STUDY

Efficacy, Tolerability, and Safety of Calcipotriol Ointment in Disorders of Keratinization

Results of a Randomized, Double-blind, Vehicle-Controlled, Right/Left Comparative Study

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Background and Design: Disorders of keratinization are a heterogeneous group of diseases that have in common a defect in cornification. The bioactive form of vitamin D_3 has been shown to modulate epidermal proliferation and differentiation. The purpose of the present study was to determine the effect of the synthetic vitamin D_3 calcipotriol in a randomized, double-blind, placebo-controlled, right/left comparative study. The 67 patients included in the study were at least 12 years of age and had the following diseases: ichthyosis vulgaris (n=9), X-linked ichthyosis (n=8), congenital ichthyosis (n=10), hereditary palmoplantar keratoderma (n=20), keratosis pilaris (n=9), and Darier's disease (n=11). Calcipotriol ointment (50 μg/g) and placebo (vehicle of calcipotriol ointment) were applied to all patients twice daily for up to 12 weeks. The patients were allowed to use up to 120 g of calcipotriol ointment per week.

Results: At the end of the treatment regimen, calcipotriol ointment had an effect on the improvement of the ichthyoses, although to a variable degree. No therapeutic effect was detected in palmoplantar keratoderma or keratosis pilaris. Eight of 12 patients with Darier's disease had to be withdrawn because of skin irritation or a worsening of the disease. Skin irritation occurred in 18 cases (26%) only on the calcipotriol-treated side, and in one case (1%) only on the placebo-treated side. Nine cases (13%) had irritation on both sides. The amount of calcipotriol ointment used per week was lowest in palmoplantar keratoderma (mean, 11.8 g/wk; range, 2.1 to 25.6 g/wk) and highest in congenital ichthyosis (mean, 59.3 g/wk; range, 11.4 to 94.7 g/wk). There was no clinically significant change of serum calcium levels during the treatment period.

Conclusion: Short-term treatment with calcipotriol ointment (50 μg/g) used in amounts up to about 100 g/wk is moderately efficacious, well-tolerated, and safe in adult patients with various ichthyoses.

(Arch Dermatol. 1995;131:556-560)

DISORDERS OF keratinization comprise a heterogeneous group of diseases characterized by dry and scaly skin.[1] They include the ichthyoses, Darier's disease, pityriasis rubra pilaris, keratodermas, and follicular keratoses. The disorders of keratinization are chronic, often inherited, diseases with onset in childhood. Treatment is often unsatisfactory, although lubrication with ointments or creams may soften the skin, and topical preparations containing salicylic acid may remove the scaling. In some of the disorders, retinoids administered topically, but mainly systemically, are effective.[2] Because of the associated risk of severe side effects, the systemic retinoids are only used in severe and widespread cases.

Although the disorders of keratinization are a heterogeneous group of diseases, they have in common a defect in cornification. The underlying pathogenic mechanisms involve disordered keratinocyte differentiation and/or proliferation.[1] In addition to the epidermal changes, some of the disorders show dermal inflammation and immunologic changes. The biologically active form of vitamin D_3, 1,25-dihydroxyvitamin D_3, has been demonstrated to stimulate the terminal differentiation of epidermal keratinocytes and to inhibit the proliferation of epidermal keratinocytes.[3] At least in vitro 1,25-dihydroxyvitamin D_3 modifies differentiation by stimulating the switch of suprabasal cells into cornified cells.[4] Apparently, 1,25-dihydroxyvitamin D_3 induces terminal differentiation of epidermal keratinocytes without changing their keratin gene expression in vitro.[5] By modi-

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PATIENTS AND METHODS

STUDY DESIGN AND PATIENTS

The study was designed as a prospective, randomized, double-blind, right/left comparative study of calcipotriol (50 μg/g) and placebo ointment (vehicle of calcipotriol ointment), both applied twice daily. The ingredients of the vehicle were disodium hydrogen phosphate, polyoxyethylene-2-stearylether, propylene glycol, tetracemine disodium, DL-α-tocopherol, petrolatum, liquid paraffin, and water. The study was conducted in two centers in Denmark and in one center in the Netherlands. Patients were not treated during summertime. The study was divided into two phases. After a washout phase of 2 weeks during which the patient used only an emollient, the patients were given double-blind treatment with calcipotriol ointment on one side of the body and placebo ointment on the other side for 12 weeks or until clearance on one side. The criterion for including patients was a clinical and histologic diagnosis of one of the following dyskeratoses: ichthyosis vulgaris, X-linked ichthyosis, congenital ichthyosis, Darier's disease, pityriasis rubra pilaris, hereditary palmoplantar keratoderma, and keratosis pilaris. The diagnosis of X-linked ichthyosis was based on an established human steroid sulfatase deficiency.[10]

Patients had symmetrically located lesions and were at least 12 years of age. Excluded were patients with skin infection; atopic dermatitis; and systemic treatment with retinoids, corticosteroids, or PUVA within the 8-week period prior to the washout phase. Also excluded were patients with hypercalcemia, high vitamin D or calcium intake, and significant renal or hepatic disease. Women of childbearing potential were only included if using an adequate method of contraception. All patients gave their informed consent.

All affected body areas, except for the face, scalp, and genital region, were treated with the study medications. A maximum of 120 g was dispensed to each side of the body per week. Patients with affected areas on the face and genital region used an emollient for these areas. All tubes were returned and weighed to determine the amount of ointment used. The use of other topical medications or systemic treatment for dyskeratosis was not allowed.

PATIENT OUTCOMES

Clinical assessments were done separately at weeks 0, 2, 4, 8, and 12 for the right and left sides of the body. The extent of the dyskeratotic involvement was recorded using the following scale: 0, no involvement; 1, less than 20%; 2, 20% to 39%; 3, 40% to 59%; 4, 60% to 79%; and 5, 80% to 100% for each of the following regions: arms, legs, and trunk. The investigator also assessed the severity of the following signs: in ichthyosis vulgaris and keratosis pilaris, scales and roughness; in X-linked ichthyosis, scales, roughness, and hyperpigmentation; in Darier's disease, scales, erythema, papules, crust, and excoriation; in pityriasis rubra pilaris, scales, thickness, and erythema; in hereditary palmoplantar keratoderma, scales, thickness, erythema, and fissuring; and in congenital ichthyosis, scales, roughness, and erythema. These signs were assessed using the following scale: 0, absent; 1, slight; 2, moderate; and 3, severe. Furthermore, the investigator assessed the overall response to the treatment compared with baseline using the following 6-point scale: worse, no change, slight improvement, moderate improvement, marked improvement, and cleared. The patients assessed the overall response to treatment using the same scale. Blood samples for hematology and blood chemistry analyses, including serum total calcium levels, were taken before the start of treatment, after 2 weeks' treatment, and at the end of treatment.

STATISTICAL ANALYSIS

Comparison of treatment effects at the end of the double-blind treatment period was based on intrapatient variations of the calcipotriol-treated side and the placebo-treated side. With respect to the investigator's and patient's overall assessment, the number of patients with the calcipotriol-treated side superior to the placebo-treated side were compared with the number of patients with the placebo-treated side superior to the calcipotriol-treated side by binomial tests. Total sign score differences from baseline to end of double-blind treatment period were calculated for both treatment sides separately and compared using a one-sample *t* test.

For adverse events the number of patients reporting adverse events on the calcipotriol-treated side only was compared with the number of patients reporting adverse events on the placebo-treated side only by binomial tests.

All statistical tests were two sided, and a 5% significance level was used.

fying the epidermal growth pattern, vitamin D_3 may improve disorders of keratinization. However, neither X-linked ichthyosis nor ichthyosis vulgaris has responded to treatment with either oral 1α-hydroxyvitamin D_3[6] or topical 1,25-dihydroxyvitamin D_3.[7]

Calcipotriol is a synthetic vitamin D analogue that is as effective as 1,25-dihydroxyvitamin D_3 in binding to the vitamin D receptor and in stimulating epidermal differentiation.[8] Compared with 1,25-dihydroxyvitamin D_3, calcipotriol, however, is about 100 to 200 times less potent in its effect on calcium metabolism in rats.[8] In clinical studies, calcipotriol ointment (50 μg/g) has been shown to be effective and safe for the treatment of psoriasis vulgaris.[9] The purpose of the present study was to determine whether topical calcipotriol is effective, tolerated, and safe in disorders of keratinization.

RESULTS

Sixty-nine patients were randomized to receive treatment (**Table 1**). However, one patient included in the Darier's disease group had Hailey-Hailey disease. Furthermore, one patient with lamellar ichthyosis left the study before any collection of efficacy or safety data. Therefore, efficacy and safety data were only available for 67 patients. The subgroup of hereditary palmoplantar keratoderma had 20 patients randomized, while the other groups consisted of eight to 12 patients each. The sub-

group of congenital ichthyosis was heterogeneous, consisting of one patient with epidermolytic hyperkeratosis (bullous ichthyosiform erythroderma of Brocq, autosomally dominantly inherited), two patients with lamellar ichthyosis (nonerythrodermic autosomal recessive lamellar ichthyosis), two patients with Sjögren-Larsson syndrome, one patient with ichthyosis linearis circumflexa, two patients with congenital ichthyosiform erythroderma (erythrodermic autosomal recessive lamellar ichthyosis), and two patients with ichthyosis bullosa of Siemens. No case of pityriasis rubra pilaris was randomized. At baseline there was no clinically significant difference in the total sign score on the right and left sides (data not shown). Fifteen of the 69 randomized patients withdrew from the double-blind treatment regimen (**Table 2**). Adverse events were the reason for withdrawal in nine of 15 cases (see below). It was remarkable that seven of 12 patients with Darier's disease withdrew because of lesional-perilesional irritation or worsening of the disease. In accordance with the high number of withdrawals, the mean duration of double-blind treatment was only 6.1 weeks in Darier's disease, compared with 9.6 to 12.3 weeks in the other subgroups. **Table 3** shows the investigator's overall assessment of the treatment response to calcipotriol and placebo at the end of treatment. Marked improvement or clearance was observed on the calcipotriol-treated side in five of nine cases with ichthyosis vulgaris, in four of eight patients with X-linked ichthyosis, and in eight of 10 cases with congenital ichthyosis, but the difference between calcipotriol and placebo was only statistically significant for X-linked ichthyosis (P=.03) and congenital ichthyosis (P=.02). The patient's overall assessment at the end of the treatment period is tabulated in the same way (**Table 4**). According to the patients, marked improvement or clearance was observed on the calcipotriol-treated side in four of nine patients with ichthyosis vulgaris, in four of eight patients with X-linked ichthyosis, and in seven of 10 patients with congenital ichthyosis. Only in X-linked ichthyosis did the difference between calcipotriol and placebo reach statistical significance (P=.03).

Table 1. Number and Demographic Data of Patients Randomized

Disease	n	No. (%) of Male Subjects	Age, y (Mean, Range)
Ichthyosis vulgaris	9	5 (56)	34.1 (16-52)
X-linked ichthyosis	8	8 (100)	34.4 (16-50)
Congenital ichthyosis	11	5 (45)	32.4 (16-55)
Darier's disease	12	7 (58)	38.6 (18-79)
Keratoderma	20	12 (60)	29.7 (11-57)
Keratosis pilaris	9	1 (11)	23.4 (16-45)
All Patients	**69**	**38** (55)	32.0 (11-79)

Table 2. Reason for Withdrawal From Double-blind Treatment

Disease	No. of Adverse Events	No. of Unacceptable Responses	No. of Voluntary Defaults	Total No.
Ichthyosis vulgaris (n=9)	0	0	0	**0**
X-linked ichthyosis (n=8)	1	0	1	**2**
Congenital ichthyosis (n=11)	0	0	1	**1**
Darier's disease (n=12)	6	1	1*	**8**
Palmoplantar keratoderma (n=20)	1	0	1	**2**
Keratosis pilaris (n=9)	1	1	0	**2**
Total (N=69)	**9**	**2**	**4**	**15**

**This patient had Hailey-Hailey disease.*

The total sign score, defined as the sum of the severity scores for each side of the body, could have a minimum range of 0 to 6 for ichthyosis vulgaris and keratosis pilaris and a maximum range from 0 to 15 for Darier's disease. The decrease in the total sign score at the end of the treatment period was greater on the calcipotriol-treated side than on the placebo-treated side in ichthyosis vulgaris, X-linked ichthyosis, and congenital ichthyosis (**Figure**). In congenital ichthyosis this reduction in the total sign score on the calcipotriol-treated side was statistically highly significant compared with the placebo-treated side (P=.0015) (Figure). There was no statistically significant difference between calcipotriol and placebo in the mean total sign score or overall assessment in other subgroups of dyskeratosis (data not shown).

The adverse events reported or observed during the treatment period were almost exclusively localized to the skin and consisted almost exclusively of various forms of lesional and perilesional irritation (**Table 5**). No irritation was detected in congenital ichthyosis. Lesional-perilesional irritation was more often seen on the calcipotriol-treated side (P<.001). Skin irritation was most common in X-linked ichthyosis and Darier's disease. While only a single patient with X-linked ichthyosis was

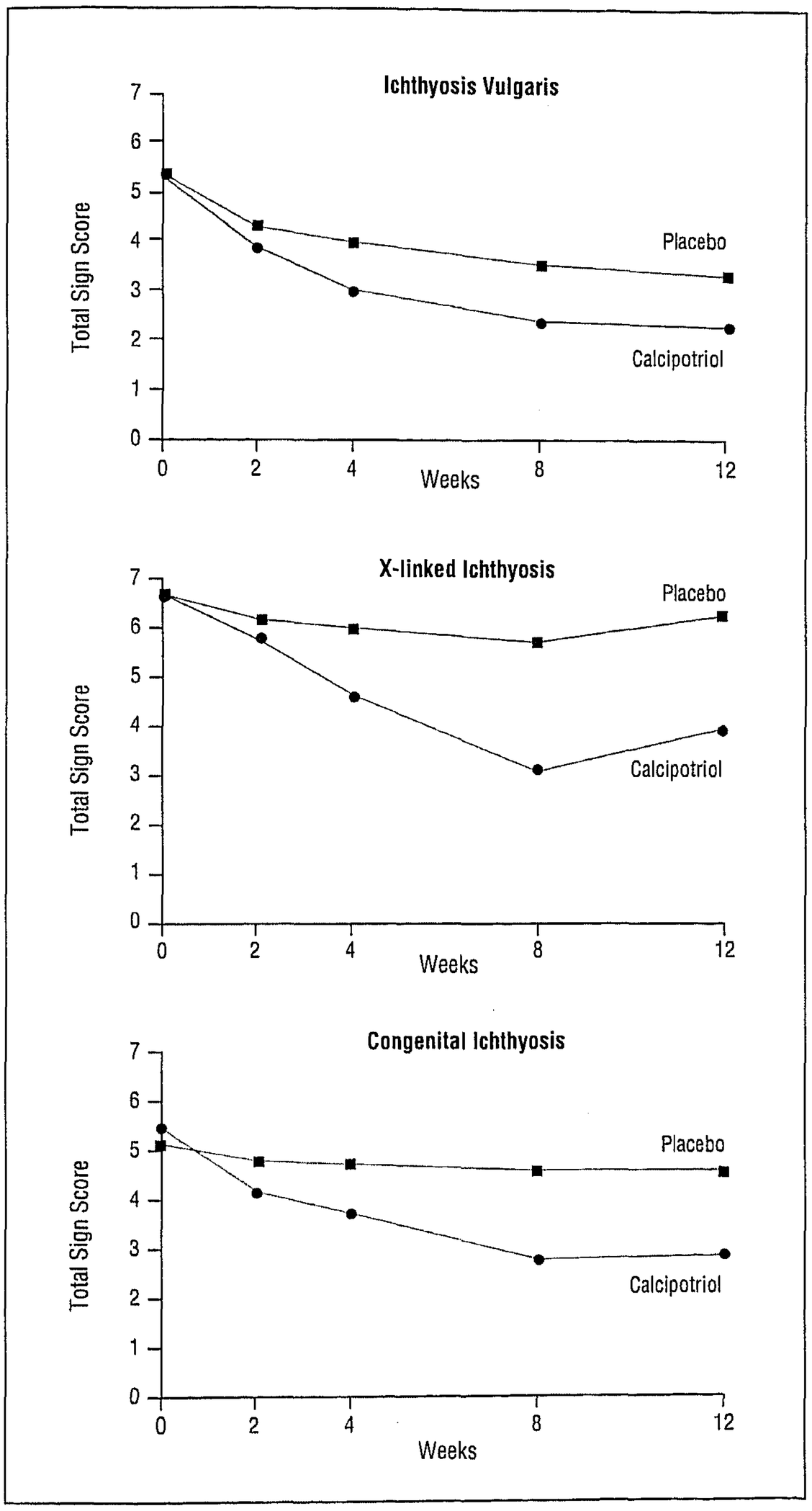
Table 3. Investigator's Overall Assessment of Treatment Response at End of Treatment Period

	Calcipotriol/Placebo, No. of Patients					
Disease Cleared	Worse	No Change	Slight Improvement	Moderate Improvement	Marked Improvement	Cleared
Ichthyosis vulgaris (n=9)	0/0	0/0	2/4	2/4	5/0	0/1
X-linked ichthyosis (n=8)	0/0	1/2	0/4	3/2	4/0	0/0
Congenital ichthyosis (n=10)	0/0	1/4	0/4	1/1	8/1	0/0
Keratoderma (n=20)	0/0	9/11	6/5	3/1	2/2	0/1
Keratosis pilaris (n=9)	2/1	1/2	2/3	2/3	2/0	0/0
Darier's disease (n=11)	8/5	0/4	2/0	1/2	0/0	0/0

Table 4. Patient's Overall Assessment of Treatment Response at End of Treatment Period

Disease Cleared	Calcipotriol/Placebo, No. of Patients					
	Worse	No Change	Slight Improvement	Moderate Improvement	Marked Improvement	Cleared
Ichthyosis vulgaris (n=9)	0/0	0/0	3/5	2/3	4/0	0/1
X-linked ichthyosis (n=8)*	0/1	0/3	0/2	3/1	4/1	0/0
Congenital ichthyosis (n=10)	0/1	1/4	0/3	2/1	0/0	. . .
Keratoderma (n=20)	0/0	8/10	8/5	3/2	1/2	0/1
Keratosis pilaris (n=9)	2/1	2/4	0/0	3/3	2/1	0/0
Darier's disease (n=11)	8/5	0/3	1/1	2/1	0/1	0/0

**For one of the patients, the calcipotriol-treated side was not assessed.*



Change in the mean total sign score during treatment with calcipotriol ointment (50 μg/g) and placebo ointment in ichthyosis vulgaris (n=9), X-linked ichthyosis (n=8), and congenital ichthyosis (n=10).

withdrawn because of skin irritation, six patients with Darier's disease withdrew because of lesional-perilesional irritation. The amount of calcipotriol ointment used per week was lowest in palmoplantar keratoderma (mean, 11.8 g/wk; range, 2.1 to 25.6 g/wk) and highest in congenital ichthyosis (mean, 59.3 g/wk; range, 11.4 to 94.7 g/wk). With respect to the change in the serum total calcium level from baseline to the end of the treatment period, the subgroup X-linked ichthyosis showed a minor, but statistically significant, reduction (P=.045). No subgroup showed any statistically significant increase in the serum total calcium level (data not shown).

Table 5. Lesional-Perilesional Irritation Reported and/or Observed in Disorders of Keratinization

Disease	Calcipotriol Side, No. (%)	Placebo Side, No. (%)	Both Sides, No. (%)
Ichthyosis vulgaris (n=9)	2 (22)	1 (11)	0
X-linked ichthyosis (n=8)	6 (57)	0	0
Congenital ichthyosis (n=10)	0	0	0
Palmoplantar keratoderma (n=20)	5 (25)	0	2 (10)
Keratosis pilaris (n=9)	2 (22)	0	2 (22)
Darier's disease (n=12)	3 (25)	0	5 (42)
Total No. of Irritations	**18** (26)	**1** (1)	**9** (13)

COMMENT

The results of the present study indicate that topical treatment with calcipotriol for 12 weeks is moderately efficacious in various forms of ichthyosis. Palmoplantar keratoderma and keratosis pilaris seem to be unresponsive to calcipotriol, whereas Darier's disease may worsen during treatment with calcipotriol, probably due to the irritating capacity of calcipotriol ointment. The presence of eroded and fissured lesions in Darier's disease may be the reason for the increased susceptibility to become irritated by calcipotriol ointment. Except for Darier's disease, the cutaneous side effects in the dyskeratotic disorders were similar to those observed in psoriasis with respect to their nature, severity, and frequency.[9] Among the ichthyoses, X-linked ichthyosis and congenital ichthyosis were particularly responsive to calcipotriol. The group with congenital ichthyosis is very heterogeneous, and the low number of patients in each subtype does not allow any conclusions as to any variation in the responsiveness to calcipotriol. In contrast to calcipotriol, neither oral 1α-hydroxyvitamin D_3[6] nor topical 1,25-

dihydroxyvitamin D_3[7] is reported to improve X-linked ichthyosis or ichthyosis vulgaris. The reason for this apparent discrepancy is most likely that 1α-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 were used in doses that were too low. Thus, the applied concentration of 1,25-dihydroxyvitamin D_3 (1 μg/g) has no significant effect on psoriasis.[11,12]

A major concern during treatment with vitamin D analogues is whether percutaneously absorbed vitamin D may change calcium metabolism. In large-scale studies of psoriasis, it has been found that a weekly dose of up to 100 g of calcipotriol ointment (50 μg/g) does not change the serum calcium levels.[9] Furthermore, the biochemical markers of calcium and bone metabolism do not change in psoriatic subjects receiving a mean calcipotriol dose of 40 g/wk[13] or 100 g/wk.[14] In the present study, during which patients were allowed to use up to 120 g/wk, no significant changes in serum calcium levels were found. This indicates that patients with disorders of keratinization are not more likely than psoriatic subjects to develop hypercalcemia after topical application of calcipotriol. However, it should be borne in mind that only half of the affected skin lesions were treated with calcipotriol. In some of the patients with more widespread disease, it might have been impossible to treat all lesions with the allowed amount of calcipotriol (120 g/wk). As recommended for psoriasis, calcipotriol ointment (50 μg/g) was applied twice daily in the dyskeratoses. It is, however, possible that application of calcipotriol ointment once daily is efficacious for the treatment of ichthyosis. If so, 120 g of calcipotriol ointment per week might be sufficient in most patients.

Vitamin D and its analogues have multiple actions on the cellular and molecular levels, and it still has not been sorted out whether vitamin D analogues work in psoriasis by modifying keratinocyte differentiation/proliferation or whether their immunosuppressive effects are important for their antipsoriatic effect. The fact that treatment with calcipotriol can improve the ichthyoses supports the idea that calcipotriol in vivo has an effect on epidermal differentiation and/or proliferation independent of immunomodulation.

It can be concluded that topical treatment with calcipotriol (50 μg/g) for 12 weeks can induce a moderate improvement of various forms of ichthyoses. While calcipotriol is well tolerated in ichthyosis, it may worsen Darier's disease, probably due to its irritating capacity. Although ichthyosis may be responsive to calcipotriol treatment, large-scale studies, but especially long-term studies, are needed to confirm the present results. If calcipotriol ointment is used for the treatment of ichthyosis, it is important that the weekly dose be kept below 120 g. If calcipotriol is applied twice daily, about 15% to 20% of the body surface can be treated, but application once daily makes it possible to increase the treated skin area. The safety and efficacy of this alternative approach warrants further investigation. If topical calcipotriol is found to be efficacious and safe in long-term large-scale studies, this treatment may be of great benefit to patients severely affected by ichthyosis. Also, it should be investigated whether it is beneficial to combine calcipotriol with a retinoid. In addition to a simple additive effect of these two classes of compounds, an interaction might occur on the molecular level, leading to a synergistic effect.[15]

Accepted for publication March 30, 1994.

The study was sponsored by Leo Pharmaceutical Products, Copenhagen, Denmark.

The authors want to thank Søren Pedersen, MScEng, for the statistical analyses.

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