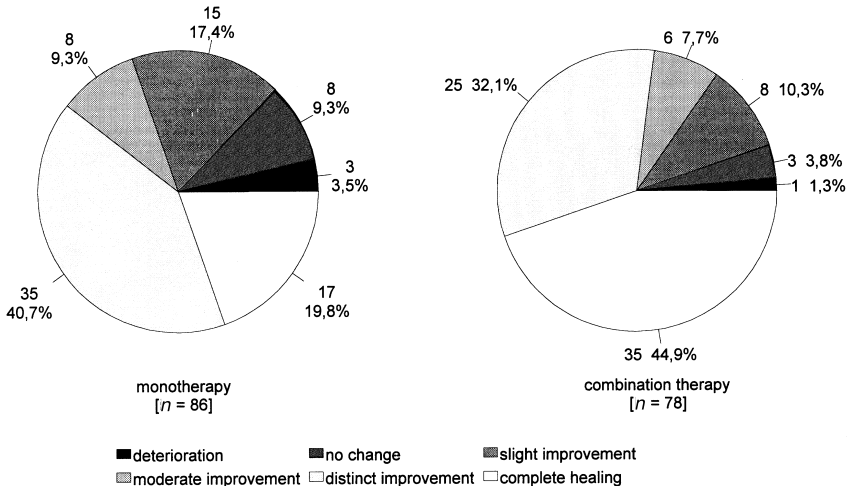

Figure 2. Assessment of the clinical symptoms of psoriasis by the investigator; intention to treat analysis after 6 weeks therapy or at premature withdrawal (includes only patients with at least 4 weeks therapy).

therapy group, the mean PASI decreased from 5·7 at the beginning of therapy to 3·2 after the initial 2-week monotherapy. During the next 4 weeks (under combination therapy) the PASI decreased to 1·0; at 8 weeks after the end of therapy the PASI increased to 2·4. Comparing the two treatments showed a significant advantage for the combination therapy after 2 and 6 weeks ($P < 0{\cdot}001$; Fig. 1).

Global assessment

For the investigator's assessment at the end of therapy, the monotherapy group comprised 17 patients (20%) with 'complete healing' and 35 (41%) with 'distinct improvement'. Thus, there were 52 high responders (60·5%). The other patients in this group showed 'moderate improvement' at best (low responders). In the combination therapy group, 35 patients (45%) showed 'complete healing' and 25 (32%) a 'distinct improvement'; thus 60 patients (77%) were classified as high responders and the others as low responders (Fig. 2). There was no major difference between the global assessment by the patients and that of the investigators.

High and low responders

After the initial 2 weeks of treatment (which was the same in both groups, i.e. calcipotriol monotherapy), there were 50 low responders (58%) in the monotherapy group and 41 (50%) in the combination therapy group (Fig. 3). Of the 50 low responders in the former, 49 continued therapy and at the end of 6 weeks of calcipotriol monotherapy, there were 22 (25%) low responders. Of the 41 low responders in the combination therapy group, 39 continued treatment with the combination and at the end of 6 weeks calcipotriol treatment (2 weeks monotherapy and 4 weeks combination) there were only 12 (15%) low responders. Comparing the two treatment groups showed significant advantages for the combination therapy ($P = 0{\cdot}0189$).

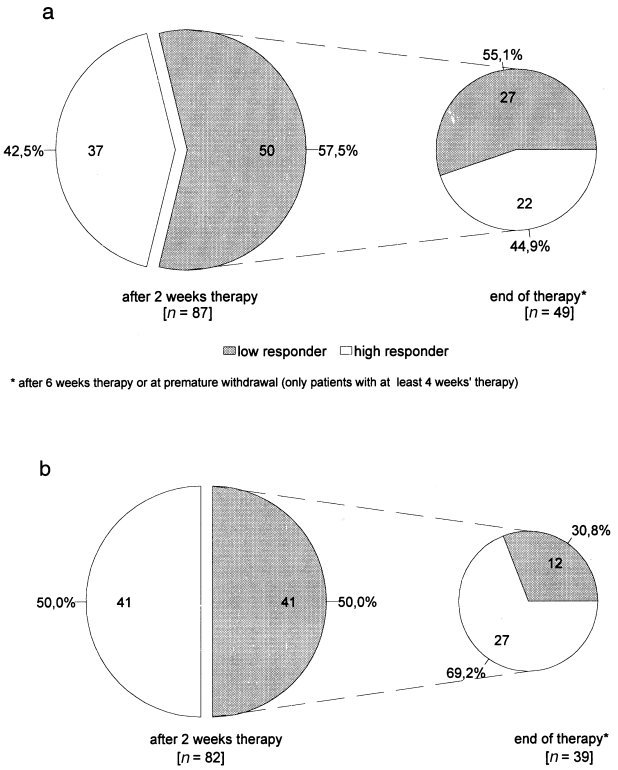

Figure 3. High and low responders after 2 weeks of therapy and at the end of therapy: (a) monotherapy and (b) combination therapy group.

Evaluation of safety and tolerability

Twenty patients (23%) in the monotherapy and 13 (16%) in the combination therapy group reported local or general adverse events (AEs) during therapy. Local AEs were reported in 13 patients (15%) in the monotherapy and in six (7%) in the combination therapy group. The most frequently reported local AEs were erythema, burning and pruritus. Nearly all local AEs were mild or moderate except in two patients (monotherapy) with severe AEs (pruritus, burning sensation of the skin and erythema). Two patients withdrew from the study because of the burning sensation after wiping sweat off their face with contaminated hands (monotherapy) and after an eczematous reaction (combination therapy).

General AEs were documented for 11 patients (12%) in the monotherapy and for seven (8·5%) in the combination therapy group. Most of these AEs could not be related to the study medications. Two patients were withdrawn from the study as their serum calcium levels were above the upper normal range. Both monotherapy and combination therapy were safe treatments, causing no serious AEs.

Discussion

As calcipotriol and betamethasone valerate work by interacting with different receptor subtypes (vitamin D or glucocorticoid receptors), an additive or synergistic effect could theoretically be expected. Therefore, the combination of topical calcipotriol and betamethasone valerate was assessed to determine whether there is such an effect in those patients who do not respond to calcipotriol alone. The results clearly show that the combination of both drugs leads to an additive clinical effect in terms of reduced psoriatic symptoms. Fewer local AEs were reported with combination therapy than in the monotherapy group. In particular, erythema, the most frequently reported local AE, was significantly reduced by an alternate application of calcipotriol and betamethasone valerate. Erythema is thought to be caused by the irritative potential of calcipotriol and might be neutralized by the anti-inflammatory action of betamethasone valerate.

This combined regimen reduced the hazards associated with the long-term use of topical corticosteroids (atrophy, rebound), as well as the irritation associated with calcipotriol. Thus the combination therapy can be recommended for 'low responders', i.e. those who do not respond well to treatment with 2 weeks of calcipotriol alone.

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References

1 Kragballe K, Beck H-J, Sogaard H. Improvement of psoriasis by a topical vitamin D_3-analogue (MC 903) in a double-blind study. *Br J Dermatol* 1988; **119:** 223–30.
2 Kragballe K. Treatment of psoriasis by the topical application of the novel cholecalciferol analogue calcipotriol (MC 903). *Arch Dermatol* 1989; **125:** 1647–52.
3 Staberg B, Roed-Petersen J, Menne T. Efficacy of topical treatment in psoriasis with MC 903, a new vitamin D analogue. *Acta Derm Venereol (Stockh)* 1989; **69:** 147–50.
4 Kragballe K, Fogh K. Long-term efficacy and tolerability of topical calcipotriol in psoriasis. *Acta Derm Venereol (Stockh)* 1991; **71:** 475–8.
5 Dubertret L, Wallach D, Souteyrand P *et al.* Efficacy and safety of calcipotriol (MC 903) ointment in psoriasis vulgaris. *J Am Acad Dermatol* 1992; **27:** 893–8.
6 Nieboer C, Verburgh CA. Psoriasis treatment with vitamin D_3 analogue MC 903. *Br J Dermatol* 1992; **126:** 302–3.
7 Finzi AF. The modern approach: New combined treatments for psoriasis. *Acta Derm Venereol (Stockh)* 1994; **186:** 105–6.
8 Kragballe K, Gjertsen BT, de Hoop D *et al.* Double-blind, right/left comparison of calcipotriol and betamethasone valerate in treatment of psoriasis vulgaris. *Lancet* 1991; **337:** 193–6.
9 Cunliffe WJ, Berth-Jones J, Claudy A *et al.* Comparative study of calcipotriol (MC 903) and betamethasone 17-valerate in patients with psoriasis vulgaris. *J Am Acad Dermatol* 1992; **26:** 736–43.
10 Landi G, Pierleoni M, Polverelli M, Fioravanti F. Calcipotriol, a new topical drug in the treatment of psoriasis: controlled trial vs. Clobetasol. *G Ital Dermatol Venereol* 1993; **128:** 89–93.
11 Berardesca E, Vignoli GP, Farinelli N *et al.* Non-invasive evaluation of topical calcipotriol versus clobetasol in the treatment of psoriasis. *Acta Derm Venereol (Stockh)* 1994; **74:** 302–4.
12 Bruce S, Epinette WW, Funicella T *et al.* Comparative study of calcipotriene (MC 903) ointment and fluocinonide ointment in the treatment of psoriasis. *J Am Acad Dermatol* 1994; **31:** 755–9.
13 Berth-Jones J, Chu AC, Dodd WAH *et al.* A multicentre parallel-group comparison of calcipotriol ointment and short-contact dithranol therapy in chronic plaque psoriasis. *Br J Dermatol* 1992; **127:** 266–71.
14 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:** 247–57.
15 Van der Vleuten Carine JM, de Jong E, Rulo E *et al.* In-patient

treatment with calcipotriol versus dithranol in refractory psoriasis. *Eur J Dermatol* 1995; **5:** 676–9.
16 Kragballe K. Vitamin D and derivatives. In Dubertret L (ed.) *Psoriasis*. Brescia: ISED, 1994: 124–34.
17 Kragballe K. Combination of topical calcipotriol (MC 903) and UVB radiation for psoriasis vulgaris. *Dermatologica* 1990; **181:** 211–4.
18 Kerscher M, Plewig G, Lehmann P. Combination therapy of psoriasis vulgaris with a narrow band UV-B light (Philips TL 01, 311 nm) and calcipotriol. *Akt Dermatol* 1993; **19:** 151–4.
19 Frappaz A, Thivolet J. Calcipotriol in combination with PUVA. A randomised double-blind placebo study in severe psoriasis. *Eur J Dermatol* 1993; **3:** 351–4.
20 Molin L, Liberton H, van Weelden H *et al*. Efficacy and safety of calcipotriol ointments in combination with UVB-therapy. *Satellite Symposium, 3rd congress of European Academy of Dermatology and Venerology in Copenhagen*, September 1993.
21 Speight EL, Farr PM. Calcipotriol improves the response of psoriasis to PUVA. *Br J Dermatol* 1994; **130:** 79–82.
22 Quirino AP, Resende C. Mesquita-Guimaraes. PUVA and topical calcipotriol in psoriasis study of ten patients. *Psoriase Rev* 1995; **1:** 15–22.
23 Grossmann RM, Thivolet J, Claudy A *et al*. A novel therapeutic approach to psoriasis with combination calcipotriol ointment and very low-dose cyclosporine: results of a multicenter placebo-controlled study. *J Am Acad Dermatol* 1994; **31:** 68–74.
24 Bagot M, Grossman R, Pamphile R *et al*. Additive effects of calcipotriol and ciclosporine A. from in-vitro experiments to in-vivo applications in the treatment of severe psoriasis. *C R Acad Sci Paris, Life Sci* 1994; **317:** 282–6.
25 Fredriksson T, Pettersson U. Severe psoriasis—oral therapy with a new retinoid. *Dermatologica* 1978; **157:** 238–44.