Acta Derm Venereol (Stockh) 1994; 74: 398–402

Efficacy and Safety of the 20-epi-vitamin D_3 Analogue KH 1060 in the Topical Therapy of Psoriasis: Results of a Dose-ranging Study

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KH 1060 is a 20-epi-vitamin D_3 analogue, structurally related to 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$). In vitro, KH 1060 is much more potent than $1,25(OH)_2D_3$ in regulating cell growth and T lymphocyte mediated immune responses, despite a similar calcemic activity in vivo. Therefore, KH 1060 is of potential interest in the treatment of psoriasis and other diseases characterized by accelerated cell growth and T lymphocyte activation. In a multicenter, prospective, randomized, double-blind, vehicle-controlled right/left comparative study, patients with plaque-type psoriasis vulgaris were randomly assigned to one of the following treatment groups: (I) KH 1060 ointment 0.2 μg/g versus placebo ointment, (II) KH 1060 ointment 0.2 μg/g versus KH 1060 ointment 0.04 μg/g, and (III) KH 1060 ointment 0.2 μg/g versus KH 1060 ointment 1 μg/g. All treatments were given twice daily for 6 weeks. Sixty-four of the 70 randomized patients completed the study. At the end of treatment, no difference was demonstrated between KH 1060 0.04 μg/g and vehicle, whereas significantly increasing improvement was found for the doses KH 1060 0.2 μg/g and KH 1060 1 μg/g. According to the investigator's overall assessments at the end of treatment, KH 1060 1.0 μg/g and KH 1060 0.2 μg/g produced a marked or moderate improvement in most patients. Mild lesional irritation was observed after treatment with KH 1060 as well as with placebo. One patient was withdrawn because of an eczematous reaction, where KH 1060 1.0 μg/g was applied. There was no change of serum calcium levels during the treatment. In conclusion, at the dosages tested topical KH 1060 induces a moderate improvement of psoriasis without causing any significant side-effects. ***Key words: epidermal proliferation; T lymphocytes.***

(Accepted March 23, 1994.)

Acta Derm Venereol (Stockh) 1994; 74: 398–402.

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Receptors for calcitriol, 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), the biologically active form of vitamin D_3, have been demonstrated in epidermal keratinocytes (1), dermal fibroblasts (2) and activated lymphocytes (3). In cultured epidermal keratinocytes, $1,25(OH)_2D_3$ inhibits proliferation and induces terminal differentiation (4, 5). Furthermore, $1,25(OH)_2D_3$ interferes with T lymphocyte activation induced by antigens, mitogens and cytokines (6, 7). Therefore, $1,25(OH)_2D_3$ and other vitamin D_3 analogues have been suggested to possess immunosuppressive properties. KH 1060 is a synthetic 20-epi-vitamin D_3 analogue (Fig. 1). Although similar to $1,25(OH)_2D_3$ in receptor-binding affinity, KH 1060 is at least 1000 times more potent in inhibiting cell proliferation of the histiocytic lymphoma cell line U937 (8) and in suppressing T lymphocyte activation in vitro (8). Furthermore, KH 1060 can prolong mouse skin allograft survival at doses as low as 0.02 μg/kg/day (9) and improve experimentally induced autoimmune disease in rats (10). Despite this high potency both in vitro and in vivo, KH 1060 is comparable to $1,25(OH)_2D_3$ in its ability to influence 24-hour urinary calcium excretion in rats during a 7-day dosing period (8). Compared to the synthetic vitamin D_3 analogue, KH 1060 is about 100 times more potent in its effects on keratinocytes and lymphocytes, but also about 100 times more calcipotropic. Because of these pharmacological properties, it may be advantageous to use KH 1060 in skin diseases in which accelerated cell growth and T lymphocyte activation are believed to play a pathogenic role. Topically applied $1,25(OH)_2D_3$ has been shown to be efficacious for the treatment of psoriasis (11, 12), and in large scale studies the vitamin D_3 analogue calcipotriol is both efficacious and safe in psoriasis (13–15). The purpose of the present study was to determine whether the potent effects of KH 1060 on cell proliferation and T lymphocyte activation translate into a stronger anti-psoriatic effect of topically applied KH 1060.

MATERIAL AND METHODS

Study design

This was a multicenter, prospective, double-blind, vehicle-controlled, right/left comparative, dose-ranging study. After a 2-week wash-out period, patients were randomly assigned to one of the following groups: (I) KH 1060 ointment 0.2 μg/g versus placebo ointment (KH 1060

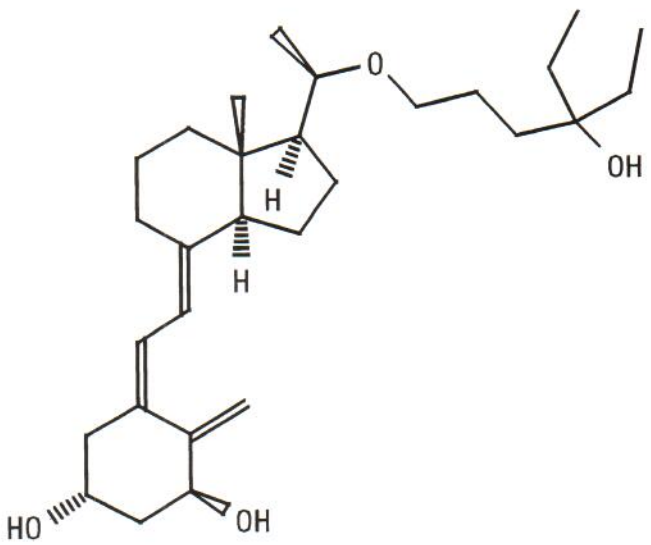

Fig. 1. Chemical structure of KH 1060.

 ISSN 0001-5555

Table I. *Baseline characteristics of treatment groups*

	Treatment groups		
	0.2 μg/g vs. 0 ($n=14$)	0.2 μg/g vs. 0.04 μg/g ($n=29$)	0.2 μg/g vs. 1.0 μg/g ($n=27$)
Sex			
no. of males (%)	9 (64)	16 (55)	17 (63)
Age			
mean	42.8	42.8	51.5
range	20–70	22–74	24–73
Duration of psoriasis (years)			
mean	14.2	24.3	27.3
range	1–32	3–70	6–67
PASI			
mean	6.3	7.6	10.2
range	2.1–15.4	1.8–19.2	1.8–21.6
Difference of PASI between sides			
mean	0.13	0.09	0.26
confidence limit	–0.06–0.32	–0.25–0.44	–0.20–0.72

ointment vehicle), (II) KH 1060 ointment 0.2 μg/g versus KH 1060 ointment 0.04 μg/g, or (III) KH 1060 0.2 μg/g versus KH 1060 ointment 1.0 μg/g. The ointments were applied twice daily to all psoriatic lesions, excluding the scalp, for 6 weeks.

Study drug

The vehicle of the ointment had the following constituents: disodium hydrogen phosphate, POE stearylether, propyleneglycol, DL-alpha-tocopherol, petrolatum, paraffin liquid and purified water. One tube of 30 g of each assigned trial medication was provided per week.

Patients

Seventy patients of either sex, age range 18–75 years, with plaque-type psoriasis vulgaris, stable in extent and severity for at least 2 weeks prior to the start of treatment, symmetrically distributed, were included. They received no systemic anti-psoriatic treatment for at least 8 weeks and no topical anti-psoriatic treatment for at least 2 weeks prior to the start of treatment. Excluded were patients with hypercalcemia or significant renal and hepatic disease. Women of child-bearing potential were only included if using an adequate method of contraception. Pregnant and breast-feeding women were excluded. All patients gave their signed informed consent to participate in the study. The study was approved by the local Ethics Committee.

Study procedures

Visits took place at week –2, 0 (randomization), 1, 2, 4 and 6. At every visit the investigator assessed the extent and severity of the patient's psoriasis separately for each side of the body, using a modified psoriasis area and severity index (PASI), which could range from 0 to 64.8 (14). Also, the investigator and the patient made an assessment of the overall response to therapy compared with baseline: worse, no change, minimal improvement (less than 50%), moderate improvement (51%–75%), marked improvement (76%–99%), clearance (100%). The efficacy analyses were based on the end-of-treatment results. Laboratory examinations consisted of hematology and blood chemistry at week –2 and week 6.

Statistical analysis

The sample size was chosen to provide a statistical power of approximately 0.80 to detect a difference in PASI of at least 12% between the treatment groups at a Type I error rate of 0.05 for a two-tailed hypothesis, assuming a standard deviation of difference of 20%. Comparison of the investigator's overall assessment and the patient's overall assessment was performed as a binomial test on the number of times one side of a patient was assessed to be better or worse than the other. The

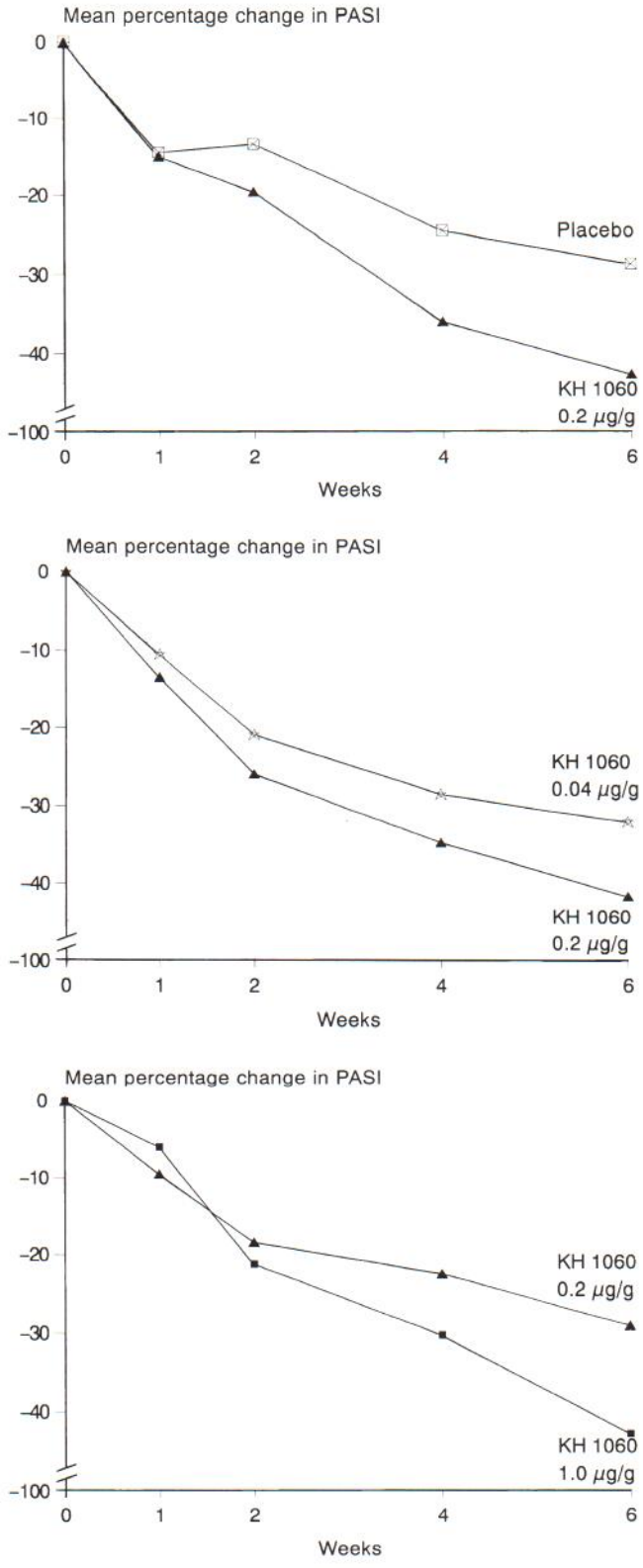

Fig. 2. Change in PASI from baseline to subsequent control visits for the paired treatment with KH 1060 (A, B and C).

Table II. *Percentage change in PASI from baseline to the end of treatment for the paired treatments*

Reference treatment	Test treatment	No	% Change of reference	% Change of test	Difference between reference and test	P*
	Placebo	13	–43	–29	14	0.045
KH 1060 0.2 μg/g	KH 1060 0.04 μg/g	27	–42	–32	10	0.06
	KH 1060 10 μg/g	25	–29	–44	–14	0.006

* P-value in paired t-test.

analysis of PASI was for each group performed by comparing the end-of-treatment result of PASI for the reference treatment KH 1060 0.2 μg/g (X) to those for one of the three test treatments (Y): KH 1060 0.04 μg/g, KH 1060 1 μg/g, and vehicle by analysing the difference (D = Y – X) within patients. In order for us to find any dose related effect, all 4 treatments were analysed together, using one-way analyses of variance on the derived parameter: D = Y – X classified by group. The frequency of adverse events was compared between treatment groups by chi-squared tests or Fisher's exact test in the event of very small observed frequencies. Changes in laboratory parameters within treatment groups were tested using one-sample *t*-tests. *P*-values below 0.05 were regarded as significant.

RESULTS

Study population

Six patients were withdrawn during the wash-out phase, because they did not comply with the eligibility criteria. The baseline characteristics of the 70 patients randomized to receive treatment are shown in Table I. First, the three groups were compared with respect to PASI at baseline, and comparison was performed between the sides of the patients classified by treatment. No difference in PASI was found between treatment sides within patients, and the difference between sides for the three groups was similar. However, significant differences were seen in mean PASI at baseline between the groups (Table I). This difference was further investigated for the reference treatment (KH 0.2 μg/g) for the whole treatment period by using a three-way analysis of variance with repeated measurements classified by 1) groups, 2) patients within groups and 3) visits. This analysis was performed on PASI and the derived parameters, change in PASI, and percentage change in PASI. The result of this analysis showed that the derived parameter percentage change in PASI was similar between the three groups in terms of development by time and level. Furthermore, it was independent of the baseline value of PASI. Thus, test results based on differences between sides within patients on percentage change in PASI were valid and independent of the observed difference between groups in levels of PASI. Six patients withdrew during the treatment, 5 voluntarily; and 1 patient stopped using study drugs 5 days before the last visit because of an adverse event. This patient was included in the efficacy analysis.

Study medication

The mean amount of study medication used per week was greatest in the group treated with KH 1060 0.2 μg/g and KH 1060 1.0 μg/g, which is in accordance with the higher baseline PASI in this group. The amount of ointment used per week was constant throughout the study. Also, there was no difference in the use on the right and the left side. The weekly amount of ointment used on each side did not exceed 30 g (data not shown).

Efficacy

Fig. 2 A–C shows the percentage change in PASI levels for the paired treatments during therapy. The percentage change in PASI at the end of treatment is found in Table II. All treatments induced an improvement. The differences between the paired treatments were statistically significant, except between KH 1060 0.2 μg/g and KH 1060 0.04 μg/g ($p = 0.06$). Furthermore, comparing the differences (test reference) in the three groups showed no significant difference: KH 1060 0.04 μg/g versus KH 1060 0.2 μg/g (14%) and vehicle versus KH 1060 0.2 μg/g (10%). The pooled mean difference for these two groups was significant (11%, $p = 0.01$). Thus, no difference in the effect of treatment was demonstrated between KH 1060 0.04 μg/g and vehicle, whereas a significantly increasing effect was demonstrated for the doses KH 1060 0.2 μg/g and KH 1060 1.0 μg/g.

The investigator's overall assessment of the efficacy at the end of treatment is shown in Fig. 3. According to these assessments, the differences between the paired treatments were statistically significant and dose-related. The assessments made by the patients were similar, although the difference between KH 1060 0.2 μg/g and placebo did not reach statistical significance (data not shown).

Clinical adverse event

A total of 22 adverse events, out of which 17 were considered by the investigator to be possibly or probably related to the treatment, were reported by 21 patients (Tables III, IV and V). These adverse events were all localized to the skin. Sixteen patients (23%) reported 16 adverse events on the KH 1060-treated side, while 5 patients (45%) reported 5 adverse events on the placebo-treated side. Lesional/perilesional irritation was the most common adverse event, reported by 11 out of 70 patients (16%) on KH 1060 treated skin and by 3 out of 14 patients (27%) on placebo treated skin only. One patient withdrew because of red and irritated eczematous skin on the side treated with KH 1060 1.0 μg/g. This adverse event was reported at week 6 and had disappeared within 1 week on discontinuing trial medication.

Laboratory examinations

The laboratory analyses provided no evidence that hemopoietic, hepatic or renal functions were adversely affected by the treat-

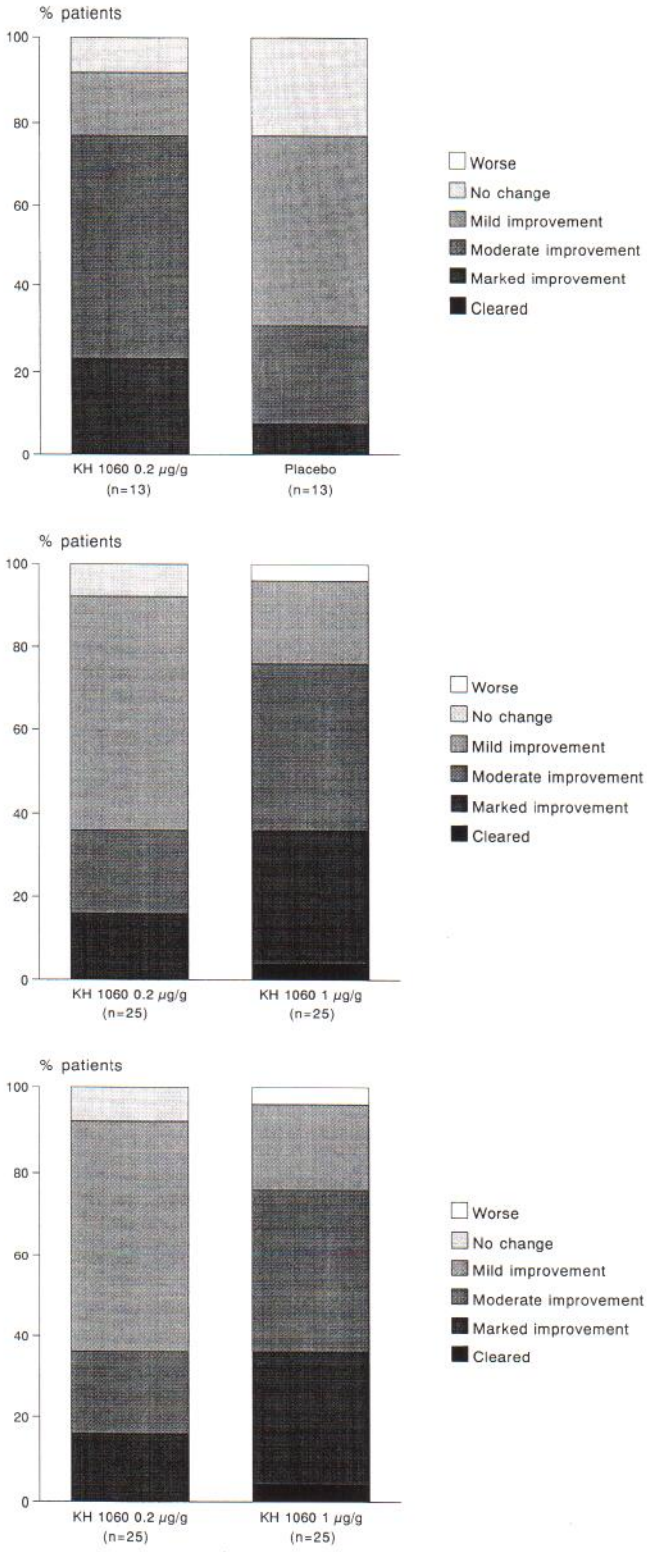

Fig. 3. Investigator's overall assessment of treatment response at the end of treatment for the paired treatments with KH 1060 (A, B and C). *P*-value in McNemar test (KH 1060 0.2 µg/g/ placebo: 0.022; KH 1060 0.02 µg/g/KH 1060 0.04 µg/g: 0.004 KH 1060 0.2 µg/g/KH 1060 1.0 µg/g: 0.002).

Table III. *Adverse events reported or observed during treatment with KH 1060 ointment 0.2 µg/g and placebo ointment (n = 14)*

	KH 1060 0.2 µg/g no. ptt sides (%)	Placebo no. ptt sides (%)	Both sides no. ptt (%)
Lesional/perilesional irritation			
Itching		3 (21)	2 (14)
Redness	2 (14)		
Various skin			
Ezcema			1 (7)
Papulous skin			1 (7)
Erosion		1 (7)	
New psoriasis		1 (7)	

ments. Mean serum calcium (total) did not change during the study.

DISCUSSION

The present study has shown that topical treatment with KH 1060 (0.04 µg/g 0.2 µg/g and 1.0 µg/g) induces a dose dependent improvement of psoriasis. At the doses tested KH 1060 was well tolerated. The maximum amount of KH 1060 ointment applied on each side of the body was 30 g per week, and hypercalcemia did not develop.

The anti-psoriatic effect of KH 1060 was observed at concentrations much lower than those reported for other D_3 vitamins: calcitriol ($1,25(OH)_2D_3$) (3–15 µg/g) (11, 12), calcipotriol (25–50 µg/g) (13) and tacalcitol (2–4 µg/g) (16). This means that the clinical potency of topical KH 1060 to some extent reflects its strong in vitro activities. However, even the highest KH 1060 concentration (1.0 µg/g) reduced the mean PASI by only 43% which is less than, or similar to, calcipotriol 50 µg/g (13–15).

Skin irritation is a well established side effect of calcipotriol ointment 50 µg/g (12–14). Mild lesional irritation was also reported during KH 1060 treatment, although not more often than with placebo ointment. Facial irritation, which has been reported for calcipotriol, was not observed in any of the 23

Table IV. *Adverse events reported or observed during treatment with KH 1060 ointment 0.04 µg/g and KH 1060 ointment 0.2 µg/g (n = 29)*

	KH 1060 0.2 µg/g no. ptt sides (%)	KH 1060 0.04 µg/g no. ptt sides (%)	Both sides no. ptt (%)
Lesional/perilesional irritation			
Itching, pain	2 (7)		
Redness	1 (3)		1 (3)
Various skin			
Ezcema	1 (4.2)		
Contact dermatitis			1 (3)

Table V. *Adverse events reported or observed during treatment with KH 1060 ointment 0.2 μg/g and KH 1060 ointment 1.0 μg/g (n = 27)*

	KH 1060 0.2 μg/g no. ptt sides (%)	KH 1060 1.0 μg/g no. ptt sides (%)	Both sides no. ptt (%)
Lesional/perilesional irritation			
Itching, pain	1 (4)		
Redness	1 (4)		1 (4)
Various skin			
Red, irritated			
Ezcematous skin		1*(4.3)	
Impetigo	1 (4)		

patients (33%) who had psoriatic lesions in the face or on the scalp.

It is concluded that low concentrations of the vitamin D_3 analogue KH 1060, a potent regulator of cell growth and immune responses, are well tolerated, safe and moderately efficacious for the topical treatment of psoriasis vulgaris. Because of its strong immunosuppressive effects, KH 1060 may also be of interest in the treatment of auto-immune skin diseases.

ACKNOWLEDGEMENTS

The authors want to thank Mrs. Gitte Bergholdt for typing the manuscript and Susanne Møller, M.Sc.Stat. for the statistical analysis. The study was sponsored by Leo Pharmaceuticals, Copenhagen, Denmark.

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