

Tacrolimus ointment in the treatment of occupationally induced chronic hand dermatitis

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Background: Occupational hand dermatitis (OHD) is a common and often chronic condition. Usage of topical corticosteroids is limited in long-term therapy because of potential side-effects. New treatment options are highly appreciated.

Objective: To study efficacy and safety of tacrolimus in patients suffering from OHD.

Patients and Methods: In a prospective, open, multicentre study, 29 patients with OHD of predominantly mild-to-moderate severity were treated with tacrolimus ointment (Protopic® 0.1%) during a 4-week active treatment period with twice daily application followed by a 2-month optional treatment period. Efficacy was evaluated by the use of a standardized hand eczema score and by clinical severity rating, conducted on all study visits (screening, baseline and weeks 2, 4, 6, and 12). Adverse events were recorded for safety evaluation.

Results: The hand eczema score declined significantly after 2 weeks of treatment compared with baseline and further declined until the end of the study. Finally, 12 (44%) patients were clear of hand eczema. Worsening of the dermatitis occurred in 2 patients (7%). Clinical grading indicated improvement too. Overall tolerability was good.

Conclusion: Topical tacrolimus might be an efficacious treatment option for chronic OHD. Blinded and randomized controlled studies are necessary to confirm the results of this pilot study.

Key words: allergic contact dermatitis; irritant contact dermatitis; occupational; occupational contact dermatitis; tacrolimus ointment; therapy. © Blackwell Munksgaard, 2008.

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Occupational contact dermatitis of the hands is a common skin condition, which often requires lengthy dermatological treatment, leads to sick leave and job loss and, therefore, induces a high socio-economical burden in Germany (1, 2). Even when avoidance of causative irritants and allergens is achieved, prognosis of hand dermatitis may be poor (3, 4). Recent studies have highlighted the association of occupational hand dermatitis (OHD) with low quality of life and depression (5, 6). Topical corticosteroids and ultraviolet (UV) light irradiation are the most important treatment options together with optimized personal protection and skin care measures in long-term therapy (7, 8). However, cortico-

steroids might induce adverse effects, such as atrophy, even if substances with favourable benefit-to-side-effect ratio are used (9). New treatment options for recalcitrant hand dermatitis are therefore highly appreciated, both by patients and by physicians.

Topical immunomodulators, such as tacrolimus, have been successfully implemented in the therapy of moderate-to-severe atopic dermatitis and found their way into therapy guidelines and position papers (10). Their anti-inflammatory capacity has been approximated as being equal to moderately potent topical corticosteroids (11). Tacrolimus reduces peptidyl-prolyl isomerase activity by binding to specific cell plasma immunophilin

(FKBP12) and therefore inhibits calcium-dependent signal transduction in T cells, which leads to impairment of synthesis of proinflammatory cytokines, which are crucial in the development and maintenance of contact dermatitis (12). Besides inhibitory effects on T-cell activation and cytokines, there are effects on dendritic cells such as antigen-presenting Langerhans' cells and inflammatory dendritic epidermal cells (13). Unlike corticosteroids, topical calcineurin inhibitors do not induce skin atrophy. Safety of tacrolimus has been affirmed for long-term treatment up to 4 years in atopic dermatitis (14). Tacrolimus, therefore, is of interest to occupational dermatologists. Tacrolimus has already been shown to be beneficial in other eczematous diseases (15–18), and one randomized, observer-blinded study focussed on treatment of dyshidrotic palmoplantar eczema together with mometasone furoate (19). However, to our knowledge, its efficacy in OHD has not yet been studied.

We therefore intended to evaluate the efficacy and safety of tacrolimus (Protopic® 0.1% ointment) in a panel of patients with chronic OHD in a prospective, open, multicentre investigator-driven clinical trial.

Materials and Methods

Four centres in Germany were involved in this study. The protocol was approved by the institutional ethics committee in advance. The study was performed between November 2004 (first patient in) and September 2005 (last patient out).

Patients aged at least 18 years, suffering from OHD according to history and clinical diagnosis, were included after written informed consent. Exclusion criteria were topical corticosteroid ther-

apy within the previous 14 days as well as previous UV irradiation, intake of systemic corticosteroids or other immunosuppressive drugs or retinoids within the previous 4 weeks, hypersensitivity towards ingredients of the study medication and/or the standardized skin care product (Alfason® repair), and pregnancy or lactation.

During the screening visit (V0), after obtaining informed consent, an experienced occupational dermatologist established the diagnosis according to the clinical picture and the case history, taking occupational exposure characteristics, work-related relapses, and results of previous allergy testing into consideration. The hand dermatitis was classified as irritant contact dermatitis (ICD), allergic contact dermatitis (ACD), and/or atopic hand eczema. The Erlangen atopy score was determined in each subject (20).

At baseline (V1), inclusion criteria were checked again. The hand dermatitis was rated for both hands separately according to the Jena Hand Eczema Score (JHS, Table 1) and a standardized clinical severity rating (Table 2), which referred to the area affected by eczema. The study medication (Protopic 0.1% ointment) was handed out together with a standardized skin care product (Alfason® repair). Participants applied the study medication twice daily and refrained from other topical drugs as well as ointments, other than the standardized skin care, which they used *ad libitum*.

Subsequent study visits were conducted after 2 weeks (V2) and 4 weeks (V3). The mandatory 4-week treatment period was followed by another 8-week optional active treatment period. Therefore, from V3 onwards, the panellists either continued with the study medication as demanded or ceased and carried on with the skin care alone,

Table 1. Jena Hand Eczema Score (JHS)*

Area score						
Area affected (%)						Score
0–20						1
21–40						2
41–60						3
61–80						4
81–100						5
Severity score						
Score	Vesicles/cm ² (V)	Erythema (E)	Scaling (S)	Infiltration (I)	Lichenification (L)	Fissuring (F)
0.25	—	—	Mild	—	Mild	—
0.5	—	—	Moderate	—	Moderate	—
1	<2	Mild	Severe	Present	Severe	Fine
2	2–8	Moderate	—	—	—	Broad
3	>8	Severe	—	—	—	—

*JHS sum score = V + E + S + I + L + F × areal score.

Table 2. Clinical severity

Mild	Dorsal aspects of knuckles, interdigital areas or palms/dorsal areas partially affected
Moderate	Dorsal aspects of knuckles, interdigital areas and palms/dorsal areas partially affected
Severe	Total dorsal hand and fingers or total palm and fingers affected

depending on their skin states. This individual application mode (regular use, irregular use, ceased) was recorded on the subsequent study visits. The same applied for the following study visits, which were performed after 6 weeks (V4) and 12 weeks (V5).

Clinical investigations as well as hand eczema scores and severity rating were performed at each visit. Adverse events were recorded. Particular attention was paid to local side-effects as well as to any other adverse effects. In case of local itching, burning, and/or redness, participants were requested to give a severity rating (mild, moderate, severe).

Diagnoses as well as professions were analysed by descriptive means. The JHS was analysed with respect to significant changes in the course of the study. Differences between baseline values (V1) and the following visits (V2–V5) referred to the respective dominant hands and were tested for significance by using the non-parametric Wilcoxon test (SPSS 13.0 for Windows). $P \leq 0.05$ was considered significant. Adverse events were considered with respect to safety evaluation.

Results

Study population characteristics

Altogether, 31 patients (19 females and 12 males) were screened in the study. 2 patients failed enrolment. Mean age of the enrolled population was 38.5 years [range 20–65 years, $SD = 10.8$]. 2 patients dropped out after V4 because of relapse of breast carcinoma and persistent, severe hand dermatitis, respectively. However, both were analysed in the safety population ($n = 29$). Accordingly, 27 patients (16 females and 11 males) passed the study per protocol (PP).

Table 3 shows sex, occupations, and diagnoses of the subjects. The majority were professionally exposed to typical irritant skin hazards, e.g. wet work, detergents, and disinfectants. In 90% (26 of 29 patients), the diagnosis of ICD was established. However, in many patients, multifactorial aetiology of the dermatitis was evident. Accordingly, some patients received more than one diagnosis. ACD was diagnosed in 5 patients (17%) and in 4

of them, ICD as well as an atopic skin diathesis (ASD) was additionally detected. Altogether, ASD was diagnosed in 12 patients (41%) clinically and by the Erlangen atopy score, which was 9.4 points on average (range 0–28, $SD = 7.7$, median 9 points). ACD was diagnosed in only one subject. None of the subjects suffered from typical atopic palmar eczema, which is clinically characterized by erythema, dyshidrotic vesicles, scaling, and fissures primarily located on the palms. In all but one patient, the right hand was dominant. Previous patch testing had been conducted in all except 2 participants. In 16 subjects, the patch tests had not shown any sensitizations, whereas 11 patients had one ($n=3$), two ($n=3$), or more sensitizations. However, the sensitizations detected were not regarded as relevant for the present dermatitis in many cases. Nickel was most commonly found to be positive (5 patients). 2 subjects each were allergic to potential cosmetic or topical drugs ingredients, such as fragrance mix, propolis, myroxylon pereirae, and benzalkonium-chloride, and to rubber materials, respectively. At baseline, the severity of the hand dermatitis was clinically mild to moderate in the majority of the subjects. The majority had been previously treated with topical corticosteroids for variable periods with temporary and clinically limited effect.

Efficacy

One patient ended the study prematurely before the final visit (V5) because of persistent severe hand eczema. In the PP group, the JHS of the predominantly affected hand was 6.45 ($SD = \pm 6.08$, range 1.25–24.75) at baseline (V1) and declined to 2.64 ($SD = \pm 1.85$, $P < 0.001$) after 2 weeks of treatment (V2). A further slight decline to 1.90 ($SD \pm 1.63$) was observed until the next visit (V3). After V3, the JHS continued on a low level (Fig. 1). The differences compared with baseline were significant for all visits for the dominant hands as well as for the non-dominant (left) hands ($P < 0.001$). At least 50% improvement of the JHS was achieved in 16 (59%) subjects after 4 weeks of treatment (V2) and in 19 (70%) at the final visit. Worsening of the skin condition, as indicated by an increased score, was noticed in 2 (7%) subjects, each at V2 and the final visit. At the final visit, altogether 12 subjects (44%) were totally clear of hand eczema, as indicated by a score of 0 on the dominant hand. In accordance with the scoring results, the clinical severity grading indicated increasing numbers of subjects with clearance or mild dermatitis, whereas the numbers of severe dermatitis decreased with the course of the trial (Fig. 2).

Table 3. Subjects' sex, occupations, and clinical diagnoses

Subject	Sex	Occupation	Diagnosis			
			ICD	ACD	ASD	Unclassified
1	M	Tiler	x			
2	F	Nurse	x			
3	F	Lab assistant	x			
4	M	Warehouse clerk	x		x	
5	F	Waitress	x			
6*	M	Fork lift driver				x
7	F	Sales woman	x		x	
8	M	Metal worker	x			
9	F	Hair dresser	x	x	x	
11	M	Optician	x			
12	M	Metal worker	x		x	
13	M	Bricklayer	x	x	x	
14	F	Lab assistant	x			
15*	F	Nurse	x		x	
16	F	Technical lab assistant	x			
17	F	Technical lab assistant	x		x	
18	F	Screen printer	x		x	
19	F	Physician assistant	x		x	
102	F	Household assistant	x			
103	M	Tiler	x			
104	M	Locksmith	x			
201	M	Car industry worker		x		
202	F	m.d.	x		x	
203	M	Car industry worker	x	x	x	
205	F	Cleaner	x	x	x	
301	F	Worker (scissors production)	x			
302	F	Cleaner	x			
303	F	m.d.	x			
304	M	Physiotherapist	m.d.	m.d.	m.d.	m.d.
<i>n</i> = 29			26 (90%)	5 (17%)	12 (41%)	1 (3%)

ACD, allergic contact dermatitis; ASD, atopic skin diathesis according to Erlangen atopy score; f, female; ICD, irritant contact dermatitis; m, male; m.d., missing data.

*Drop out.

Regarding the necessity of active treatment after week 4 (V3), until V4, 12 out of 29 patients (41%) had stopped application of the study medication completely because of their favourable skin states. 15 patients (52%) continued the study medication either on a regular (4 patients; 14%) or on an irregular (11 patients; 38%) basis (data of 2 patients missing for this item). From V4 until the end of the study, 11 (40.7%) out of 27 subjects who performed the last visit were able to abandon active treatment completely, while 13 (48.1%) continued sporadically. Only 1 subject (3.7%) continued active treatment on a regular basis until the end of the study.

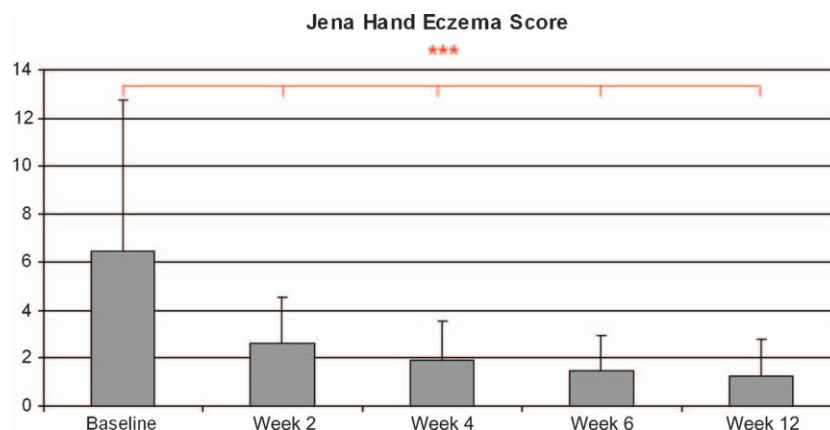
Safety

None of the subjects dropped out the study prematurely because of adverse effects attributed to the study medication. Altogether, 5 adverse events were recorded. From these, one resulted in premature termination (relapse of breast carcinoma, which was unlikely to be related to the study medication). 2 subjects suffered from a relapse of their

Herpes labialis, which was regarded as possibly related to potential locally immunocompromised skin because of Protopic. However, recurring Herpes labialis is common whenever ASD is present. One subject reported facial flushing immediately after application of the study medication in combination with intake of alcoholic beverages, which was categorized as probably related to the study medication, because of well-known side-effects reported for the drug (scientific information).

With respect to local tolerability, transient reactions were reported that were in the range of the well-known side-effects of the preparation. These were rated mild to moderate by all subjects affected. In particular, burning, itching, and redness after application were reported that did not prevent the subjects continuing the treatment in any case. In detail, 4 (13.8%) subjects reported 'mild' and 1 (3.4%) subject 'moderate' burning at V2, while 17 (58.6%) did not notice any burning. Mild itching was reported by 5 (17.2%) subjects at V2, while none experienced 'moderate' or 'severe' itching. Mild redness was noticed by 3 (10.3%) subjects, whereas 19 (65.5%) did not notice any.

Fig. 1. Sum scores of the Jena Hand Eczema Score (JHS) in the course of the study (dominant hands, per protocol population, $n = 27$). *** $P < 0.001$ (Wilcoxon test).



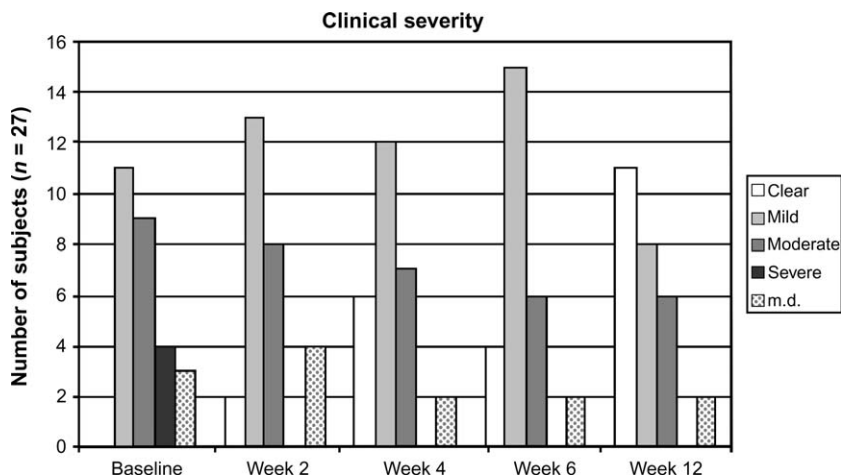
At V3, only 2 (6.9%) subjects each reported mild burning and itching, respectively, while none had noticed moderate or severe burning or itching. Only one subject complained about transient moderate redness after application. However, data of 7 subjects were missing for these items.

Discussion

Treatment with tacrolimus resulted in a significant decline of the JHS already after 2 weeks of treatment. In the course of the study, a further mild decline was observed in spite of the fact that only 52% of the subjects continued with the active treatment after week 4. This effect may be attributed to the efficacy of the study medication on the one hand. On the other hand, the stable disease level in this study period stresses the importance of adequate skin care in the successful management of hand dermatitis (21, 22). In addition, it might be argued that the comparatively low severity of the dermatitis at baseline, which was mild to moderate in the majority, contributed to the low disease level in the course of the study. After 4 weeks of

active treatment, at least 50% improvement was achieved in 52% of the subjects. This was the case in 67% at the end of the study, and 44% were completely clear of dermatitis at the final visit. Related to the poor prognosis that is well known in occupational dermatitis, the response rate in this pilot study appears favourable in spite of the possibly confounding standardized skin care (3, 4). Nevertheless, we are aware that the beneficial outcome of this trial does not necessarily implicate clinical relevance in terms of quality of life as well job satisfaction and ability of staying in the job without sick leave. In the current trial, the study period was considered too short to expect relevant effects; therefore, quality-of-life assessments were not included. In one randomized, investigator-blinded trial, the efficacy of topical tacrolimus 0.1% was compared with that of topical mometasone furoate 0.1% in dyshidrotic palmar eczema. The dyshidrotic area and severity index showed a more than 50% reduction of baseline values after 2 weeks of active treatment both for tacrolimus ($P = 0.003$) and for mometasone furoate ($P = 0.022$) in palmar areas (19).

Fig. 2. Clinical severity of the dominant hands according to affected area in the course of the study (dominant hands, per protocol population, $n = 27$). m.d., missing data.



Unfortunately, only 16 subjects were included in the trial.

There are only very few studies available dealing with any kind of treatment of chronic OHD on the secondary prevention level that can be compared with our results (23–26). Different variables and inability to perform blinded studies as well as difficulties to enrol large numbers of subjects are the main drawbacks in planning and conducting clinical trials on OHD as far as non-experimental controlled field studies are considered (27). Conducting controlled randomized and blinded studies is desirable in occupational dermatology. However, for ethical reasons, we decided against a blinded, placebo-controlled study in our panel. Otherwise, the subjects would have been at risk of further worsening and sick leave as well as job loss. Accordingly, some methodological aspects have to be discussed. The subjects might have been influenced by the study procedures and might have changed their exposure behaviours at their work places. It is well known that personal skin protection and educational measures are efficacious in secondary and tertiary prevention of occupational contact dermatitis (8, 28, 29). Although counselling was not explicitly included in this study, it is likely that attention towards proper skin protection might have been elevated during the study period. Furthermore, distribution of standardized skin care alone can be assumed to have contributed to the improvement of the skin states because adequate skin care is an important tool to promote barrier regeneration (23, 30). The proportion of effect that was caused by the skin care cannot be quantified. However, this confounder was accepted in this study because it would neither be ethical nor be realistic to exclude usage of any skin care products besides any active treatment. Standardized skin care was considered especially important in the voluntary active treatment period after week 4, which aimed at imitating clinical practice that is often characterized by 'active treatment on demand' by the patients. In a controlled study, we would propose to include a comparative design, e.g. tacrolimus together with skin care versus skin care alone, which would require a much larger panel or a cross-over design.

The subjects enrolled in this clinical trial suffered from primarily mild-to-moderate hand dermatitis attributed to irritant exposure in the majority. In addition, in 41% patients, ASD was detected. These findings are consistent with results from the literature and characterize a typical population of patients affected with OHD (31–33). ICD often occurs in the first instance and promotes development of secondary ACD because

of chronic barrier impairment and increased barrier permeability as well as because of chronic inflammation. ASD is considered the most important risk factor for development of OHD (32, 34). For ethical reasons, patch testing was not included in this trial. Instead, previous patch and allergy testing results were considered. This indicates some bias and might have caused underestimation of the proportion of allergic diseases. However, whenever ACD is diagnosed in an occupational setting, elimination of the allergen is the first option, which can be achieved by technical, organizational, or by personal protective measures. Patients with ACD are therefore not the target population for therapy trials like the present one.

Because the number of subjects with ACD was small in this trial, it is difficult to draw any conclusions regarding efficacy with respect to different aetiology of the hand dermatitis, e.g. it could be expected that tacrolimus might be more effective in ACD versus ICD. Altogether, 3 of the subjects who were diagnosed with ACD cleared completely, while 2 had a less than 50% improvement with respect to JHS reduction.

The JHS used in this study is comparable to the recently proposed hand eczema severity index (HECSI) that was already validated for its inter- and intra-observer reliability (35). Both the JHS and the HECSI are intended to provide a clinical grading system for more objective and accurate assessment of the severity of hand dermatitis, which can be used in clinical studies. Both scoring systems relate to the system of the psoriasis area and severity index (PASI) insofar as they are based on rating the intensities of different typical clinical symptoms of eczema in relation to the hand area concerned, which is also used in the PASI. However, when the current study was conducted, the HECSI was not yet available.

When considering the safety results, the local adverse events were in the range of the already well-known reactions described in the scientific information of the preparation, such as redness, burning, and itching (12). However, these expected reactions were only reported by 20% of the panellists and declined in number as well as in intensity after the first 2 weeks. This comparatively low rate might indicate that the sensitivity depends on the localization, e.g. the hands might be less prone compared with the flexures or face (14). Otherwise, it can be speculated that patients affected with chronic hand dermatitis probably do not pay as much attention to those side-effects as patients affected by atopic dermatitis. One subject experienced facial flushing, which is a well-known uncomfortable, but harmless, side-effect (36). It cannot be excluded that

flushing was caused by facial contamination with the preparation rather than by systemic effects. Because recurring labial herpes is more common in patients with ASD, it is uncertain whether the two relapses observed during the study were related to the study medication. Altogether, tacrolimus ointment was well tolerated by the subjects.

In conclusion, topical treatment with tacrolimus should be further investigated as a potential treatment option to be used in rotational treatment in chronic occupational contact dermatitis. In particular, this would be appreciated to reduce topical corticosteroids in mild-to-moderate ICD. At present, the preparation can only be used 'off label' outside the declared indications based on an individual therapeutic decision, which requires additional consent. It has to be taken into account that topical calcineurin inhibitors are incompatible with UV light irradiation and therapy, which is a disadvantage in chronic hand dermatitis (10). This circumstance would at least necessitate consequent application of topical UV light blockers on the hands during summer time, especially in outdoor workers, although increased risk of non-melanoma skin cancer caused by topical calcineurin inhibitors and UV irradiation is still under debate (37). Finally, the results presented in this pilot study should be regarded as preliminary and be followed by randomized controlled clinical trials, which compare the efficacy of tacrolimus with that of mild or moderate potent topical corticosteroids or, alternatively, treatment with tacrolimus together with skin care versus skin care alone, as far as mild OHD is considered.

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