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Tacalcitol ointment in the treatment of psoriasis vulgaris: a multicentre, placebo-controlled, double-blind study on efficacy and safety

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Summary

Tacalcitol is a vitamin D analogue which has been developed for the therapy of psoriasis vulgaris. The treatment with a twice daily application of 2 μg/g ointment is efficacious and safe in Japanese patients. The objective of this randomized, placebo-controlled, intraindividual right–left comparison was to investigate the efficacy and safety of 8 weeks' therapy with a once daily application of a 4 μg/g tacalcitol ointment in Caucasian psoriatics.

The data on 122 male and female patients were analysed. The score sum of erythema, infiltration and desquamation was influenced significantly more by tacalcitol ointment than by placebo ($P < 0{\cdot}0001$) at every control point, starting from week 2. With regard to the individual symptoms of desquamation, infiltration and erythema, the treatment with tacalcitol was also superior to placebo treatment beginning at week 2. Qualitatively, the same results were obtained with the preference assessment of both treated body sides and also the global assessments of efficacy and benefit. Symptoms of local skin irritation which may be related to the active compound or the ointment base were reported by 12·3% of patients. In only one patient, irritation required discontinuation of tacalcitol treatment. Laboratory criteria, including serum calcium, serum phosphate and serum levels of calcitonin, parathormone, 1α,24-dihydroxyvitamin D_3 and 25-hydroxyvitamin D_3, did not reveal any changes of clinical relevance during or after treatment. Furthermore, the global assessment of tolerance was good or very good in more than 90% of cases. The results of this study demonstrate that the once daily application of a 4 μg/g tacalcitol ointment is an efficacious therapy for psoriasis vulgaris in Caucasian patients, and that its tolerance is good, wherever the lesion is located, including on the face.

Several antiproliferative or immunomodulatory drugs, such as dithranol, topical corticosteroids, retinoids, methotrexate, cyclosporin A, or psoralens with UVA, have proven to be effective in the therapy of psoriasis but each of them is associated with different disadvantages. Therefore, new principles of therapy are desirable. Recently, attention has again been focused on the treatment of psoriasis with vitamin D analogues. Interest first arose when a patient's psoriasis improved while his osteoporosis was being treated with 1α-hydroxy-vitamin D_3.[1] Several studies have demonstrated that active vitamin D_3 inhibits epidermal proliferation, enhances normal keratinization and interferes with cutaneous inflammation.[2] In view of the fear of the calcipotropic potential of vitamin D_3 derivatives, which implies the risk of serious adverse events such as the calcification of such soft tissues as the kidney, further development of antipsoriatic treatment with vitamin D had to wait until new analogues with a reduced calcipotropic potential became available. In many countries, calcipotriol has been introduced for the treatment of psoriasis. This vitamin D analogue also inhibits the proliferation of keratinocytes and induces their differentiation but has a much less pronounced effect on the calcium metabolism.[3] Tacalcitol (1α,24-dihydroxyvitamin D_3; for review see Nishimura *et al.*[4]) is another synthetic analogue of calcitriol

(1α,25-dihydroxyvitamin D_3), the most active metabolite of vitamin D. The affinity of tacalcitol to the vitamin D receptor in human keratinocytes is slightly higher than that of naturally occurring vitamin D. The effect that tacalcitol exerts on the proliferation and differentiation of cultured epidermal cells is also comparable with or slightly more pronounced than that of calcitriol. This has been shown in murine epidermal cells as well as in normal human keratinocytes and in those derived from psoriatic lesions.[5–9] Clinical studies have shown good therapeutic efficacy in Japanese psoriatics with a twice daily application of a 2 μg/g tacalcitol ointment.[10–12] With regard to safety, there were neither changes in the tested laboratory criteria nor were there any serious drug-related adverse events when studies were performed with a maximum treatment duration of 12 weeks. Drug-related adverse events were also not observed in two clinical studies where a 4 μg/g tacalcitol ointment was applied twice daily for up to 4 weeks.[13,14] Furthermore, in a safety confirmation study[15] where up to 80 μg/g tacalcitol were applied once daily in an ointment for 7 consecutive days to the skin of both healthy adults and psoriasis patients, no relevant fluctuations were observed in the level of serum calcium, serum phosphate or serum creatinine. Tacalcitol was detected in the blood of one healthy volunteer but was at below the detection limit (25 pg/ml) in all other cases. No effect on intrinsic vitamin D metabolism was observed.[15]

The objective of the present double-blind, placebo-controlled clinical study was to show whether tacalcitol ointment is also efficacious and safe in the therapy of Caucasian psoriatics, as the above-mentioned data were derived from Japanese patients. Furthermore, it was desirable to reduce the frequency of application from twice daily to once daily in order to enhance patients' compliance. A concentration-finding study,[16] performed as a psoriasis plaque test, revealed that a once daily application of an ointment containing 4 μg/g tacalcitol or more provided the best efficacy. The 4 μg/g tacalcitol ointment has proven to have very good skin tolerance (Meyer-Rohn *et al.*, personal communication). Thus, the prerequisites were fulfilled to perform a phase III study with the aim of investigating the efficacy and safety of a once-daily application of a 4 μg/g tacalcitol ointment in the therapy of psoriasis vulgaris in Caucasian patients.

Methods

Study design

The study was designed as a multicentre, double-blind, placebo-controlled, randomized, intraindividual right–left comparison. Before the start of treatment, a 2-week wash-out period was required for all patients. Treatment consisted of a once daily, randomized application of either tacalcitol ointment or the base without active substance (hereafter referred to as placebo) to the selected psoriatic test lesions. Lesions were treated until they cleared but for not more than 8 weeks. There was a post-treatment follow-up period lasting until the onset of a relapse or for a maximum of 4 weeks. There were controls at weeks −2, 0, 2, 4, 6, 8 (or at the end of treatment) and 12 (or at the onset of a relapse). Medical ethical committee approval was obtained in each study centre and patients were included after having given informed consent.

Patient selection

Male and female patients, aged 15–80 years, with stable plaque psoriasis were considered for entry into the study. Females were not allowed to be or to become pregnant during the trial. Patients with an increased serum calcium or serum phosphate level (>10·5 mg/100 ml and/or >4·5 mg/100 ml, respectively) were excluded, as were patients who had received systemic or topical antipsoriatic treatment over a period of 2 months or 4 weeks respectively, prior to the start of the study. Other exclusion criteria were serious diseases, the necessity for prohibited concomitant therapy (see below), known allergy to any ingredient of the study medication, participation in another clinical trial within 4 weeks prior to the start of this study, or expected poor compliance (e.g. drug addiction). No calcium supplements or drugs influencing the calcium metabolism were allowed. The use of corticosteroids, barbiturates, phenytoin and non-steroidal anti-inflammatory drugs were also prohibited. The test areas were only allowed to be treated with either white petrolatum or an emollient during the wash-out period and the follow-up period, whereas emollients, 2–3% salicylic acid in white petrolatum, or shampoos containing tar were allowed to be applied to psoriatic lesions other than the test areas throughout the whole study period.

Psoriatic lesions chosen as test areas were allowed to be localized anywhere but on the scalp. They were required to have a score sum of >5 (definition of scores see below) for erythema, infiltration and desquamation, and at least moderate intensities (score 2) for erythema and desquamation. The difference of the score sums between the test lesions for tacalcitol and placebo treatment had to be $\leqslant 1$. The test lesions also had to be

comparable with regard to localization (almost symmetrical) and area (for each treatment up to 10% of total body surface).

Study medication and evaluation

The placebo consisted of paraffin oil, diisopropyl adipate and white petrolatum. Tacalcitol ointment additionally contained 4 μg/g tacalcitol (1α-24-dihydroxycholecalciferol). At the beginning of the study (week −2) demographic data (sex, age, height and weight) and anamnestic data (diagnosis, localization and area of lesions, outbreak of disease, duration of last attack, previous treatment, other diseases and their treatment) were gathered. Furthermore, the parameters for the efficacy and safety evaluations (see below) were assessed. Whenever the severity was described, the following scoring system was applied: 0, none; 1, slight; 2, moderate; 3, severe; 4, very severe.

The primary efficacy criterion was the score sum of erythema, infiltration and desquamation, which was assessed before the start of treatment (week 0) and at every control visit during the treatment period (weeks 2, 4, 6, 8). This criterion was chosen as it is part of the PASI score[17] but does not include the localization and extent which was not considered to be useful in an intraindividual comparison with a maximum area of 10% of total body surface.

The secondary efficacy criteria were: (i) individual scores for erythema, infiltration, desquamation and pruritus; (ii) preference assessment (left better than right, left equal to right, left worse than right); (iii) time to complete healing; (iv) area of test lesions; (v) global assessment of efficacy made by investigator and patient (1, very good; 2, good; 3, moderate; 4, poor); (vi) assessment of benefit based on the patient's experience (scale from 0, 'not beneficial', through 10, 'exceedingly beneficial'); (vii) post-treatment relapse of psoriatic lesions (by means of the individual scores for erythema, infiltration, desquamation and pruritus at week 12).

Statistical tests and safety assessment

For the primary efficacy criterion, the significance of difference was evaluated by means of the two-sided Wilcoxon matched-pairs signed-ranks test, the effect size measure being the Mann–Whitney statistic P ($X < Y$). The Mann–Whitney statistic is assessed as: 0·50, equal; 0.56, small difference; 0.64, medium-sized difference; 0.71, large difference. If P values were calculated for the secondary criteria, a symmetry test (McNemar) was used for binary data, and the paired Wilcoxon test was used for categorized data with ordered categories. The laboratory data were analysed by the Sign test, Wilcoxon ranking test or Stuart-Maxwell test and partly by the t-test. There was a statistical analysis of all randomized patients with at least one post start of treatment measurements ('intention-to-treat') and of all patients who were treated according to protocol ('per protocol').

The safety assessment comprised: (i) adverse drug events, assessed at weeks 2, 4, 6 and 8; (ii) global assessment of tolerance by investigator and patient (1, very good; 2, good; 3, moderate; 4, poor), made at week 8; (iii) haematology (white blood cell count, red blood cell count, platelet count, haemoglobin, haematocrit) evaluated before and at the end of treatment; (iv) blood chemistry (serum calcium, serum phosphate, serum creatinine, SGOT, alkaline phosphatase, LDH), evaluated at weeks −2, 0, 2, 4, 6 and 8; (v) serum calcitonin, parathormone, 1α,25-dihydroxyvitamin D_3 and 25-hydroxyvitamin D_3 assessed at four centres before and after treatment.

Results

Patients' details

One hundred and twenty-two patients were included in the intention-to-treat analysis and the safety analysis, and, as 19 patients were protocol violators, 103 patients were included in the per-protocol analysis. Protocol violations were: inadequate efficacy and/or non-permitted concomitant medication (13 patients), exacerbation of psoriasis with irritation at some test lesions (one patient), patient did not return (three patients), patient refused further participation (one patient), termination of study without known reason (one patient). Sixty patients were randomized to tacalcitol–left/placebo–right treatment, and 62 patients to placebo–left/tacalcitol–right treatment. In total 76 male and 46 female patients were included. The average age was 44·8 ± 13·69 (mean ± SD) years. They had a body weight of 78·0 ± 15·25 kg and a height of 173·1 ± 8·84 cm. They had had psoriasis for 233·5 ± 175·9 months and the duration of the last attack of psoriasis was 28·4 ± 74·8 months. On the right side of the body the test lesions comprised 5·6 ± 2·6% of the total body surface and on the left side they comprised 5·5 ± 2·7% of the total body surface.

In the majority of patients (88·5%), the test lesions for treatment with tacalcitol ointment or placebo were

localized on more than one part of the body (arbitrarily divided into face, arms, legs, dorsal and ventral trunk). The test lesions were predominantly localized on arms and/or legs, but in a quarter of all patients (24·6%), test lesions were localized on the face or on the face plus other parts of the body.

Efficacy

The pretreatment intensity of the individual criteria was judged as severe or very severe in more than half of the test areas (59%; desquamation; 65% infiltration; 72%; erythema). There was no pruritus in 29% of the test areas and in the majority of cases it was only slightly or moderately expressed (about 53%).

By the end of treatment (week 8), the score sum for erythema, infiltration and desquamation (primary efficacy criterion) had decreased on average by 4·0 score points (median: 5·0) after tacalcitol treatment and by 2·3 score points (median: 3·0) after treatment with placebo (per-protocol group). The superiority of tacalcitol vs. placebo treatment was significant ($P < 0{\cdot}0001$) from week 2 until the end of treatment. Using the Mann–Whitney effect size measure, it could be shown that the difference between the two treatments was large ($P[X < Y] \geqslant 0{\cdot}71$) at every control visit whereas there was equality between the test areas at baseline. This could be demonstrated for the per-protocol patients ($n = 103$ patients; see Fig. 1) as well as for those in the intention-to-treat group ($n = 122$ patients). Furthermore, these large differences were maintained when the data of each centre were analysed separately (centres with fewer than four patients were pooled). The differences were statistically significant at centres with more than nine patients.

The secondary efficacy criteria characterized further the response to tacalcitol and placebo treatment. (i) The intensity of the individual criteria of erythema, infiltration and desquamation is lower in the test lesions treated with tacalcitol ointment than in those treated with placebo. The superiority of tacalcitol was confirmed by the Mann–Whitney statistic: for erythema there was a medium-sized difference at week 2 ($P[X < Y] = 0{\cdot}65$) which became large [$P[X < Y] = 0{\cdot}72$) from week 6; for infiltration the difference could be qualified as large from week 4; for desquamation there was a medium-sized difference at week 2 and a large difference at week 8. For pruritus, however, there were only small differences at all control points after the start of treatment. (ii) Preference assessment revealed that the test lesions treated with tacalcitol ointment were better than those treated with placebo (Fig. 2). This difference was large beginning at week 2 for both the per-protocol group and the intention-to-treat group. (iii) Time to complete healing could not be assessed as the duration of treatment (8 weeks) was for most patients too short to permit complete healing. (iv) The area of test lesions changed by less than 1% during treatment with either of the preparations. Statistically, there was a small to medium-sized difference at week 8 (data not shown) which is without clinical relevance in this case. (v) Global assessment of efficacy revealed conformity between the investigator and the patient in 78·6% of cases and was greatly in favour of tacalcitol ointment vs. placebo ($P < 0{\cdot}0001$, $P[X < Y] = 0{\cdot}82$). The data of the per-protocol patients are summarized in Figure 3; the data of the intention-to-treat group are qualitatively the

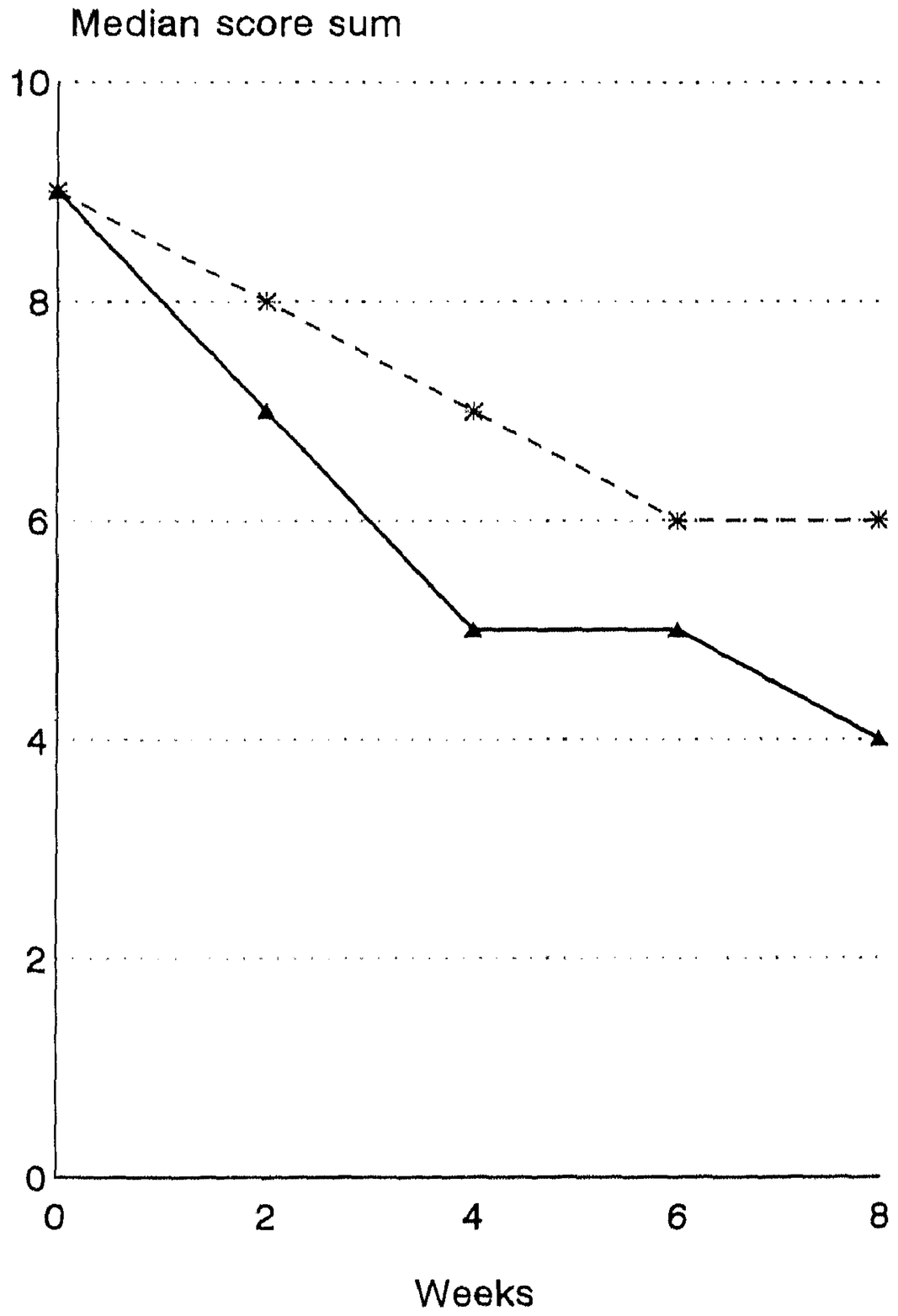


Figure 1. Median score sum of erythema, infiltration and desquamation during treatment with tacalcitol (–▲–) or with placebo (- - * - -), in per protocol patients. The difference between treatments is large ($P[X < Y] \geqslant 0{\cdot}71$) according to the Mann–Whitney statistic, and significant ($P < 0{\cdot}0001$) at every time point except baseline (week 0) where the score sums are equal.

same. (vi) By means of a scale with the two extremes 'not beneficial' (score 0) and 'exceedingly beneficial' (score 10), the benefit of tacalcitol ointment was assessed with score 7 (median) where the benefit of placebo was assessed with score 4 (median). The difference between these assessments is obviously large and it is statistically significant ($P < 0{\cdot}0001$). (vii) An exact evaluation of psoriatic relapses could not be made as in most cases the test lesions had not cleared during the 8 weeks' treatment. Nevertheless, of 97 patients who underwent a follow-up examination, 34 patients (35·1%) had an aggravation and 63 patients (64·9%) had no aggravation at all. The aggravation occurred bilaterally in 28 of these 34 patients and unilaterally in six patients (three tacalcitol, three placebo).

Tolerance and safety

Fifteen of the 122 intention-to-treat patients (12·3%) reported one or more symptoms of skin irritation. Six patients complained of a burning sensation, seven patients of pruritus, there were six cases of skin rashes (one with rhagades and erosion), and one case of rhagades. Skin irritation occurred bilaterally in four patients and unilaterally in five patients (three tacalcitol, two placebo). In six cases the body side was not documented. In the three patients where only the tacalcitol-treated test areas were affected, there were complaints of slight to severe pruritus in some of the test areas. This was accompanied by pustules in some of the test lesions in one patient, by redness and heat sensation in one other patient. Only one of the 15 patients discontinued treatment of the irritated lesions, but not of the other test lesions.

Five patients of the intention-to-treat group (4·3%) reported an adverse event. One patient had diarrhoea, one suffered from nausea, in one case a haematoma was diagnosed, in one there was slight circulatory reaction and fatigue, and one patient's skin was dry. The symptoms lasted for several days, but did not require treatment or a withdrawal of the study drugs. None of these events was considered to be drug-related.

Laboratory investigations revealed no clinically relevant effects. In the haematology parameters the Sign test showed that there were no important changes from baseline. With regard to the blood chemistry criteria, the Sign test did not reveal any important changes from baseline, whereas the Stuart-Maxwell test showed a significant, although clinically irrelevant deviation from normal in alkaline phosphatase at week 2. In addition to the statistical analysis, the data of each patient were analysed and did not show any clinically relevant changes. The serum calcium levels are shown

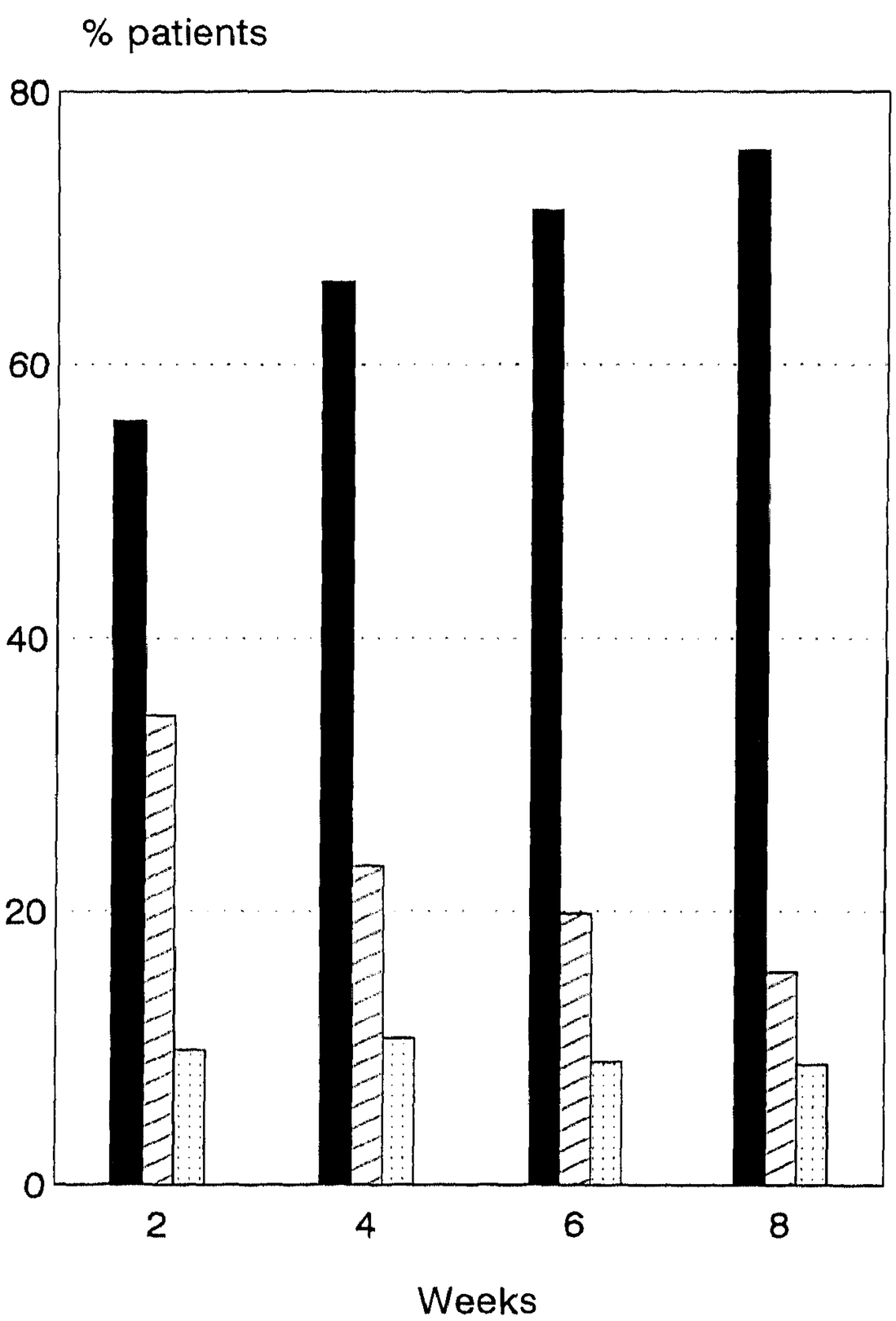


Figure 2. Preference assessment. This was made by means of a right–left comparison of the test lesions in all per-protocol patients. ■, tacalcitol better; ▨, equal; ⊡, placebo better.

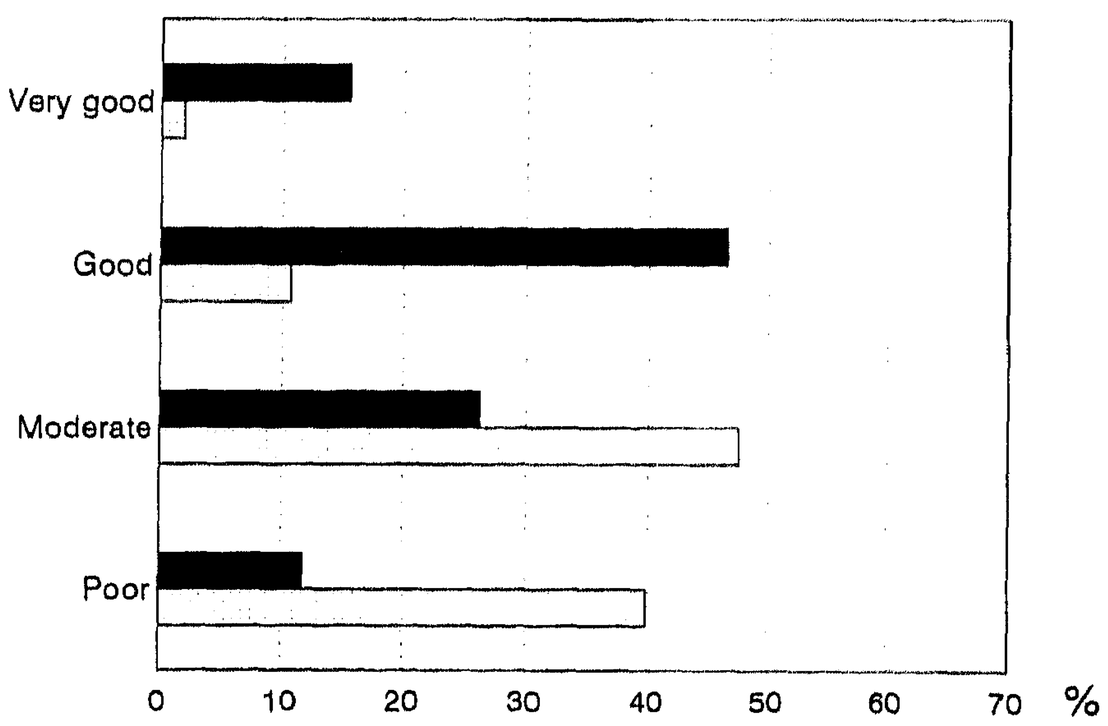
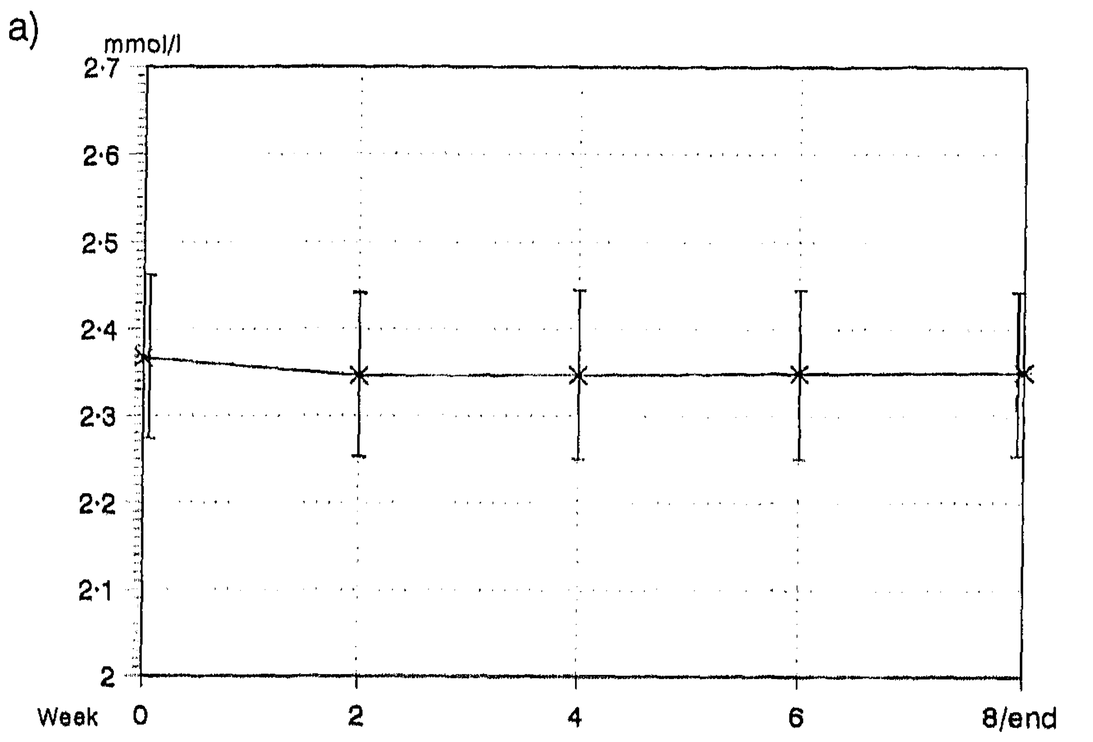


Figure 3. Global assessment of efficacy. The assessment of efficacy of treatment with tacalcitol ointment (■) or placebo (⊡) in the per-protocol group as made by the investigator is given.



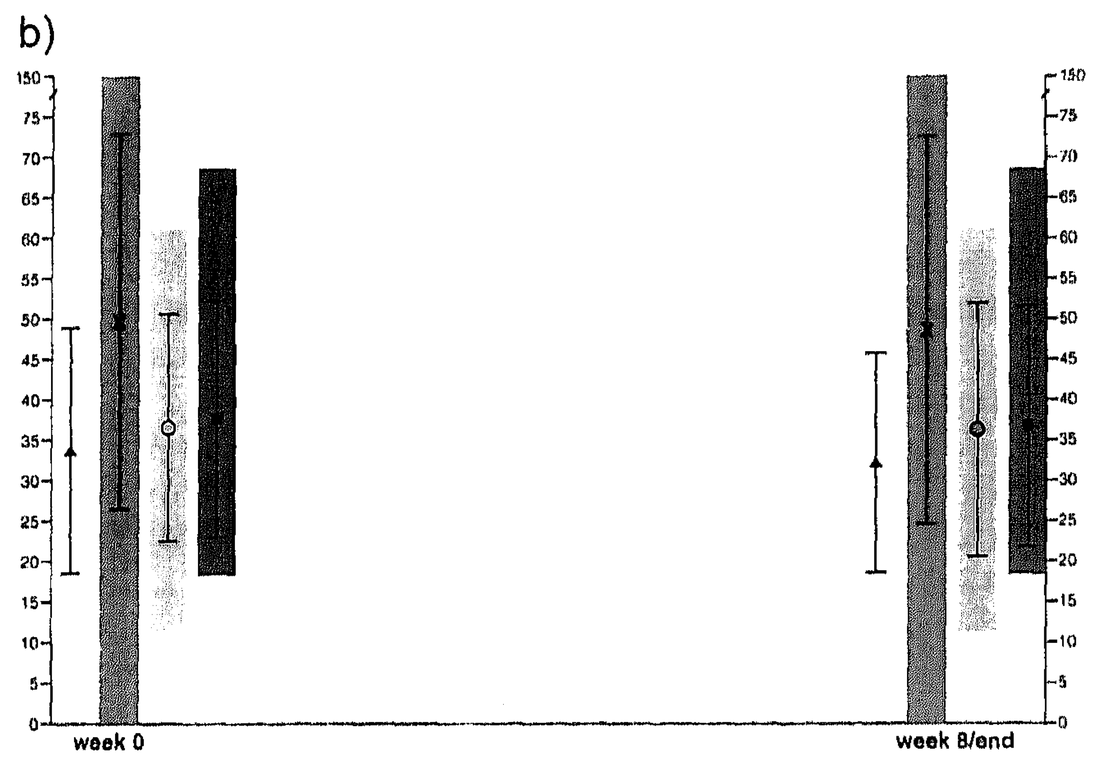


Figure 4. Indicators for calcium metabolism (mean ± standard deviation). (a) Serum calcium levels (—x—; in 122 patients, all centres). (b) Serum calcitonin (x; [pg/ml]), parathormone (○); [pg/ml]), 1α25-dihydroxyvitamin D_3 (■; [pg/ml]), 25-hydroxyvitamin D_3 (▲; [ng/ml]). The respective normal ranges are given as backgrounds of the statistical values (of 84 patients, four centres).

in Figure 4a. No significant changes (Sign test) were observed during the 8 weeks' treatment period. In 84 patients serum calcitonin, parathormone, 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 were monitored. No significant changes in these parameters (Wilcoxon ranking test, *t*-test) were found (Fig. 4b).

The tolerance of tacalcitol treatment was considered by the investigator to be good or very good in 118 of 119 patients (99·2%), and the corresponding value for the placebo treatment was 98·3%. The patients confirmed good or very good tolerance in 113 of 118 cases (95·8%) for tacalcitol and in 111 cases (94·1%) for the placebo.

Discussion

The data demonstrate the efficacy of this tacalcitol ointment in the treatment of psoriasis vulgaris in Caucasian patients and its superiority vs. the base without the active substance. It was possible to show the efficacy by means of a set of different criteria which either describe the symptoms of psoriasis in detail, or give a more complex although less quantifiable impression of the development of the disease. Most of the criteria revealed a large difference between the tacalcitol treatment and the placebo treatment, frequently apparent from the first control visit. By means of statistical analysis per study centre it could be shown that only 12 patients were required to demonstrate a statistically significant, large difference between treatments. The influence of tacalcitol on pruritus and area of test lesion was only slightly better than that of placebo. However, these small differences were without clinical relevance. For the area of the test lesions an indirect effect could have been expected through the action on the efficacy criteria. However, the duration of treatment in this study might have been too short to influence the area of the test lesions. A recent publication states[18] that individual lesions resolve without decrease in area until clearance occurs. In the present investigation, a consistent observation was the pronounced reduction of all efficacy scores including erythema. The intensity of erythema decreased from mainly very severe to mainly moderate or slight after tacalcitol treatment, whereas placebo treatment only reduced the erythema to mainly severe or moderate intensity.

With regard to safety, there were neither any drug-related serious adverse events nor were there deviations in the laboratory parameters which were of clinical relevance. From all safety data, it can be concluded that there was no indication of any influence on the systemic calcium metabolism. Hypercalcaemia has been observed for vitamin D_3 analogues.[19–22] Further studies on the long-term safety of tacalcitol are in progress.

Symptoms of local skin irritation were observed or reported (in the case of pruritus) by 15 patients. In this respect it is relevant to note that the patients were permitted to treat face and flexures, i.e. areas which are relatively susceptible for irritation to vitamin D_3 analogues. It is possible that the irritations are related to the study medication. Nevertheless, they did not occur more frequently in the tacalcitol-treated areas than in the placebo-treated lesions. It should be noted that pruritus is also a symptom of psoriasis. In some patients it was impossible to distinguish whether pruritus was part of the manifestation of this disease or a drug-related adverse event. In spite of the reported local skin irritation, the tolerance was assessed as good or very good in the majority of cases. It was also encouraging for

further treatment with tacalcitol that the therapy of psoriatic lesions on the face with this medication was well tolerated. Of 30 patients whose test areas were also localized on the face, only two reported symptoms of local skin irritation there.

Calcipotriol (50 μg/g) in ointment is the vitamin D_3 analogue which has been available in many countries for 3 years. This analogue has proven to be effective, has been well accepted although irritation of the skin was a limitation in up to 25% of the patients.[19,23] In Japan, an ointment with tacalcitol has been available for 2 years and has proven to be effective and well-tolerated; less than 1% of the patients showed irritation of the skin.[4] Calcitriol (3 μg/g) in ointment twice daily has been reported to be effective in the treatment of psoriasis.[24] However, again irritation limits the use of this compound in up to 15% of the patients (van de Kerkhof, personal communication). Up to 3% of the patients had to discontinue treatment due to severe irritation (van de Kerkhof, personal communication). It has been difficult to make a direct comparison between the vitamin D_3 analogues with respect to efficacy and tolerance as no comparative studies are available to date. However, the present study suggests that tacalcitol 4 μg/g in ointment, applied once daily has a relatively low potential to induce irritation.

It can be concluded from the present investigation that a once daily topical treatment with a 4 μg/g tacalcitol ointment is efficacious in the therapy of psoriasis vulgaris in the majority of Caucasian patients. Of course it would be desirable to have data of long-term therapy as well as data of extensive treatment (more than 10% of body surface). The present study, however, does not provide any evidence of a modulation of systemic calcium metabolism. In view of the relatively low irritancy and the marked effect on erythema it is attractive to speculate that tacalcitol may become a mainstay in the treatment of flexural and facial psoriasis. Tacalcitol ointment therefore has the potential to establish itself as a valuable therapeutical option in the spectrum of antipsoriatic pharmaceutics.

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References

1 Morimoto S, Kumahara Y. Patient with psoriasis cured by 1α-hydroxyvitamin D_3. *Med J Osaka Univ* 1985; **35**: 51.

2 Norman AW, Bouillon R, Thomasset M (eds). *Vitamin D: Gene Regulation Structure–Function Analysis, and Clinical Application: Proceedings of the Eight Workshop on Vitamin D*. Berlin: de Gruyter, 1991.

3 Kragballe K, Iversen L. Calcipotriol: a new typical antipsoriatic. *Dermatol Ther* 1993; **11**: 137–41.

4 Nishimura M, Hori Y, Nishiyama S, Nakamizo Y. Topical 1α-24 (R)dihydroxyvitamin D_3 for the treatment of psoriasis. Review of the literature. *Eur J Dermatol* 1993; **3**: 255–61.

5 Matsunaga T, Yamamoto M, Mimura H *et al.* 1,24 (R)-dihydroxyvitamin D_3, a novel active form of vitamin D_3 with high activity for inducing epidermal differentiation but decreased hypercalcemic activity. *J Dermatol* 1990; **17**: 135–42.

6 Matsumoto K, Hashimoto K, Kiyoki M *et al.* Effect of 1,24 R-dihydroxyvitamin D_3 on the growth of human keratinocytes. *J Dermatol* 1990; **17**: 97–103.

7 Kobayashi T, Okumura H, Azuma Y *et al.* 1α24 R-dihydroxyvitamin D_3 has an ability comparable to that of 1α,25-dihydroxyvitamin D_3 to induce keratinocyte differentiation. *J Dermatol* 1990; **17**: 707–9.

8 Glade CP, van Erp PEJ, van Hooijdonk CAEM *et al.* Topical treatment of psoriatic plaques with 1α,24 dihydroxyvitamin D_3: a multiparameter flowcytometrical analysis of epidermal growth, differentiation and inflammation. *Acta Derm Venereol (Stockh)* 1995; **75**: 381–5.

9 Farkas B, Bonnekoh B, Mahrle G, Dobozy A. Regulatory effect of calcitriol, calcipotriol and tacalcitol: a direct comparison in the human keratinocyte line HACAT. *Arch Dermatol Res* (in press).

10 Kimura H, Nishiyama S, Nakamizo Y *et al.* Investigation of the usefulness of TV-02 ointment for patients with psoriasis—right and left comparison test with betamethasone valerate ointment. *Western Jpn Dermatol* 1989; **51**: 963–9.

11 Kimura H, Nishiyama S, Nakamizo Y *et al.* Investigation of the clinical effects of TV-02 ointment on psoriasis. *Western Jpn Dermatol* 1989; **51**: 970–9.

12 Eto M, Nishiyama S, Nakamizo Y *et al.* Study on the efficacy of TV-02 ointment for psoriasis—results of a double blind comparative clinical study of the left and right sides with a placebo (ointment base) as a control. *Nishinihon J Dermatol* 1991; **53**: 1252–61.

13 Nishiyama S, Goto M, Ohkawara A *et al.* Study for setting optimal concentration of TV-02 ointment. *Nishinihon J Dermatol* 1989; **51**: 310–16.

14 Kato T, Tadaki T, Terui T, Tagami H. Treatment of psoriasis by synthetic bioactive vitamin D_3, 1α,24-hydroxycholecalciferol ointment. *Acta Dermatol (Kyoto)* 1989; **84**: 431–6.

15 Eto M, Nishiyama S, Nakamizo Y *et al.* Safety confirmation study on TV-02 ointment to patients with psoriasis. *Nishinihon J Dermatol* 1989; **51**: 317–24.

16 Baadsgaard O, Traulsen J, Roed-Petersen J, Jakobsen HB. Optimal concentration of tacalcitol in once-daily treatment of psoriasis. *J Dermatol Treat* 1995; **6**: 145–50.

17 Frederiksson T, Pettersson U. Severe psoriasis – oral therapy with a new retinoid. *Dermatologica* 1978; **157**: 238–44.

18 Speight EL, Farr PM. Plaque area is a poor measure of response of psoriasis to treatment. *Br J Dermatol* 1994; **131**: 443 (Abstract.).
19 Ramsay CA, Berth-Jones J, Brundin G *et al.* Long-term use of topical calcipotriol in chronic plaque psoriasis. *Dermatology* 1994; **189**: 260–4.
20 Saurat J-H, Gumowski-Sunek D, Rizzoli R. Topical calcipotriol and hypercalcaemia. *Lancet* 1991; **337**: 1287 (Letter).
21 Hardman KA, Heath DA, Nelson HM. Hypercalcaemia associated with calcipotriol (Dovonex) treatment. *Br Med J* 1993; **306**: 896.
22 Hoeck HC, Laurberg G, Laurberg P. Hypercalcaemic crisis after excessive topical use of a vitamin D derivative. *J Intern Med* 1994; **235**: 281–2.
23 Poyner T, Hughes IW, Dass BK, Adnitt PI. Long-term treatment of chronic plaque psoriasis with calcipotriol. *J Dermatol Treat* 1993; **4**: 173–7.
24 Langner A, Venjans H, Stapor V *et al.* 1α,25-dihydroxyvitamin D_3 (calcitriol) ointment in psoriasis. *J Dermatol Treat* 1992; **3**: 177–80.