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Long-term Efficacy and Tolerability of Topical Calcipotriol in Psoriasis

Results of an Open Study

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Calcipotriol is a non-calcaemic vitamin D_3 analogue. In short-term studies, topically applied calcipotriol is both efficacious and safe for the treatment of psoriasis vulgaris. The purpose of the present study was to determine the efficacy and safety of calcipotriol ointment in patients treated for approximately 6 months. Fifteen patients with plaque-type psoriasis were treated daily with calcipotriol ointment 50 μg/g. After treatment for 6 weeks there was a significant alleviation of erythema, infiltration and scaling. This degree of improvement was maintained throughout the study, except in one patient, who was withdrawn at week 15 because of minimal improvement. At the end of treatment, 80% of the patients showed a moderate improvement at least. Local adverse events occurred in 3 patients. These were mild and transient. Hypercalcaemia or other laboratory abnormalities did not develop in any patient. Morphometric examination of biopsies taken from perilesional skin (i.e. skin exposed to calcipotriol) at the end of treatment did not show signs of epidermal or dermal atrophy compared with uninvolved psoriatic skin. Although only a limited number of patients participated in the study, these results indicate that calcipotriol ointment 50 μ/g is both efficacious and safe for the long-term treatment of psoriasis. ***Key words: Psoriasis; Calcipotriol calcium; Vitamin D_3; Long-term treatment.***

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Calcipotriol (MC 903) is a new vitamin D_3 analogue (1), which in the human histiocytic lymphoma cell line U 937 has as high an affinity as calcitriol, the natural bioactive form of vitamin D_3, for the vitamin D_3 receptor (2). In addition, calcipotriol is as active as calcitriol in inducing differentiation and inhibiting proliferation of human keratinocyte cultures (3). At the same time, the effect of calcipotriol on calcium metabolism in rats is approx. 1/200 that of calcitriol (2). This unique pharmacologic profile of calcipotriol indicates that it may be an efficicacious and well-tolerated topical drug for the treatment of psoriasis. This was confirmed in recent double-blind, placebo-controlled studies (4, 5, 6).

Furthermore, the results of a multicentre trial have shown calcipotriol 50 μ/g ointment to be superior to betamethasone 17-valerate 0.1% ointment for psoriasis vulgaris (7).

These results are based on clinical studies in which patients were treated for 6–8 weeks. Because psoriasis is a chronic disease, it is important to determine whether long-term treatment with topical calcipotriol is also efficacious and safe. The purpose of the present study was to assess the efficacy and tolerability of topical calcipotriol in psoriatic patients treated for approximately 6 monts.

PATIENTS AND METHODS

Patients

This was an open, prospective study of calcipotriol ointment in psoriasis vulgaris. Patients were to be treated for about 6 months (26 weeks). All patients had initially responded to treatment with calcipotriol ointment in an 8-week clinical trial (6), but had later experienced a recurrence of their disease. When admitted to the present study, from 4 to 17 weeks had elapsed since stopping the previous treatment with calcipotriol. In the meantime, the patients had not received any anti-psoriatic treatment.

Excluded were patients with hypercalcaemia, impaired renal and/or hepatic function, were taking calcium tablets or tablet còntaining more than 400 i.u. of vitamin D per day. Patients were not permitted to take any other medication that could affect the course of the disease. All patients gave their informed consent to join the study. The study was approved by the local medical ethics committee.

Study drugs

Ointment containing calcipotriol 50 μg/g was kindly provided by Leo pharmaceutical products, Denmark. The drug, up to 100 g per week, should be applied twice daily without occlusion to all affected skin areas. Calcipotriol ointment was not allowed on the face or scalp; instead, patients applied an emollient or a low-strength corticosteroid.

Table I. *Characteristics of patients included in the study*

Female/male (%)	47/53
Age (years)	42 (21–71)
Duration of psoriasis (years)	18 (2–39)
Per cent skin involved	14 (5–30)

Values are means. Ranges are shown in parentheses.

At each monthly visit the investigator recorded the severity of the psoriatic lesions on a 4-point scale (0: absent; +3: severest) for the three parameters: erythema, thickness, and scaling. This was done separately for each of the three areas: upper extemities, trunk, lower extremities. At each visit the patient made an assessment of the overall response to therapy considering both the extent and the degree of the disease, compared with the start of treatment, on a 6-point scale (−1: worse; +4: cleared).

Blood samples for analysis of whole blood count and measurement of serum alkaline phosphatase, aspartate aminotransferase, bilirubin, creatinine, total calcium and phosphate, were taken before starting therapy and at monthly intervals thereafter. At each visit the investigator put to the patient a general, non-leading question concerning adverse events. If the patient's answer to the open question was "no", no further questions were asked. Furthermore, the investigator examined the patient regarding adverse effects on the skin.

Histologic examination

At the end of the treatment, 4-mm punch biopsies were taken from perilesional skin (exposed to calcipotriol ointment) and from univolved skin approximately 10 cm from lesional skin (not exposed to calcipotriol ointment). Biopsies were obtained from 8 of the 15 patients. To analyse the presence of skin atrophy the following parameters were determined by light microscopic examination of biopsy specimens stained with hematoxylin and eosin: the thickness of epidermis, measured as the distance from the compact stratum corneum to the basal membrane between the rete ridges; the thickness of the papillary dermis measured as the distance from the top of the dermal papillae to the superficial vascular plexus. In addition, the degree of atrophy of the reticular dermis was graded on a 4-point scale from 0 to 3 (0: absent; 3: severest) based on the cellularity, fibre thickness, hyalinization and architecture. Adnexal atrophy was graded on a similar scale.

Statistical analysis

The change in clinical parameters and the change in labortory examinations were tested for statistical significance by one-sample *t*-tests. The comparison of skin biopsies was done by two-sample *t*-test. A *p*-value below 0.05 was considered significant.

RESULTS

The demographic data of the 15 psoriatic patients recruited for the study are shown in Table I. Most patients had disease of moderate severity. The 15 patients were treated for a mean of 31 weeks (range 15–41 weeks). One had only a temporarily satisfactory improvement and was withdrawn at week 15. Most patients applied calcipotriol ointment twice daily. However, during parts of the study up to 4 patients applied drug only once daily. The patient withdrawn because of lack of efficacy had applied the drug once daily throughout the study.

Treatment with calcipotriol ointment resulted in a marked and statistically significant decrease of erythema, thickness and scaling (Fig. 1). This improvement was present as early as at week 6 and was maintained throughout the treatment. The investiga-

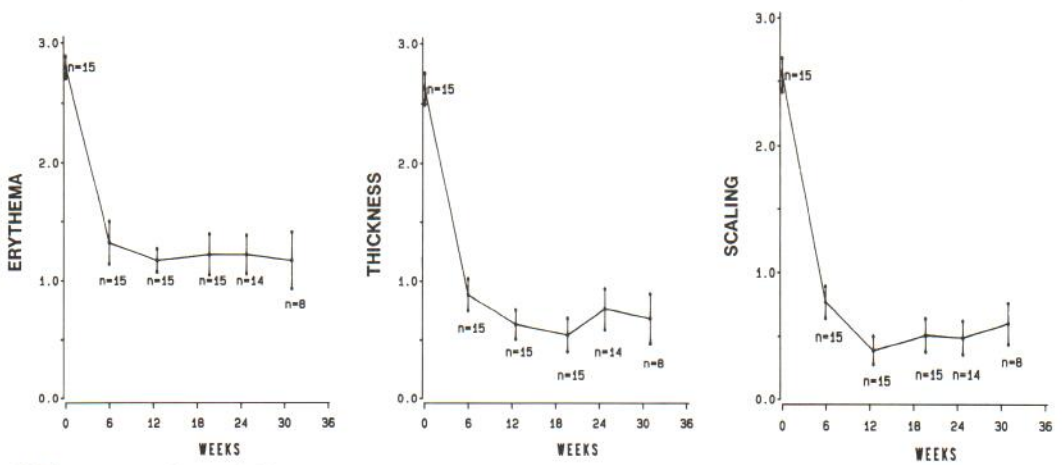

Fig. 1. The mean erythema, thickness and scaling of psoriatic lesions during treatment with calcipotriol ointment. Vertical range bars indicate S.E.M. Difference between start of treatment and each of the following visits: $p < 0.01$ for erythema, thickness and scaling.

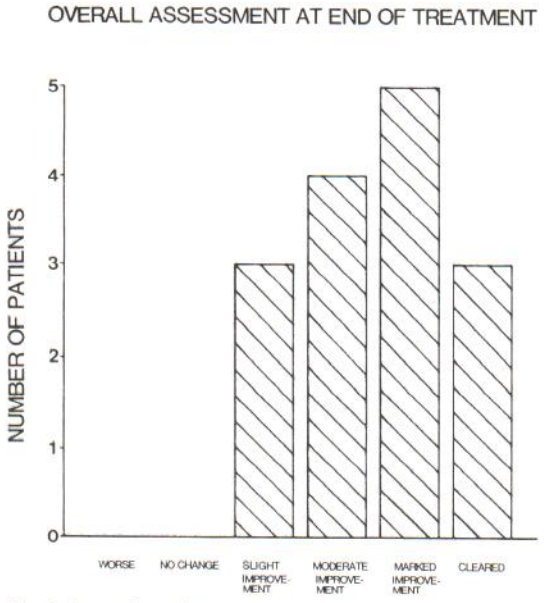

Fig. 2. Investigator's overall assessment of improvement of psoriasis at the end of treatment with calcipotriol ointment 50 μg/g compared with the start of treatment ($n=15$). Difference between start of treatment and end of treatment: $p < 0.001$.

tor's overall assessment of the improvement compared with the start of treatment showed that 80% of the patients had experienced at least a moderate improvement (Fig. 2).

A total of 3 adverse events (lesional irritation ($n=2$); facial dermatitis ($n=1$)) were reported by 3 patients. The facial dermatitis was treated with 1% hydrocortisone cream. After stopping hydrocortisone, the facial dermatitis did not recur despite continued use of calcipotriol ointment on trunk and extremities. Calcipotriol was not used on the face. Laboratory analyses did not show any consistent changes. In particular, there were no clinically important or consistent changes of serum calcium (Table II).

Skin biopsies were obtained from 8 of the 15 patients at the end of treatment. The thickness of the epidermis and of the papillary dermis was similar in uninvolved psoriatic skin (not exposed to calcipotriol) and in perilesional skin (exposed); for epidermis: 0.066±0.030 mm and 0.091±0.029 mm, respectively, and for papillary dermis: 0.103±0.0045 mm and 0.105±0.32 mm, respectively. Mild atrophic changes of the reticular dermis were found in the uninvolved skin in 1 patient. Mild adnexal atrophy of the perilesional skin was found in 1 patient. Mild to moderate adnexal atrophy was present in both uninvolved and perilesional skin in 2 patients (data not shown).

DISCUSSION

The results of the present study suggest that long-term treatment with calcipotriol ointment in psoriasis vulgaris is both efficacious and safe. It should be stressed, however, that only a limited number of patients participated and that these were selected in the sense that they had previously responded favourably to treatment with calcipotriol ointment.

Although the average degree of improvement was maintained during the treatment, individual variations were observed. Such clinical variations may reflect spontaneous changes in disease activity rather than temporary tachyphylaxis to the treatment. The same holds true for the patient withdrawn because of insufficient improvement which, in this particular case, may also have been due to the fact that the drug was only applied once daily throughout the study.

The adverse events recorded were few and similar to those seen in previous short-term studies with calcipotriol ointment (6, 7). Although based on a limited number of patients, these findings indicate that long-term calcipotriol treatment is tolerated just as well as short-term treatment. Also, there were no signs of a cumulative effect of calcipotriol treatment on systemic calcium metabolism.

It is well documented that long-term treatment with topical corticosteroids can cause skin atrophy. Because calcipotriol and other biologically active vitamin D_3 analogues can inhibit the proliferation of keratinocytes (3, 7) and fibroblasts (9) in vitro, skin exposed to calcipotriol ointment was examined for histologic signs of epidermal and dermal atrophy. At

Table II. *Serum calcium before and during treatment of psoriasis with calcipotriol ointment 50 μg/g*

Week	*n*	Serum calcium (mmol/l)
0	12	2.42±0.08
6	9	2.39±0.06
12	9	2.33±0.13
20	10	2.40±0.07
25	9	2.39±0.06
31	8	2.39±0.07

Values are means ± SD.

the end of treatment, there were no differences between perilesional (exposed) skin and uninvolved (non-exposed) skin. The reason for choosing perilesional skin instead of lesional skin is that the presence of mild psoriatic changes in lesional skin might prevent the detection of epidermal atrophy.

In conclusion, this study indicates that calcipotriol ointment is an efficacious and safe treatment for the long-term treatment of psoriasis vulgaris. If these results are confirmed in larger scale studies, topical calcipotriol might be considered as the drug of choice for the topical treatment of psoriasis.

REFERENCES

1. Calverley MJ. Synthesis of MC 903, a biologically active vitamin D analogue. Tetrahedron 1988; 43: 4609–4619.
2. Binderup L, Bramm E. Effects of a novel vitamin D analogue on cell proliferation and differentiation in vitro and on calcium metabolism in vivo. Biochem Pharmacol 1988; 37: 889–895.
3. Kragballe K, Wildfang I-L. Effect of MC 903 (calcipotriol), a novel vitamin D_3 analogue, on proliferation and differentiation of human epidermal keratinocytes in vitro. Arch Dermatol Res 1990; 282: 164–167.
4. Kragballe K, Beck H-I, Søgaard H. Improvement of psoriasis by a topical vitamin D_3 analogue (MC 903) in a double-blind study. Br J Dermatol 1988; 119: 223–230.
5. Staberg B, Roed-Petersen J, Menn T. Efficacy of topical treatment in psoriasis with MC 903, a new vitamin D_3 analogue. Acta Derm Venereol (Stockh) 1989; 69: 147–150.
6. Kragballe K. Treatment of psoriases by the topical application of the novel vitamin D_3 analogue calcipotriol. Arch Dermatol 1989; 125: 1647–1652.
7. Kragballe K, Gjertsen BT, de Hoop D, et al. Calcipotriol, a novel principle in the treatment of psoriasis vulgaris. Results of a double-blind multicenter, right-left comparison with betamethasone 17-valerate. Lancet 1991; i: 193–196.
8. Smith EL, Walworth NC, Holick MF. Effect of 1A,25-dihydroxy-vitamin D_3 on the morphologic and biochemical differentiation of cultured human epidermal keratinocytes grown in serum-free conditions. J Invest Dermatol 1986; 86: 709–714.
9. MacLaughlin JA, Gange W, Taylor D, Smith E, Holick MF. Cultured sporiatic fibroblasts from involved and uninvolved sites have partial but not absolute resistance to the proliferation inhibition activity of 1,25-dihydroxy-vitamin D_3. Proc Natl Acad Sci USA 82: 5409–5412, 1985.