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Efficacy of Topical Treatment in Psoriasis with MC 903, a New Vitamin D Analogue

BENT STABERG, JYTTE ROED-PETERSEN and TORKIL MENNÉ

Department of Dermatology, Gentofte Hospital, Copenhagen, Denmark

In 10 in-patients with chronic plaque psoriasis, the antipsoriatic effect of MC 903, a new synthetic analogue of vitamin D was evaluated. In each patient two symmetrical located psoriatic plaques were selected for the study. Topical treatment with MC 903 cream (containing 1.2 mg MC 903 per g cream) was compared with placebo cream in a double-blind, controlled, left–right, randomized way during 6 weeks of therapy. Compared with baseline, the clinical (erythema, scaling and infiltration) improvement was significant after 1 week of therapy with MC 903 cream, while lateral comparison showed MC 903 cream significantly better than cream base after 4 weeks of therapy ($p < 0.05$). Measurements of skin blood flow by the laser Doppler technique in evaluating the disease activity was not superior to the clinical assessments. In 3 patients the psoriatic lesions treated with MC 903 cream cleared completely during 6 weeks of therapy. No essential adverse reactions were observed. MC 903 has a potent effect on cell proliferation and cell differentiation, but has minimal effect on calcium metabolism. It is concluded that this synthetic vitamin D analogue is potentially useful in the treatment of psoriasis.

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B. Staberg, Department of Dermatology, Gentofte Hospital, DK-2900 Hellerup, Denmark.

The cutaneous synthesis of vitamin D in response to ultraviolet radiation exposure is the most important factor in maintaining vitamin D status in Man (1, 2). The skin is not only the site of vitamin D synthesis, but also a target organ for 1,25-dihydroxy-vitamin D_3 ($1,25(OH)_2D_3$), which is the biologically most active metabolite of vitamin D.

Previous studies have demonstrated receptors for $1,25(OH)_2D_3$ in many tissues in the body, including the skin (3). In cultures of human keratinocytes, incubation with this hormone resulted in a time- and a dose-dependent decrease in cell proliferation and a stimulation of terminal differentiation (4). Initial studies indicated that this mechanism might be defective in psoriatic skin (5). Recently, however, it has been shown that the response of cultured psoriatic keratinocytes and fibroblasts to $1,25(OH)_2D_3$ was identical with that observed in cultures of normal, healthy skin (6).

The serum concentration of $1,25(OH)_2D_3$ in patients with disseminated psoriasis is reduced as compared with a control group, suggesting an abnormal vitamin D metabolism in psoriatics (7). In open, uncontrolled studies, local and systemic treatment with active vitamin D metabolites improved psoriasis (6, 8, 9). However, both systemic and topical use of $1,25(OH)_2D_3$ implies a potential risk of hypercalciuria and hypercalcaemia (6).

We have therefore studied the antipsoriatic effect of MC 903, a new synthetic vitamin D analogue with potent effects on cell proliferation and cell differentiation, but with a much lower risk of inducing hypercalcaemia (10, 11). In the present investigation the effect of topical treatment with this analogue was compared with placebo cream in a double-blind, controlled, left–right, randomized study in patients with chronic plaque psoriasis.

METHODS

Patients and design

This study was a randomized, double-blind, controlled, left–right comparison of MC 903 cream (Leo Pharmaceutical Products, Copenhagen, Denmark) (10, 11) twice daily, versus cream base twice daily. Ten informed in-patients (26–76 years old, mean 50 years) with symmetrical plaque-type psoriasis vulgaris were selected for the study. All had normal serum calcium, serum creatinine, aspartate aminotransferase and alkaline phosphatase.

MC 903 cream (water/oil emulsion) containing 1 200 µg MC 903 per g cream and the control drug (cream base) were evenly applied with a finger tip (about 0.125 g) twice daily on 100 cm^2 large symmetrical psoriasis plaques. Treatment with MC 903 cream and cream base was continued during hospitalization for a period of 6 weeks. All patients received concomitant topical treatment with a dithranol preparation and a moisturizing cream on the remaining part of the involved body surface. No other either topical or systemic anti-psoriatic treatment was permitted.

Blood samples for standard laboratory examinations, including serum calcium and serum phosphate and analysis of

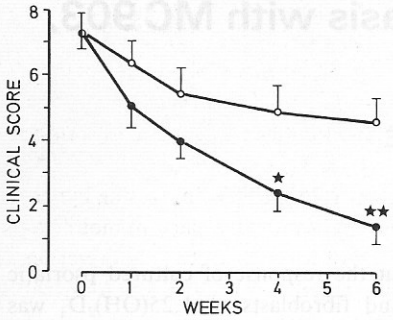

Fig. 1. Bilateral comparison of mean values of clinical score for 10 patients during treatment with MC 903 cream (●) and cream base (○). * $p<0.05$; ** $p<0.01$. Vertical range bars indicate ±SEM.

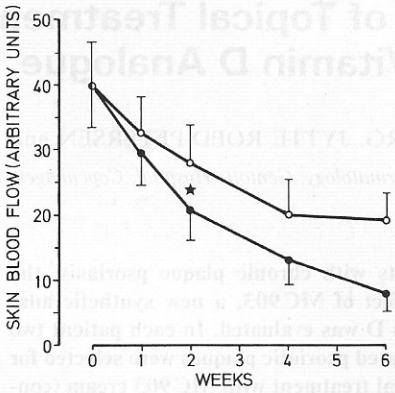

Fig. 2. Bilateral comparison of mean values of skin blood flow for 10 patients during treatment with MC 903 cream (●) and cream base (○). * $p<0.05$. Vertical range bars indicate ±SEM.

urine (protein, glucose, ketones), were taken before treatment and at weeks 1, 2, 4, and 6.

Clinical assessment

Clinical assessment of infiltration, erythema, and scaling of the selected psoriatic plaques was performed by one of the authors when the therapy was started and at weeks 1, 2, 4, and 6. Each clinical parameter was given a score (0: not present, 1: slight, 2: moderate, 3: severe) (12). The *clinical score* was calculated as the sum of these three parameters, the highest possible score would be 9.

Skin blood flow measurements

At each clinical assessment the skin blood flow (SBF) in the selected plaques was measured by the laser Doppler technique (Periflux®, Perimed, Sweden) (13). In each skin site the recorded SBF (arbitrary units) was the mean value of five measurements (14).

Statistical analysis

Differences in clinical scores, SBF and changes in laboratory parameters during treatment with MC 903 cream and cream base were tested for statistical significance using the Wilcoxon matched pairs test. *p*-values >0.05 were regarded as not significant.

RESULTS

The overall clinical response in the 10 patients is shown in Fig. 1. Treatments with MC 903 cream and cream base both induced a gradual decrease in clinical score during the study. Compared with baseline, the clinical improvement was significant after 1 week of therapy with MC 903 cream ($p<0.01$), and after 2 weeks of treatment with cream base ($p<0.05$). Lateral comparison showed a significantly better clinical effect of therapy with MC 903 cream than with cream base treatment after 4 ($p<0.05$) and 6 ($p<0.01$) weeks (Fig. 1). In 3 of the patients the psoriatic lesions treated with MC 903 cream cleared completely during 6 weeks of therapy.

Before therapy, skin blood flow (SBF) was about nine-fold higher in lesional skin than in healthy skin. After 2 weeks of treatment with both MC 903 cream and cream base, SBF was significantly decreased as compared with SBF before treatment was initiated ($p<0.05$) (Fig. 2). At all evaluations after starting therapy (weeks 1, 2, 4, and 6), mean values of SBF were lower in the skin areas treated with MC903 cream than in those treated with cream base. However, mostly due to rather large variation in SBF values, these differences were only significant at the measurement after 2 weeks of therapy ($p<0.05$) (Fig. 2).

Beside one patient who experienced a slight stinging in both MC 903 and cream base treated skin areas, no local or systemic adverse reactions were observed. Blood and urine analyses were within normal limits and did not change significantly during the treatment period.

DISCUSSION

In the present double-blind, controlled, left–right randomized study, we have demonstrated a significant beneficial effect of a new synthetic vitamin D analogue (MC 903) for topical treatment of psoriasis. The clinical improvement was significant after 1 week of treatment with MC 903 cream when compared with the pre-clinical score and after 4 weeks of therapy, when compared lateral with placebo cream base treat-

ment (Fig. 1). This difference in delay to observed clinical response of MC 903 treatment was due to a significant clinical improvement also observed in skin areas treated with cream base. The significant effect of the cream base was probably due to the fact that therapy was performed during hospitalization.

Measurements of skin blood flow by the laser Doppler technique can be used to obtain a quantitative parameter of the disease activity during evaluation of antipsoriatic treatment (14). However, in the present study this technique was not superior to objective clinical assessment of infiltration, erythema and scaling, performed by trained dermatologists in estimating disease activity.

Preliminary and open studies have indicated that psoriasis may respond to topical or systemic treatment with active metabolites of vitamin D (8, 9). Kato et al. (8) treated 11 patients with psoriasis topically with $1,24(OH)_2D_3$, a new synthetic analogue of $1,25(OH)_2D_3$. Application of $1,24(OH)_2D_3$ ointment twice daily under occlusion produced complete clearance in 10 of 15 tests within 1–4 weeks. In 7 patients, 0.12% betamethasone 17-valerate ointment under occlusion was applied to lesions symmetrically as a control. The clinical improvement was nearly the same for both treatments, but the response to steroid was the quicker (8).

In an open study by Morimoto et al. (9) 40 psoriatics were treated in different ways with active forms of vitamin D. It was found that oral 1α-hydroxyvitamin D_3 (1.0 μg/day) and 1,25-dihydroxyvitamin D_3 applied topically (0.5 μg/g of base) twice daily under occlusion were most successful in producing improvement. Mean time to response was 2.7 months for peroral treatment and 3.3 weeks for the topical treatment. No controls were performed in the peroral part of the study, while in the patients who received topical therapy, the untreated plaques showed no change. In the above cited trials (8, 9) no side effects were observed.

Recently, Holick et al. have reported an effect of both oral and topical $1,25(OH)_2D_3$ in the treatment of psoriasis (6). However, in this preliminary report the exact treatment procedure and mean time to clearance were not given. Although no side effects were observed, it was pointed out that treatment with active vitamin D metabolites implies a potential risk of disrupting calcium metabolism and causing hypercalciuria and hypercalcaemia (6).

In the present study we used MC 903, a new synthetic analogue of vitamin D with potent effects on cell proliferation and cell differentiation but with a much lower risk of inducing hypercalcaemia (10, 11). In in vitro studies MC 903 was found to be as potent as $1,25(OH)_2D_3$ in inducing cell differentiation and in inhibiting cell proliferation (11). In vivo investigations in rats showed that MC 903 was at least 100 times less active than $1,25(OH)_2D_3$ in causing hypercalciuria, hypercalcaemia and bone calcium mobilization (11). The effects of MC 903 on cell proliferation and differentiation, together with the low classical vitamin D activity, should make this compound an ideal candidate for the treatment of human proliferative disorders (11). In the present clinical study on patients with psoriasis, this suggestion has been fully supported.

In conclusion, previous preliminary, open studies (6, 8, 9), taken together with the present controlled, double-blind investigation, strongly indicates that vitamin D metabolites or synthetic vitamin D analogues are potentially useful in the treatment of psoriasis. The synthesis of new vitamin D analogues with minimal effects on calcium metabolism and with potent effects on cell proliferation and cell differentiation, corresponding to the compound used in the present study, may lead to a quite new treatment principle in psoriasis. Whether therapy with vitamin D analogues might favourably be combined with different well-established anti-psoriatic treatment modalities, is at present not certain. In the present study, no essential adverse reactions were observed. Until now, however, no studies have focused on possible long-term complications when treating psoriasis with vitamin D analogues.

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