

# Double-blind, Placebo-controlled, Randomized, Right – left Study Comparing Calcipotriol Monotherapy with a Combined Treatment of Calcipotriol and Diflucortolone Valerate in Chronic Plaque Psoriasis

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A double-blind, randomized clinical study was conducted to compare the efficacy and tolerability of twice-daily topical calcipotriol treatment with a combination treatment of calcipotriol once a day in the morning and diflucortolone valerate in the evening. Sixty-three patients with a clinical diagnosis of chronic plaque psoriasis and comparable psoriatic lesions on both sides of the body were included. After a wash-out phase of 1 week, psoriatic lesions were treated for 4 weeks with calcipotriol ointment twice daily on one side of the body and a combination of calcipotriol and diflucortolone valerate ointment on the other side. The treatment period was followed by a period of 4 weeks without any treatment. The psoriasis area and severity index (PASI) was used to compare the 2 groups. Furthermore, the overall therapeutic results were assessed independently by the investigators and by the patients. Both treatment regimens showed a significant, nearly identical, reduction in PASI. The mean PASI for calcipotriol alone was 5.7 at baseline, 1.9 after 4 weeks of treatment and 3.8 at the end of the follow-up period. For combination therapy, these values were 5.7, 1.8 and 3.8, respectively. There was a statistically significant advantage in favor of combined calcipotriol and diflucortolone valerate treatment at weeks 1 and 2 ( $p < 0.05$ ); however, at the end of the treatment phase the difference between the 2 therapies was not significant. Subjective evaluation of efficacy by both the investigators and the patients revealed no difference between the 2 treatments. The frequency of side effects (e.g. irritation) was low in both groups. In conclusion, both therapies were effective for the treatment of chronic plaque-type psoriatic lesions. The combination of calcipotriol and a topical steroid appeared to produce a more rapid clinical response and was shown to be as effective as calcipotriol therapy alone. **Key words:** psoriasis; calcipotriol; diflucortolone valerate..

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## INTRODUCTION

The vitamin D<sub>3</sub> analog calcipotriol is well established as an effective first-line therapy in chronic plaque psoriasis. Although highly effective, vitamin D<sub>3</sub> analogs can cause problems, including persistent erythema at the site of the former psoriatic plaques, irritation and, rarely, allergic contact dermatitis of

lesional or perilesional skin. In recent years, different treatment regimens have been devised to optimize therapy and minimize associated adverse events. Studies have compared calcipotriol monotherapy with a variety of other topical anti-psoriatic drugs, as well as with different combination therapies (1–7). Calcipotriol and corticosteroids constitute one such combination therapy that has been investigated. This combination was chosen as steroids represent an effective alternative treatment for psoriasis and are also a first-line therapy for treatment of contact dermatitis, which can be a problem associated with calcipotriol therapy.

The aim of our study was to investigate whether the combination of calcipotriol and the topical steroid diflucortolone valerate is as effective as calcipotriol monotherapy, and to ascertain whether the addition of a corticosteroid reduced the incidence/severity of residual erythema and the incidence of contact dermatitis that can be associated with calcipotriol monotherapy.

## MATERIAL AND METHODS

### Study design

The investigation was a double-blind, placebo-controlled, randomized, right – left study, conducted in two Departments of Dermatology (Graz and Vienna). Calcipotriol monotherapy with 0.005% calcipotriol ointment (Psorcutan<sup>®</sup>-Salbe; Schering Wien GmbH) twice daily was compared with a combination therapy of 0.005% calcipotriol ointment in the morning and 0.1% diflucortolone valerate ointment (Nerisona<sup>®</sup>-Fettsalbe; Schering Wien GmbH) in the evening. The study was carried out according to good clinical practice guidelines.

### Patients

Patients of both genders were eligible for the study if they satisfied the following inclusion criteria: age > 19 years; chronic plaque psoriasis with an unchanged clinical appearance for  $\geq 2$  weeks; and comparable, symmetrical psoriatic lesions on both sides of the body.

Patients with exanthematic, erythrodermic or pustular types of psoriasis were excluded, as were patients with an affected area of > 30% of the total body surface. Further exclusion criteria were: systemic drug therapy with vitamin D, calcium or drugs known to have an influence on the course of psoriasis (e.g. lithium,  $\beta$ -blockers, corticosteroids); pregnancy or lactation; hepatitis B, HIV and other infectious diseases (herpes, tuberculosis, syphilis); other concurrent dermatoses; and hypercalcemia, severe hepatic or renal diseases.

### Treatment schedule

After a wash-out phase of 1 week without any topical therapy, treatment was started with calcipotriol twice daily on one half of the

body and a combination therapy of calcipotriol in the morning and diflucortolone valerate in the evening on the other half. Four weeks of treatment were followed by a further 4-week follow-up period.

#### Clinical assessment

Patients were examined 1 week prior to the start of treatment, at baseline, and after 1, 2 and 4 weeks of treatment. They were then re-examined at weeks 6 and 8 during the 4-week, treatment-free, follow-up period. Thus, in total, the patients were examined on 9 separate occasions. The severity of psoriasis was evaluated by a single investigator at each center (W. S. in Graz, H. M. in Vienna), using the psoriasis area and severity index (PASI). Furthermore, at each visit, treatment response was assessed independently by the investigators and by the patients, starting 1 week after the beginning of treatment. The response was rated separately for both sides of the body and scored in one of 7 categories (complete healing, marked improvement, slight improvement, no improvement, slight deterioration, marked deterioration, extreme deterioration) with respect to change since the last clinical evaluation. Additionally, at the end of the follow-up period, patients were asked for a global assessment of their condition, rating the overall therapeutic efficacy of each treatment as good, satisfactory or bad.

Laboratory parameters, including complete blood count, bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, creatinine, phosphate, calcium, albumin and total protein, were measured before enrollment in the study and at the end of the follow-up period. All adverse events, both objective and subjective, were recorded at each visit.

#### Statistics

The strategy for statistical analysis was based on the intention-to-treat principle. All data underwent a descriptive statistical analysis. The primary endpoint (PASI) was analyzed using a 2-period analysis-of-variance model, according to Pocock (8).

All the given type I error probabilities are 2-sided and refer to the individual test. The 2-sided 5% level was defined for statistical significance of the primary endpoint. The statistical software employed was a proprietary development written in IBM APL2 for PCs. This software has been tested according to the guidelines of the European Organization for Quality (9).

## RESULTS

Sixty-three patients (34 men, 29 women; mean age  $47 \pm 15.4$  years; range 19–83 years) were included in the trial. The mean duration of psoriasis was  $141 \pm 124$  months. Of these patients, 4 had never previously received any treatment; the majority, however, had previously used corticosteroids as monotherapy or in combination with tar preparations or dithranol. A further 26 patients had also received treatment with phototherapy (UVB, PUVA), some in combination with

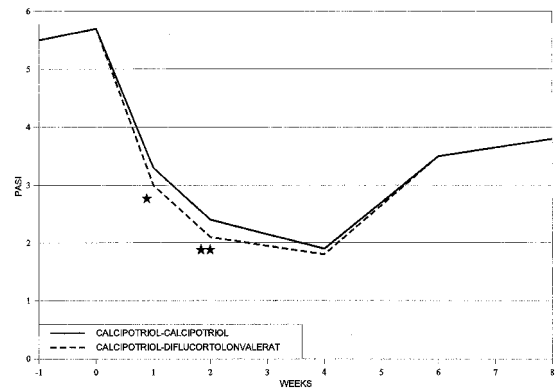


Fig. 1. Mean PASI before (-1) and during treatment (weeks 0–4) and in the follow-up period (weeks 4–8). Statistically significant differences between treatments: \* $p < 0.05$ , \*\* $p < 0.01$ .

systemic drug therapy (retinoids, methotrexate). Overall, the median duration of previous treatment regimens was 7 months.

A total of 58 of the 63 patients completed the study. Compliance was excellent (>90%), and the course of treatment was never interrupted for >5 days. One patient had to be withdrawn during the treatment phase due to lesional and perilesional contact dermatitis of the lower extremities. A further 4 patients were withdrawn due to concomitant diseases (arthralgia, erysipelas, climacteric symptoms and dyshidrotic eczematous dermatitis).

#### Efficacy

Baseline PASI values were similar for both sides of the body. Treatment with both calcipotriol alone and with the combination of calcipotriol and diflucortolone valerate resulted in a rapid and marked reduction of the PASI during the treatment phase of the study, the greatest improvement being observed during the first 2 weeks (Table I; Fig. 1). A statistically significant benefit of combination treatment over calcipotriol monotherapy ( $p < 0.05$ ) was observed after 1 (PASI 3.3 vs. 3.0) and 2 weeks of treatment (PASI 2.4 vs. 2.1). However, at the end of the treatment phase after 4 weeks of treatment and during the follow-up period no significant difference between the 2 treatment groups was detected.

Analysis of the PASI data for individual criteria (psoriatic area, erythema, infiltration, scaling) revealed a slight benefit for combination therapy in terms of reduction of scaling during the treatment period. However, this benefit did not achieve statistical significance.

Table I. Effect of calcipotriol monotherapy and calcipotriol and diflucortolone valerate combination therapy on PASI. Mean values with SDs in parentheses

Therapy	Week						
	- 1	0	1	2	4	6	8
	Treatment phase				Follow-up		
Calcipotriol (am); calcipotriol (pm)	5.5 (2.7)	5.7 (2.9)	3.3 (2.1)	2.4 (1.6)	1.9 (1.4)	3.5 (2.4)	3.8 (2.4)
Calcipotriol (am); diflucortolone valerate (pm)	5.5 (2.6)	5.7 (2.9)	3.0 (1.8)	2.1 (1.3)	1.8 (1.2)	3.5 (2.2)	3.8 (2.3)
<i>P</i>	Ns	ns	0.039	0.0077	ns	ns	ns

Complete healing of psoriatic plaques occurred in 4 patients, but not all individual lesions responded to the same extent.

### Tolerance

Both treatment regimens were generally well tolerated. Slight-to-moderate itching and burning at lesional sites was observed with both treatments, occurring in 6 patients associated with calcipotriol monotherapy and 8 patients associated with combination therapy. There were no statistically significant differences between the 2 treatments; however, these side effects tended to be milder and to occur later with combination therapy than with calcipotriol monotherapy. One patient receiving calcipotriol monotherapy developed severe contact dermatitis and had to be withdrawn from the study. No contact dermatitis occurred in response to combination therapy. Laboratory parameters showed no severe abnormalities in any of the patients in the study.

### Subjective evaluation of efficacy

Subjective assessments by investigators and patients made during therapy, as well as global assessment by the patients at the end of the study, revealed no difference between the 2 treatments.

## DISCUSSION

Several well-designed studies have shown that calcipotriol is an effective treatment for mild-to-moderate chronic plaque psoriasis (1, 2), but an insufficient response to therapy can be expected in 5–20% of patients. In addition, although generally well tolerated, calcipotriol monotherapy can cause local irritation, as well as burning and itching sensations and, rarely, allergic contact dermatitis. In recent years, several clinical trials have been conducted to optimize the efficacy of calcipotriol by using combination therapy. These therapeutic regimens have included the combination of calcipotriol with PUVA (10), UVB (11–14), cyclosporin (15, 16) and acitretin (17). Furthermore, several trials have compared the efficacy of calcipotriol alone and topical preparations such as dithranol (2) and corticosteroids in monotherapy (1), as well as in combination with calcipotriol (3–7). It can be seen from the results of these studies that calcipotriol can be combined effectively with practically every other systemic or topical psoriatic therapy.

Calcipotriol and corticosteroids are both known to be effective in the treatment of psoriatic lesions. A beneficial effect of the combination therapy of calcipotriol with diflucortolone valerate might therefore be expected due to the binding of calcipotriol and corticosteroids at different cellular receptors. As they show a different mode of action, combination therapy could result in an additive or synergistic effect on psoriatic plaques. Furthermore, side effects such as irritation due to calcipotriol or atrophy of the skin due to corticosteroids could probably be minimized by a combination therapy which results in lower total doses of both components.

In the right–left comparative study reported here it has been shown that a combination treatment of calcipotriol with diflucortolone valerate is at least as effective as calcipotriol monotherapy. The results suggest a more rapid response at

the beginning of treatment with the combination therapy, a significantly greater reduction in the PASI values being observed at weeks 1 and 2. At the end of the 4-week treatment period, however, no difference in response to therapy could be demonstrated. Detailed analysis of the PASI values revealed no significant differences with respect to changes in erythema, infiltration or area of psoriatic lesions, but a slight benefit was observed in favor of combination treatment in terms of reduction of scaling, mainly in the first 2 weeks of treatment. This effect did not, however, reach statistical significance, probably due to the relatively small number of patients in the study which did not allow accurate detection of small differences. Complete healing of psoriatic plaques was achieved in only 4 patients; however, this was not an unexpected outcome due to the relatively short duration of the treatment phase of the study.

Both treatments were well tolerated, with only mild side effects such as itching and burning. There was no significant difference in the frequency of side effects between the 2 treatments. Only 1 severe local adverse event was seen, a case of contact dermatitis occurring in response to calcipotriol monotherapy and leading to the withdrawal of the patient from therapy. In response to combination treatment, no irritation or contact dermatitis was noted, presumably as a consequence of the lower total dose of calcipotriol and the suppressive effect of diflucortolone valerate.

Based on the results of our study it can be concluded that the combination of calcipotriol and diflucortolone valerate to treat chronic plaque psoriasis is at least as effective as calcipotriol monotherapy and may offer some clinical advantages. The response rate with combined calcipotriol and diflucortolone valerate may be more rapid than that with calcipotriol alone and side effects such as itching and burning may be less intense with combination therapy. These findings are in agreement with expectation from a theoretical perspective, but require confirmation in a larger, longer-term study.

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