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Long-term efficacy and safety of once daily treatment of chronic plaque psoriasis with tacalcitol ointment

Tacalcitol (Curatoderm® 4 µg/g ointment, once daily) was shown to be effective and safe in the treatment of patients with chronic plaque psoriasis in a previous multicentre, placebo-controlled double-blind study. After a 4-week medication-free interval, an open-label, prospective study was started with a planned minimum duration of 12 weeks. The maximum treatment and observation period was to last up to 60 weeks. The objective was to investigate the efficacy and safety of tacalcitol under the conditions of long-term psoriasis management.

Three centres with a total of 90 patients participated in the long-term study project. Eighty-one patients had completed the initial double-blind study as scheduled and 58 patients entered the long-term phase with tacalcitol ointment. Forty-two patients completed at least 12 weeks of treatment. The mean duration of treatment was 24.8 weeks. In individual cases, the maximum treatment period was 62 weeks. After 4 weeks of treatment there was a substantial improvement of the sum score (erythema, infiltration, desquamation), which was defined as the primary efficacy criterion. This response was maintained throughout the study.

Systemic safety variables did not show any clinically relevant influence of tacalcitol on calcium metabolism. In particular, serum calcium, creatinine, phosphate and nocturnal urine alpha-1-microglobulin remained unaffected by continuous application of the study medication.

Transient symptoms of local side effects such as burning, itching, pain and irritation were reported by only 8 of the 58 patients. These were considered to be due to either the psoriasis or tacalcitol. In 6 patients these side effects were reported as "moderate" or "mild". No patient was withdrawn for safety reasons.

In conclusion, this study indicates that tacalcitol ointment is an effective and safe treatment for the long-term control of psoriasis vulgaris. These results are to be supported by further large-scale studies and in patients with more extensive psoriatic lesions. (*Key words: psoriasis, tacalcitol, vitamin D₃.*)

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Vitamin D₃ analogues represent a major innovation in the treatment of psoriasis today [1-4]. During the last 5 years, calcipotriol (50 µg/g) ointment has become a first line therapy for this condition. Calcipotriol treatment is generally accepted for long-term management of psoriasis, although irritation of the skin has been experienced by 25% of the patients and required discontinuation of treatment in approximately 6% of the patients [5, 6].

In Japan, tacalcitol (2 µg/g ointment, twice daily) is the vitamin D₃ analogue which has become the mainstay in the routine treatment of psoriasis [7-10]. Irritation following tacalcitol application has been recorded in less than 1% of the patients [7-10]. The clinical efficacy of this formulation proved to be comparable to twice daily treatment with betamethasone valerate 1 mg/g ointment [11].

Recently, a European, dose-finding study was carried out to assess the optimal concentration and the clinical efficacy of

once daily application of tacalcitol (0.25-16 µg/g ointment) [12]. Concentrations above 4 µg/g did not enhance the antipsoriatic efficacy, whereas lower concentrations were significantly less effective. A multicentre, placebo-controlled, intraindividual, left-right comparative study was performed with 122 patients to investigate the clinical efficacy, side effects and tolerability of this dosage regimen in Caucasian patients with chronic plaque psoriasis [13]. The application of tacalcitol ointment once daily (4 µg/g for 8 weeks) proved to be an effective, safe and well-tolerated antipsoriatic treatment. The objective of the present study was to investigate the efficacy and safety of tacalcitol ointment 4 µg/g, applied once daily under the conditions of long-term psoriasis management. This study was performed in patients who had previously participated in the placebo-controlled study and addressed the following questions: (1) can the clinical efficacy of tacalcitol ointment, as confirmed by the 8-week placebo-controlled study, be maintained during a

long-term study, (2) does long-term use of this vitamin D₃ analogue affect systemic safety variables, (3) what is the frequency and severity of irritation of the skin during long-term therapy, (4) what is the overall assessment of patients and investigators regarding global improvement and usefulness of this treatment?

Study characteristics

General introduction

An open-label, prospective study was performed to investigate the efficacy and safety of tacalcitol (4 µg/g ointment, once daily) in the long-term treatment of psoriasis. All patients had been previously included in a multicentre, placebo-controlled, intraindividual, left-right comparative study on the efficacy and safety of a short-term treatment with the identical tacalcitol formulation [13]. Upon completion of the double-blind phase and a medication-free follow-up period of 4 weeks, each patient who was interested and had completed the double-blind study could enter the long-term phase.

A total of 146 patients were enrolled in the original double-blind study in 15 centres. One hundred and twenty-six patients completed the double-blind phase of 8 weeks. Twenty patients withdrew for the following reasons: inadequate efficacy (5 patients), prohibited therapy and inadequate efficacy (4), incompatible therapy (4), adverse event (1), healing (1) other reasons (5).

The long-term study was performed in three of the 15 centres participating in the multicentre study.

Patient selection

Patients with chronic plaque psoriasis were enrolled at 3 academic centres. All subjects had already fulfilled the inclusion and exclusion criteria which were the same as for the 8-week placebo-controlled study [13]. In brief, out-patients of either sex aged between 15 and 80 years, females of childbearing age if they were using adequate contraception and patients with normal serum calcium or phosphate were included. Systemic or topical antipsoriatic therapy other than tacalcitol treatment within 2 months or 4 weeks respectively prior to the start of the study was considered to be an exclusion criterion. Other exclusion criteria were serious diseases, known allergy to the study medication, medication interfering with the course of psoriasis or systemic calcium metabolism. All patients gave informed consent prior to the study.

Study medication and treatment

Tacalcitol ointment was applied once daily by the patients to all affected areas except the scalp. The formulation contained (4 µg/g) 1 α ,24-dihydroxy-cholecalciferol (tacalcitol) in the inactive ingredients paraffin oil, diisopropyl adipate and white petrolatum; 100 g tubes were filled with the preparation.

Use of the study medication was restricted to a maximum of 20 g once daily and a long-term maximum supply of 2,000 g per patient.

Patients received a 4-week supply of study medication at the start of the long-term period and again at 4-week intervals. The patients were permitted to discontinue treatment after a minimum duration of 12 weeks. They were regarded as drop-outs if treatment was stopped before this time. Patients could discontinue therapy because of clearing, side effects or if they wished to do so. The scheduled maximum treatment and observation period was to be 60 weeks.

Efficacy assessments

At the start of the open-label, long-term phase (week 0) and subsequently every fourth week, clinical efficacy criteria were assessed by the investigator. The extent of the psoriatic test area was recorded as percentage of the total body surface and assessed at baseline and at regular visits. The symptoms erythema, infiltration and desquamation were recorded using a 5-point scale from 0 = "none" to 4 = "very severe". In addition, at each visit the symptoms erythema and desquamation were compared to their initial condition (week 0). The condition was rated as "deteriorated", "unchanged", "slightly improved", "moderately improved", "markedly improved" or "cured". At the end of the study, a global assessment of efficacy was made by the investigator and the patient. An assessment of usefulness was given by the patients at the end of treatment on a 10-point analogue scale of 1 = "not useful at all" to 10 = "extremely useful". The sum score (0-12) for erythema, infiltration and desquamation was defined as the primary criterion of efficacy.

Safety assessment

The occurrence of any adverse event was recorded at each visit. These events were evaluated for duration, severity (slight, moderate or severe) and a possible relationship to disease or drugs. In particular, the investigator had to pay attention to any signs of irritation, skin rashes, and other local reactions and to note their location, extent and severity.

A global assessment of tolerability was given at the end of treatment by the investigator and the patient and was rated as "very good", "good", "moderate" or "insufficient". The patient's general condition was recorded at the start and at each visit during the long-term study. The assessment was rated as "very good", "good", "moderate" or "insufficient". A clinical laboratory evaluation was performed at baseline and at each visit. The haematology comprised determination of erythrocytes, platelets, haemoglobin, haematocrit; the blood chemistry included serum calcium, inorganic phosphate, creatinine, ASAT, alkaline phosphatase and LDH. Nocturnal urine alpha-1-microglobulin was also assessed at one centre.

Statistical analysis

Open label, long-term studies are observational studies prone to a high selection bias caused by drop-outs, *e.g.* statistics are biased by self-selection of patients and *p*-values for tests with respect to baseline are also biased by the reduced sample size. Thus special analysis methods must be used and results have to be interpreted very carefully.

The most important information from such a study includes the number (and also type) of patients enrolled and the number of drop-outs during the study, which should be compiled in a life table. An indication of the efficacy and safety of drugs is given by specifying the reasons for withdrawal.

The efficacy can be plotted as individual time curves for each patient. Statistics for each point in time are not useful as these are biased by early selective withdrawal of patients with severe symptoms. Thus, only changes from baseline are quantified here by means of the Mann-Whitney coefficient, which in the case of pre-post values is simply the proportion of improved patients relative to all patients showing a changed condition. Although this takes into account only patients with observations at a specified point in time, there may also exist a bias caused by patients who have dropped out, so that

these results must also be interpreted very carefully. The Mann-Whitney coefficient can be interpreted as follows: 0.5 = pre-post values equal, 0.64 = moderately superior (relevant), 0.71 = highly superior.

Since laboratory variables that are not related to the clinical condition or quality of life may lack a selection bias, statistics could be a valid means of interpretation for this type of data.

Results

Patient selection and withdrawals

Fifty-eight of 81 patients in 3 centres entered the open-label long-term phase. The global efficacy of tacalcitol was assessed at the end of the initial double-blind study for these patients as "very good" in 10, "good" in 35, "moderate" in 10 and "insufficient" in 3 patients. Twenty-three patients did not want to enter the new, long-term study.

The mean duration of the long-term phase was 24.8 ± 17 weeks; the minimum 12-weeks treatment was completed by 42 of 58 patients (72.4%).

During this period 16 of 58 patients dropped out for the following reasons: early termination due to good response (6), inadequate efficacy (6), incompatible therapy (1), non-compliance (2), hospitalization due to other disease (1).

The maximum treatment period was 62 weeks (n = 3). After week 12, 5 patients dropped out. The reasons were inadequate efficacy (1), prohibited medication (2), other reasons (administrative reasons [1], voluntary termination of treatment when the patient was nearly cured [1]).

None of the patients terminated the open-label study because of complete clearing. In 5 patients, the test drug was not applied as recommended, *i.e.* continuously throughout the study and in 6 patients the last observation was 1 to 4 weeks after the end of treatment.

Demographic and anamnestic data

Fifty-eight patients, 18 women and 40 men, entered the long-term efficacy and safety study. The average age was 45 years

(range 19 to 78 years). All patients suffered from chronic plaque psoriasis. At the beginning of the initial double-blind phase, the duration of psoriasis since the first outbreak was 208 months (median; range 12 to 750 months) and interval since the last attack, 10 months (median; range 1 to 439 months).

The mean time interval from the end of the initial double-blind phase to the start of the open-label phase was 4.4 ± 2.6 weeks (mean \pm SD). The total extent of psoriatic lesions chosen as test areas, and calculated as percent of body surface, was 9.9 ± 3.2 (mean \pm SD) at the beginning of the initial double-blind phase for all patients, 8.3 ± 3.6 (mean \pm SD) at the end and 8.6 ± 3.9 (mean \pm SD) at the start of the open-label phase.

The sum score was 8.9 ± 1.5 (mean \pm SD) at the beginning of the double-blind phase, 4.6 ± 2.1 (mean \pm SD) at the end and 7.9 ± 2.1 (mean \pm SD) at the start of the open-label phase. These values show an increase in intensity of symptoms in the medication-free interval.

Clinical efficacy

The general impression is that the response obtained in the double-blind phase is maintained throughout the open-label phase. Apparently, patients with a higher initial value show a greater tendency to drop out. The sum score shows a tendency to improve relative to baseline even until week 8 of the study. *Figure 1* shows the results expressed as a Mann-Whitney coefficient for each point in time. There is a substantial improvement immediately (week 4) compared to the start of the open-label phase. This was maintained throughout the study. There was a steadily increasing improvement in the extension of involved test area from week 4 to week 20.

The global assessment of efficacy by the investigator and the patient are summarized in *Table 1* for a total of 58 patients. The investigator rated the efficacy as very good in 6 patients (10%), as good in 28 (48%), as moderate in 21 (36%) and as insufficient only in 3 (5%). Nine (16%) of the patients rated the efficacy as very good, 24 (41%) as good, 19 (33%) as moderate and 6 (10%) as insufficient. In 84% of the assessments the investigator and the patient were in agreement.

The usefulness of the therapy, as assessed by the patient on a 10-point analogue scale (0-10), was assessed as 7 (median).

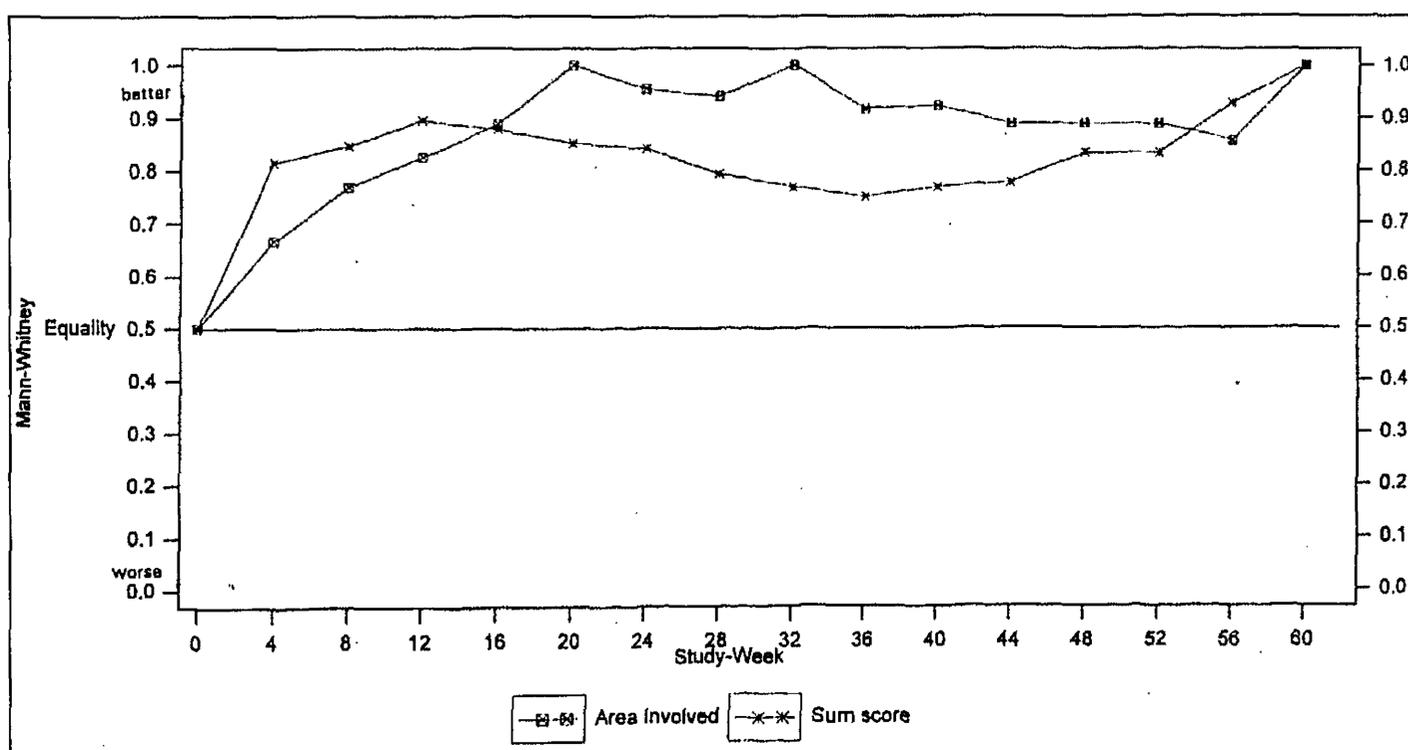


Figure 1. Involved test areas and sum score. The sum score is the sum of erythema, induration and scaling. The involved test area comprises the regions which were selected for treatment with tacalcitol.

Table I. Global assessment of efficacy by the investigator and the patient

| Efficacy assessment | Assessment of efficacy by | | | |
|---------------------|---------------------------|--------|---------|--------|
| | Investigator | (%) | Patient | (%) |
| Very good | 6 | 10.34 | 9 | 15.52 |
| Good | 28 | 48.28 | 24 | 41.38 |
| Moderate | 21 | 36.21 | 19 | 32.76 |
| Insufficient | 3 | 5.17 | 6 | 10.34 |
| Missing | — | — | — | — |
| Valid No. | 58 | 100.00 | 58 | 100.00 |

Total N = 58.

Safety

Adverse events were reported by 15 of the 58 patients (26%). All extracutaneous adverse events were considered to be unrelated to psoriasis or the study medication. In 10 of the 58 patients, adverse events related to skin were reported. In a patient with erysipelas and a patient with urticaria, relationship to the study medication was considered unlikely. In 8 of the 10 patients (13.8%) with skin reactions, these reactions were considered to be due to either psoriasis or the study medication. Three of these 8 patients reported a burning sensation, 3 itching/pain and 2 irritation. These symptoms did not increase in severity during long-term application of tacalcitol ointment. The cutaneous adverse events were documented as severe in 2 of 8 patients, as moderate in 4 and as mild in 2. Nine of the nineteen adverse events reported occurred before study week 12, six from weeks 13 to 24, three from weeks 25 to 36 and one in week 44.

Adverse events for 2 different body systems were reported in 2 patients and for 3 different body systems in 1 patient. None of the patients withdrew from the open-label phase as a result of adverse events.

The global assessment of tolerability as given by the investigator and the patient is shown in *Table II*. The tolerability was considered good or very good in 98% of the cases by the investigator and in 96% by the patient. The patients' general condition was considered good throughout the long-term study.

Laboratory investigations did not show any change of clinical importance. No patient developed hypercalcaemia.

The Mann-Whitney coefficient for serum calcium, phosphate and creatinine showed wide fluctuation, but there was no

Table II. Global assessment of tolerability by the investigator and the patient

| Tolerability assessment | Assessment of tolerability by | | | |
|-------------------------|-------------------------------|--------|---------|--------|
| | Investigator | (%) | Patient | (%) |
| Very good | 36 | 62.07 | 34 | 58.62 |
| Good | 21 | 36.21 | 22 | 37.93 |
| Moderate | 1 | 1.72 | 1 | 1.72 |
| Insufficient | — | — | 1 | 1.72 |
| Missing | — | — | — | — |
| Valid No. | 58 | 100.00 | 58 | 100.00 |

Total N = 58.

indication of negative effects of the study drug and there was no systematic negative or positive trend. Non-trivial changes after week 20 may also be explained by random fluctuation: the number of patients decreased with time.

The plot of individual data *versus* the study time for calcium, phosphate and serum creatinine also show no important changes.

The time course of the individual data for alpha-1-microglobulin in urine gives no indication of a time trend. In one patient who had suffered from hypertension since 1980, values above normal were seen throughout the long-term study, except during weeks 12 and 24.

Discussion

The results of the present study suggest that tacalcitol ointment has substantial antipsoriatic efficacy that is maintained over the long-term in the majority of patients with psoriasis vulgaris.

Eighty-one patients completed the original study as scheduled in these 3 centres and 58 patients entered the open-label, long-term phase with tacalcitol. A total of 42 patients were treated for the planned minimum duration of 12 weeks. Twenty-one patients were still in the study after week 24 and 13 after week 36. The maximum treatment and observation period was 62 weeks for 3 patients.

Only 15 patients dropped out because of inadequate efficacy, prohibited therapy or other reasons (not included in these figures are patients who withdrew of their own accord because of good results with the tacalcitol therapy).

The general impression obtained from the change in the extension of the involved test areas as a percentage with time is that the response achieved in the double-blind phase is maintained throughout the open-label phase. Apparently, patients with higher baseline values showed a greater tendency to withdraw from the study.

The same pattern was observed for the primary efficacy criterion, the sum score of the three variables: erythema, infiltration and desquamation. A tendency to improve could even be seen until study week 8. The Mann-Whitney coefficient for each point in time for the involved test area and sum score showed a substantial improvement right at the beginning (week 4) compared to baseline (week 0), which was maintained throughout the study. There was a steady improvement in the extension of the involved test area even from week 4 to week 20, which might, however, also be explained by the drop-out bias.

It can be concluded from the efficacy data that tacalcitol ointment can be applied over a long period of time with good clinical results. The sustained antipsoriatic efficacy without signs of intolerance is in line with the efficacy characteristics of long-term administration of the vitamin D₃ analogue calcipotriol [5, 6]. A quantitative comparison of clinical efficacy and safety of different vitamin D₃ analogues is not yet possible because of inadequate data.

Adverse events were reported by 15 of the 58 patients (26%). All extracutaneous adverse events as well as the erysipelas and urticaria in two patients were considered to be unrelated to psoriasis or the study medication. Burning (5%), itching/pain (5%) and irritation (3%) were considered to be due either to psoriasis or the study medication. These symptoms were transient and did not increase in severity or frequency during long-term therapy. None of the patients withdrew for safety reasons. The irritation rate of tacalcitol in

these Caucasian patients is higher compared to the irritation reported by Japanese authors. However, the relatively low concentration (2 µg/g twice daily) might be of relevance [7-11]. Irritation of the skin has been reported to be a problem for other vitamin D₃ analogues [14, 15]. The overall tolerability was considered good or very good in 98% of the cases by the investigator and in 96% by the patient. In addition, the general condition of the patients was considered good throughout the long-term study.

Based on the safety profile of tacalcitol under long-term conditions, this new treatment can be regarded as a safe approach to psoriasis management. There proved to be no influence on the general condition of the patients. Haematology and blood chemistry revealed no clinically significant changes. In particular, serum calcium, phosphate and creatinine remained within the normal range. Recently, nocturnal urine alpha-1-microglobulin (protein HC) has proved to be a valuable marker for tubular dysfunction [16], which is an early sign of calcium deposition in the parenchyme of the kidney. This marker remained unaffected as well.

The usefulness of tacalcitol ointment was judged to be 7 on a 10 point scale. This implies that tacalcitol is not the panacea of psoriasis treatment but rather represents a well-accepted, once daily treatment with a medium antipsoriatic efficacy that is maintained long-term. The excellent local tolerability suggests that tacalcitol therapy might also be indicated for the treatment of facial and flexural psoriasis. Further studies are required to compare the clinical efficacy and safety profile of tacalcitol with those of other vitamin D₃ analogues and to study the long-term efficacy and safety in larger patient populations, and with more extensive psoriasis. ■

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