

A randomized comparison of an emollient containing skin-related lipids with a petrolatum-based emollient as adjunct in the treatment of chronic hand dermatitis

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Hand dermatitis is a multifactorial skin disorder in which skin barrier impairment is involved in the pathogenesis. The development of topical agents that improve skin barrier function is therefore a promising approach for the management of hand dermatitis. Topically applied lipids may interfere with skin barrier function, and emollients containing skin-related lipids have been suggested to facilitate repair of the skin barrier. However, evidence for the superiority of emollients containing skin-related lipids over the more traditional emollients is still lacking. The aim of this study was to compare an emollient containing skin-related lipids (Locobase[®] Repair) with a traditional petrolatum-based emollient for the management of hand dermatitis. Adult males and females ($n=30$) with mild to moderate chronic hand dermatitis were treated twice daily for 2 months either with an emollient containing skin-related lipids or with a pet.-based emollient. In the case of exacerbation, the patients of both treatment groups were allowed to use a mild corticosteroid according to instructions. Both treatment regimes significantly improved clinical signs of hand dermatitis as assessed by the investigator global assessment, hand eczema area and severity score. We did not observe significant differences in the improvement of clinical signs, itching, patients' assessment of efficacy, cosmetic acceptability or usage of topical corticosteroids between both treatment groups. In conclusion, this study confirms that the frequent use of emollients may be useful in the therapy of hand dermatitis. However, we could not demonstrate the superiority of this particular emollient containing skin-related lipids in patients with chronic hand dermatitis.

Key words: ceramide; emollients; hand dermatitis; moisturizers; skin lipids; treatment. © Blackwell Munksgaard, 2003.

Accepted for publication 27 May 2003

Emollients may have various effects on the skin. They may form a covering film, which acts as a barrier for chemicals from the exterior and which restricts the loss of water and other essential substances from the interior (1). The product can be designated as a barrier cream, if the primary goal is prevention of penetration (2, 3). If the emollient restricts water loss, the stratum corneum (SC) is hydrated and the emollient can be designated as a moisturizer (4). If ingredients of the emollient penetrate the skin, these ingredients may interact with the lipids in the intercellular domain. Finally, ingredients of an emollient may enter corneocytes, eventually be metabolized and modify lipid secretory machinery of the SC (5, 6). Recently, emollients containing skin-related lipids have been

introduced. This new generation of emollients is believed to improve the skin barrier dysfunction by being incorporated into the multilayered structure of the intercellular space or in cells of the SC.

Chronic hand eczema is a common skin problem affecting approximately 2 to 10% of all patients seen by dermatologists (7). It is a multifaceted disease in which both endogenous and environmental influences are often relevant (8). The impact of the function of the skin barrier in this disorder should be emphasized. A good skin barrier helps to avoid the penetration of both allergens and irritants. One of the putative goals in the treatment of this disease therefore may be improvement of the skin barrier function by well selected emollients.

Animal studies have shown that topical mixtures of three key SC lipids, including ceramide, cholesterol and free fatty acid, when applied in optimized proportions, accelerate barrier repair following a variety of external, acute or sustained perturbations (6, 9, 10). Human studies report the efficacy of different mixtures of these physiological lipids in experimentally induced skin barrier dysfunction (11–15) and in clinical conditions involving skin barrier disturbances (16–18). However, evidence for the superiority of emollients with a specific lipid profile over the more traditional emollients is still lacking.

In a previous report, we reported on the effects of an emollient containing skin-related lipids (Locobase[®] Repair) in experimentally induced skin barrier dysfunction. In that study, Locobase[®] Repair significantly accelerated repair of barrier damage in the acute model of barrier disruption (tape stripping) as assessed by clinical, bioengineering and immunohistochemical methods (14). This paper reports on a pilot study with Locobase[®] Repair in chronic hand dermatitis. We compared the effects of this emollient containing skin-related lipids with a petrolatum-based emollient (vaselinum album/cremor lanette I ana, Dutch pharmacopoeia). Here we studied clinical effects, cosmetic acceptability and the usage of topical corticosteroids.

Materials and Methods

Patient selection

32 patients with bilateral chronic hand dermatitis entered the study after informed consent was obtained. The patients were recruited from a university hospital outpatient clinic between January 2002 and May 2002. Chronic hand dermatitis was defined as an eczematous eruption present for longer than 6 months. Patients meeting the following criteria were included:

- (1) Mild to moderate disease (according to the investigator global assessment).
- (2) Good response to class I or class II topical corticosteroids.

Exclusion criteria were:

- (1) Clinically relevant allergic or irritant contact dermatitis and the inability to avoid exposure.
- (2) Severe and very severe hand dermatitis (according to the investigator global assessment).
- (3) Severe vesiculation or bullae.
- (4) History of contact urticaria and pustular diseases.

- (5) Recent therapy with potent topical corticosteroids (class III or IV).
- (6) Recent systemic therapy or phototherapy.

Methods

This pilot study compared the efficacy of an emollient containing skin-related lipids (Locobase[®] Repair; contains ceramide 3, oleic and palmitic acid in a fatty cream base with pet., aqua, paraffin, paraffinum liquidum, glycerin, sorbitan oleate, carnauba, cholesterol, carbomer, tromethamine in unknown ratio; lipid content 63%) and a traditional pet.-based emollient (Vas/Lan; contains 50% vaselinum album and 50% cremor lanette I). On entry to the study, all patients were interviewed regarding previous course and duration of the hand dermatitis, contact factors in their work and/or hobbies, atopy and current use of emollients and topical corticosteroids. We provided information on proper skin care related to personal circumstances.

Patients were asked to discontinue the use of topical prescriptions and emollients for a wash-out period of 1 week. Patients were randomized into 2 groups: 17 participants were asked to use Locobase[®] Repair twice daily and 15 participants were asked to use pet.-based emollient twice daily. In the case of active dermatitis, all patients were allowed to use mild corticosteroid (unguentum triamcinolone 0.1% FNA, Dutch pharmacopoeia) according to the following instructions:

- (1) In case of exacerbation of the dermatitis, the patients were allowed to use the topical corticosteroid twice daily for a maximum of 1 week. After this week, the use was tapered to once daily for a maximum of 4 days a week.
- (2) In the case of clearance, the patient stopped the use of the topical corticosteroid and continued only with the emollient.
- (3) Patients were asked to record the use of the topical corticosteroid and emollients in a diary.

Besides the study medication, no other topical treatment was allowed.

Clinical evaluation

The following variables were used to monitor the efficacy of the treatment. The same study investigator blindly assessed the dermatitis at various time-points: at baseline, after 1 month and after 2 months.

To this end, we used the hand eczema area and severity score (HEAS) as described and used before (19): the hand was divided into 7 areas: the palm and the back of the hand and the 5 digits, each area having its own correction factor based on the relative size (palm and back of the hands 0.25 and the digits 0.1). Each area was evaluated for area on a scale of 0–4 (0 = 0%, 1 = 1–25%, 2 = 26–50%, 3 = 51–75% and 4 = 76–100%). We scored each area for intensity of erythema, vesicles, papules, scaling, fissures, excoriations and hyperkeratosis on a 0–3 scale (0 = none, 1 = slight, 2 = moderate and 3 = severe). We calculated a score for each area by multiplying the percentage of the affected area with the correction factor and with the sum of the intensities of the symptoms. Finally, we calculated the sum score by adding up the scores of each area.

Investigator global assessment. The investigator global assessment (IGA) was made on a scale of 0–5 (20):

- (1) Clear (0): no residual visible dermatitis.
- (2) Almost clear (1): minimal erythema and/or scaling.
- (3) Mild disease (2): clearly visible signs of dermatitis (erythema and scaling), with no hyperkeratosis, oedema, fissures or functional impact.
- (4) Moderate disease (3): moderately severe signs of dermatitis, with a few fissures and moderate functional impairment.
- (5) Severe disease (4): marked signs of dermatitis, with oedema, fissures or functional impairment.
- (6) Very severe disease (5): marked signs of dermatitis with exudation/crusting and very severe functional impairment.

Patient's evaluation

A questionnaire assessed the patient's opinion on the course of the disease after treatment (1 = worse, 2 = no change, 3 = minimal improvement, 4 = moderate improvement, 5 = marked improvement and 6 = clearing or almost clearing). The patients assessed the cosmetic acceptability of the study-emollients and rated the products as 'very poor', 'poor', 'acceptable', 'good', 'excellent' and compared this with past and current emollients (21). In this questionnaire, we also enquired about habits before and during the study in order to investigate the effect of the study protocol.

Table 1. Demographics of randomized patients

<i>Subjects baseline demographics and characteristics</i>	
Patients (n)	32
Sex (n)	10 males, 22 females
Age (years)	19–65, mean 39.15
Duration of dermatitis (years)	0.5–31, mean 10.10
<i>Subject baseline disease characteristics</i>	
Hand eczema area and severity score	3.9
Baseline IGA (0–5)	2.3
Atopy (n)	23
Atopic dermatitis	18
Bronchial asthma	7
Hay Fever	8
Hand surface involvement (n)	
Dorsum	1
Palms	2
Digits	4
Palms and digits	13
Dorsum and digits	9
Palms, dorsum and digits	3
Use of emollients 4 weeks before the study	
Twice or more per day	3
Daily	9
Sporadically	11
No use	9

IGA = Investigator global assessment.

The use of topical corticosteroids. We asked the patient to specify, when topical corticosteroids were used, in a diary. The tubes of corticosteroids were collected for weighing to determinate the amount of medication used. At the end of the study, patients were questioned regarding the use of corticosteroids.

Statistics

We used the Mann–Whitney *U*-test to test the differences in the HEAS and IGA between both treatment groups at baseline, at 1 month and at 2 months. For the differences in results between baseline and the end-of-the-study results for each treatment group, we used the Wilcoxon matched pairs test. For the patients' assessment of efficacy, itching, cosmetic acceptability and the usage of corticosteroids, we used the chi-square test of a contingency table.

Results

Efficacy

The profile of randomized patients ($n = 32$) is summarized in Table 1. 2 patients were lost to follow-up after the baseline visit because of unknown reasons. We used only their baseline characteristics. 2 patients from each group discontinued therapy during the study. One Locobase[®] Repair patient dropped out of the study at visit 1 because of deviation from the protocol. This patient was not able to use the

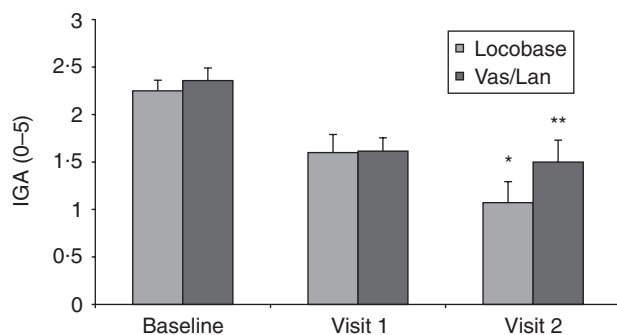


Fig. 1. Investigator global assessment (IGA). 0 = clear; 1 = almost clear; 2 = mild disease; 3 = moderate disease; 4 = severe disease; 5 = very severe disease. *Significant decrease of IGA in the group treated with corticosteroid and Locobase[®] Repair at visit 2 (end-of-treatment) in comparison with the baseline ($P=0.005$). **Significant decrease of IGA in the group treated with corticosteroid and Vas/Lan at the visit 2 (end-of-treatment) in comparison with the baseline ($P=0.007$). No significant differences between the treated groups were found.

emollient twice daily. The second dropout patient in the Locobase[®] Repair group and both dropout patients of the Vas/Lan group had to stop because of exacerbation of the hand dermatitis, which made it necessary to treat with a strong potency topical corticosteroid. The analysis at the end-of-treatment as assessed by the IGA and HEAS involved 30 patients including the 4 dropout patients. We observed a statistically significant reduction in the IGA from baseline to end-of-treatment for both treatments ($P=0.005$ Locobase[®] Repair and $P=0.007$ Vas/Lan). We also observed a significant improvement in the HEAS in both groups ($P=0.002$ Locobase[®] Repair and $P=0.02$ Vas/Lan). We did not see any statistically significant difference between the group treated with Locobase[®] Repair and the group treated with Vas/Lan (Figs 1 and 2)

Patients' assessment of efficacy

Assessment by patient of the treatment response at the end of treatment is shown in Fig. 3(a). Approximately 2/3 of patients of both groups (67.7% Locobase[®] Repair and 69.2% Vas/Lan) indicated improvement or clearance of the hand eczema. There were no significant differences between the groups. The patients' assessment of itching is shown in Fig. 3(b). At the end of treatment, itching improved or even disappeared in 75% of Locobase[®] Repair users and 69% of Vas/Lan users. There were no significant differences between the groups.

Cosmetic assessment

All patients tolerated the emollients well. Evaluation of the patients' opinion on cosmetic accept-

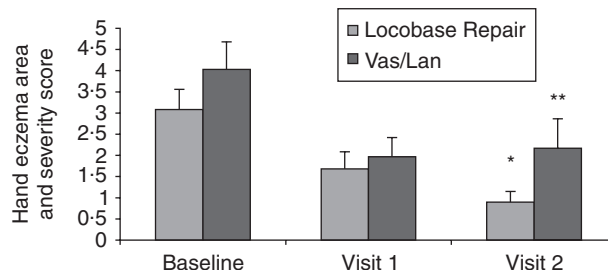


Fig. 2. Hand eczema area and severity score. For more details see *Materials and Methods*. *Significant decrease of IGA in the group treated with corticosteroid and Locobase[®] Repair at visit 2 (end-of-treatment) in comparison with baseline ($P=0.002$). **Significant decrease of IGA in the group treated with corticosteroid and Vas/Lan at the visit 2 (end-of-treatment) in comparison with baseline ($P=0.02$). No significant differences between the treated groups were found.

ability of the study-emollients showed that both groups rated the study-emollients as acceptable, good or excellent (1–5). Most patients (43.7%) using Locobase[®] Repair considered this product as good (score 4), whereas most patients (38.4%) using Vas/Lan considered it as acceptable (score 3). There was no significant difference in the patients' assessment on the cosmetic acceptability between the groups (Fig. 4). 12% of Locobase[®] Repair users and 7.6% of Vas/Lan users rated the emollient as poor. 81% considered Locobase[®] Repair as helpful in treating their skin condition in comparison with 69% of patients using Vas/Lan. 53% percent of both groups stated that the study-emollient was superior to their current emollient, and most of them were likely to continue the use of the emollient (94% Locobase[®] Repair and 85% Vas/Lan). We found no significant differences between the groups.

The use of emollients and corticosteroids

It appeared that 9 of the patients (28%) did not previously use emollients, whereas the remainder (72%) had used emollients with varying frequency. During the study, most patients (56.2% of Locobase[®] Repair group and 61.5% of Vas/Lan group) used more of the emollient than in the period of 4 weeks before the study.

As to the use of topical corticosteroids, the questionnaires showed that 62.2% of the Locobase[®] Repair group used less corticosteroids during the study than before the study in comparison with 38.4% of Vas/Lan group. Almost half of the patients of the Vas/Lan group (46.1%) stated that they had to use more corticosteroids during the study (Fig. 5). An analysis of the diaries, in which patients recorded the use of corticosteroids, showed that the Locobase[®] Repair group used

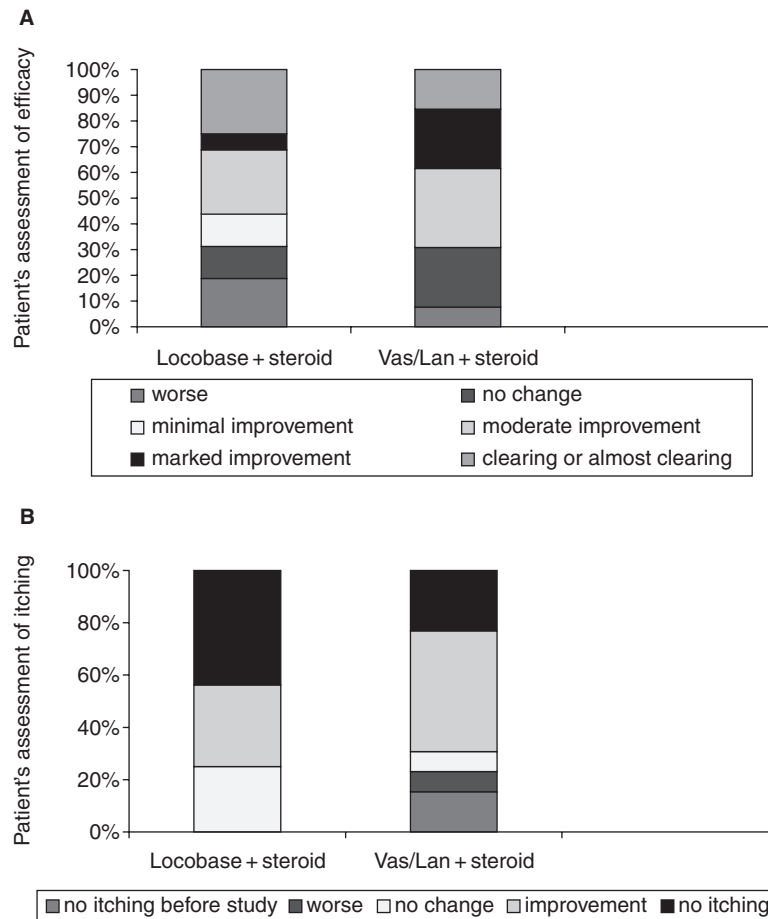


Fig. 3. Patients' assessment of (a) the response of hand eczema and (b) itching after 2 months of treatment with Locobase[®] Repair + corticosteroid or Vas/Lan + corticosteroid. No significant differences were found.

corticosteroids 1.78 days and the Vas/Lan group 1.72 days per week. On average, the amount of corticosteroids used during the study was 10.7 g for the Locobase[®] Repair group and 9.7 g for patients treated with Vas/Lan. These differences are not significant.

The effect of the protocol

To elucidate the effect of the protocol of the study, we asked whether certain changes in daily life occurred during the study.

The time the patients took for the care of their hands before the beginning of the study was (93%) 15 min per day for most patients. During the study, 56.2% of the Locobase[®] Repair users

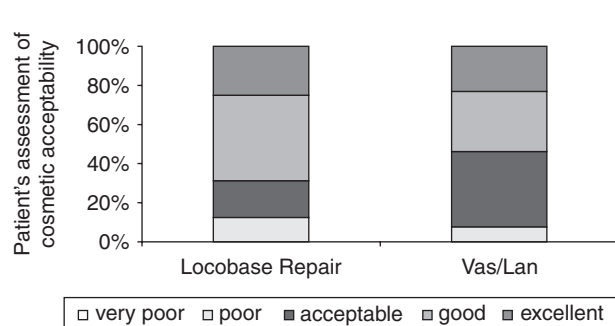


Fig. 4. Patients' assessment of cosmetic acceptability of Locobase[®] Repair and Vas/Lan. No significant differences were found.

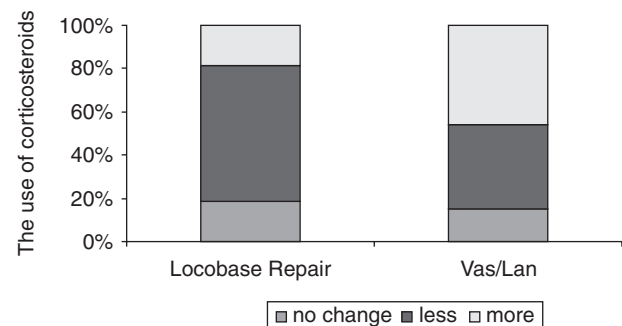


Fig. 5. Patients' assessment of the use of corticosteroids during study compared with the period before study. No significant differences were found.

spent more time on the care of their hands than before the study. The care-time of 37.5% of the patients remained unchanged. In the Vas/Lan group, 2/3 of the patients (69.2%) stated that the time did not change, whereas 37.5% of them spent more time than before the study.

At the beginning of the study, 88.9% performed daily wet work activities, of whom 14% spent even more than 2 h daily. The questionnaires showed that 22.3% of all patients decreased wet work activities and also the frequency of washing of their hands during the study. 78% of all patients did not change such habits at all.

Discussion

In the present study, an emollient containing skin-related lipids (ceramide 3, cholesterol and free fatty acids) was compared with a traditional pet.-based emollient. Active lesions were treated with a mild topical corticosteroid. Both treatment regimens significantly improved clinical signs as assessed by the IGA score and the HEAS. However, there were no statistically significant differences in improvement between both study arms. Furthermore, we did not observe significant differences in the improvement of itching, patients' assessment of efficacy and cosmetic acceptability and the usage of topical corticosteroids between both treatment groups.

Thus, the study shows that both emollients are effective in the therapy of hand dermatitis and both are cosmetically acceptable. The efficacy of traditional emollients containing pet. has already been confirmed in various skin conditions (22–26). Because of its hydrating properties, pet. has been considered as a standard emollient against which other moisturizers should be compared (27). In this study, the efficacy of Locobase[®] Repair was comparable with a pet.-containing emollient. Because of lack of significant differences and lack of statistical power as a result of small sample size, we cannot conclude whether Locobase[®] Repair is a more appropriate choice than the other emollient.

The superiority of emollients containing skin-related lipids remains a point of discussion. Previous studies have shown that the ratio and the concentration of the skin-related lipids in the emollient are crucial for the rate of barrier recovery (28). It is known that not all types of topical formulations that contain skin-related lipids are effective. Out of a number of preparations, those with a lipid ratio most comparable with that present in the human skin barrier are considered to be effective (29). It is unknown whether the ratio

and the concentration of lipid component of Locobase[®] Repair, which consists of cholesterol, semisynthetic ceramide 3, oleic acid and palmitic acid, is optimal for barrier repair in chronic hand dermatitis. Further, ceramide 3 is the only ceramide that is incorporated into Locobase[®] Repair. Research data indicate that ceramide 1 is also an important ceramide in skin, and it is unknown whether ceramide 3 can sufficiently fill the need for ceramide 1 and other natural occurring ceramides (30).

Furthermore, the effect of the application of skin-related lipids has varied depending on the method of barrier disruption. A promising effect of skin-related lipids was seen in experimental models of barrier dysfunction inflicted by tape stripping or an organic solvent. When the barrier was disrupted by treatment with detergents such as sodium dodecyl sulphate or ammonium lauryl sulfosuccinate, skin-related lipids did not accelerate barrier repair (9). This may indicate that the ability of the lipid mixture to accelerate barrier repair depends on the specific external damage, suggesting the need for damage-specific correction (31). In this study, we applied emollients in patients with chronic hand dermatitis, a skin condition characterized by a multifactor origin in which the skin barrier may be variably relevant. There is evidence that a barrier repair strategy should not only meet specific demands depending on the type of external damage but should also be adjusted to endogenous deficiencies (17, 32–34).

In conclusion, this study confirms that, related to the methodological strategies applied, the frequent use of emollients may be useful in the therapy of hand dermatitis and that patients should be encouraged to use them. However, the results of this pilot study do not support the concept of superiority of an emollient containing skin-related lipids in a heterogeneous group of patients with chronic hand dermatitis. As the composition of emollients is important, it should be further investigated whether emollients with another composition of skin-related lipids have more efficacies in different clinical conditions.

Acknowledgements

We thank M.E. Kooijmans-Otero for skilful technical assistance and all the patients who participated.

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