Hand eczema: from pathogenesis to novel treatments
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General discussion
and future perspectives
DISCUSSION

In this thesis, we focused on the pathogenesis and treatment of hand eczema. The contents of this thesis, together with recently published studies and future perspectives regarding the pathogenesis and treatment of hand eczema, are discussed in this chapter.

Although the prevalence of hand eczema has been investigated to a great extent, data on the prevalence of chronic hand eczema and the severity of hand eczema in the general population are scarce. However, data on the prevalence of chronic hand eczema and the severity of hand eczema can provide perspective on the burden of hand eczema in the general population. In Chapter 2, we found a lifetime prevalence of hand eczema in the general population of 15.0%, and a 1-year prevalence of 7.3%. The prevalence in our study was similar to the prevalence reported in a recent systematic review including 66 studies, mostly from Scandinavian countries. In this systematic review the pooled estimates for lifetime prevalence, and 1-year prevalence, were 14.5% (95% CI 12.6–16.5), and 9.1% (95% CI 8.4–9.8). The pooled lifetime prevalence of self-reported physician diagnosed hand eczema was 5.2% (95% CI 1.1–11.8). In our study, among the subjects with hand eczema in the past year, the majority (63.8%) suffered from chronic hand eczema. The majority of the subjects with hand eczema in lifetime, 56.9%, reported almost clear hand eczema at worst ever. The lifetime prevalence of severe to very severe hand eczema in the general population was 1.9%. These findings, and the lack of systemic treatment options, emphasize the need for further research on new therapeutic targets through a better understanding of the pathogenesis for chronic and severe hand eczema.

PATHOGENESIS

Since hand eczema can be a result of several aetiologies, the pathogenesis of hand eczema is complex. More insight in the pathogenesis of hand eczema might facilitate differentiation between hand eczema and other diagnoses, such as palmar psoriasis, in the future. Moreover, improved understanding of the pathogenesis could enable targeted treatment.

Clinical subtypes

Besides etiological subtypes, as mentioned in the introduction of this thesis, hand eczema can also be classified in the clinical subtypes hyperkeratotic palmar hand eczema, acute recurrent vesicular hand eczema, nummular hand eczema and pulpitis. Currently there is lack of knowledge about the pathogenesis of different clinical subtypes of hand eczema.
Hyperkeratotic hand eczema is often hard to distinguish from palmar psoriasis, due to a similar clinical presentation. Psoriasis lesions on the rest of the body, when present, can support a diagnosis of palmar psoriasis. It is also difficult to distinguish between these two conditions from a dermatopathological point of view. Palmar psoriasis shows spongiosis, which is also present in hyperkeratotic hand eczema.\textsuperscript{3,4} In a study in which the investigators histopathologically compared hyperkeratotic hand eczema, hand eczema and palmar psoriasis, it was found that a decrease or loss of the stratum granulosum happens more often in palmar psoriasis, but there was no significant difference between palmar psoriasis and hyperkeratotic hand eczema.\textsuperscript{4} Therefore, it would be beneficial to find differences in proteome, genome or biomarkers to distinguish between the two diseases. In a study by Politiek et al., immunofluorescence stainings were used to compare proteins, including epidermal barrier proteins, adhesion molecules and keratins.\textsuperscript{5} An upregulation of keratin (K)6, K16 and K17, and reduction of K9 and K14 were found for hyperkeratotic hand eczema compared to healthy palmar skin. Furthermore, there was no decrease of filaggrin and an upregulation of involucrin were found, suggesting that there is no barrier defect in hyperkeratotic hand eczema. This is in contrast to previous chronic hand eczema studies, in which patients with unspecified chronic hand eczema and hyperkeratotic-fissured hand eczema were included.\textsuperscript{6,7} It is also in contrast to studies in atopic dermatitis, in which a barrier defect is a main characteristic in both lesional and non-lesional skin.\textsuperscript{8,9} In another study, the levels of β-defensin 2 and interleukin-36γ were compared between palmar psoriasis, hyperkeratotic hand eczema and chronic hand eczema using immunohistochemistry.\textsuperscript{10} The levels of both β-defensin 2 and interleukin-36γ were higher in palmar psoriasis and hyperkeratotic hand eczema, when compared to chronic hand eczema. Since hyperkeratotic hand eczema resembled palmar psoriasis more than it resembled chronic hand eczema, the authors suggested that hyperkeratotic hand eczema might be an inflammatory disorder of its own entity with a pathogenesis that is similar to palmar psoriasis, which has been suggested in literature previously.\textsuperscript{5,10,11} These findings do not help in differentiating hyperkeratotic hand eczema from palmar psoriasis. However, a new diagnostic tool called the molecular classifier, using the genes \textit{NOS2} and \textit{CCL27}, has shown to contribute to optimized diagnostics between the two diseases.\textsuperscript{12,13} This molecular classifier is based upon an upregulation of \textit{NOS2} and a downregulation of \textit{CCL27} being associated with psoriasis, and the other way around (downregulation of \textit{NOS2} and an upregulation of \textit{CCL27}) being associated with hand eczema.\textsuperscript{13-15} A small skin sample (<1 mm) needs to be taken from the patient to extract RNA. Then, polymerase chain reaction is used to determine the level of NOS2 and CCL27 in the obtained skin sample. Subsequently, special software calculates the probability of either eczema or psoriasis based on the levels of NOS2 and CCL27. Currently studies are investigating the use of the molecular classifier. In the future, the researchers hope to be able to create a ‘lab-on-a-chip’ tool that can be easily used in daily practice.\textsuperscript{16}
For vesicular hand eczema, it has been proposed in several classifications that it can be an entity on its own, like hyperkeratotic hand eczema.\textsuperscript{17,18} In Chapter 3 of this thesis, we describe the transcriptome of vesicular hand eczema through RNA-sequencing. One of the main findings in our study was that the lesional vesicular hand eczema transcriptome shows many similarities to the lesional atopic dermatitis transcriptome, even though only two of the ten patients had a history of atopic dermatitis without current atopic dermatitis lesions. This overlap in transcriptome included an upregulation of keratinocyte host defence and inflammation genes (e.g. genes belonging to the \textit{S100A} family), epidermal differentiation (e.g. \textit{KRT6, KRT16, KRT17}), and immune signalling genes (e.g. \textit{CCL17}), and a downregulation of several skin barrier related genes (e.g. \textit{FLG, LOR}). Furthermore, we did not find significant differences between the non-lesional vesicular hand eczema transcriptome and healthy control skin transcriptome. This is in clear contrast to atopic dermatitis, since non-lesional atopic dermatitis skin significantly differs from healthy skin, showing delayed and intermittent expression of barrier genes and proteins, and increased expression of immune-related genes. It has been hypothesized that a primary dysfunctional epidermal barrier is one of the key pathways\textsuperscript{19-21} for developing hand eczema, especially since a downregulation of barrier genes and their corresponding proteins has been found in hand eczema studies.\textsuperscript{6,7,22} Since no significant differences were found between the non-lesional vesicular hand eczema transcriptome and proteome with healthy skin in our study, it can be questioned whether this is the case for vesicular hand eczema. Probably, the decreased expression of barrier proteins in lesional vesicular hand eczema is caused by the inflammatory processes. Table 1 summarizes the current knowledge of the pathogenesis of hyperkeratotic and vesicular hand eczema.

**Table 1. Pathogenesis of hyperkeratotic and acute recurrent vesicular hand eczema**

<table>
<thead>
<tr>
<th>Hyperkeratotic hand eczema</th>
<th>Acute recurrent vesicular hand eczema</th>
</tr>
</thead>
<tbody>
<tr>
<td>- No primary or secondary epidermal skin barrier defect.</td>
<td>- No primary epidermal skin barrier defect.</td>
</tr>
<tr>
<td>- Characterized by a reduction of K9 and K14, and an upregulation of K5, K6, K17 and K17.</td>
<td>- Characterized by high expression of genes/proteins involved in keratinocyte host defence and inflammation, epidermal differentiation and immune signalling, and a downregulation of genes/proteins involved in the epidermal skin barrier.</td>
</tr>
<tr>
<td>- Resembles palmar psoriasis in levels of β-defensin 2 and interleukin-36γ.</td>
<td>- Show a large overlap with the atopic dermatitis lesional transcriptome, which suggests that similar pathways as seen in atopic dermatitis may be present in this clinical subtype, including a Th1, Th2 and Th17 pathway.</td>
</tr>
<tr>
<td>- A downregulation of \textit{NOS2} and an upregulation of \textit{CCL27} might distinguish hyperkeratotic hand eczema from palmar psoriasis.</td>
<td>- The inflammatory response is thought to cause a secondary epidermal skin barrier defect, as epidermal skin barrier impairment is not found in non-lesional skin.</td>
</tr>
</tbody>
</table>
TREATMENT

The treatment of severe chronic hand eczema remains a challenge, especially since the hands are continuously exposed to potential allergens and irritants. Furthermore, the use of topical treatments throughout the day can cause great inconvenience to patients. There is in particular a lack of treatment options for patients with severe hand eczema, which has a substantial prevalence in the general population as we reported in Chapter 2.

Biologicals

Dupilumab is one of the most promising treatment options for chronic hand eczema, since it has shown long-term effectiveness and safety in atopic dermatitis.\(^{23-25}\) It is a human monoclonal antibody targeting the α subunit of the IL-4 receptor (IL-4Rα), which results in the inhibition of IL-4 and IL-13. An elevation of IL-4 and IL-13 results from Th2 response that occurs in atopic dermatitis, which causes inflammation and contributes to barrier dysfunction. In a placebo-controlled trial to evaluate the efficacy of dupilumab on moderate-to-severe atopic dermatitis, biopsies were evaluated to study the effect of dupilumab on gene and protein expression.\(^{26}\) Inhibition of the IL4Rα by treatment with dupilumab did not only normalize the gene expression of IL-13, but also of other type 2 inflammation genes including IL-31, CCL17, CCL18 and CCL26, and genes involved in Th17/Th22 activity, including IL-17A, IL-22, CCL18 and CCL26. Dupilumab also improved the skin barrier, as treatment with dupilumab resulted in increased expression of epidermal differentiation, barrier and lipid metabolism genes including FLG, LOR, claudins and ELOVL3. Moreover, dupilumab reduced the infiltration of immune cells in the skin and epidermal hyperplasia, as it decreased the expression of K16 and MKi67 gene expression. Taking this knowledge about the therapeutic actions of dupilumab into account, dupilumab can be effective in not only atopic hand eczema, but also in other subtypes of hand eczema. As described in Chapter 3, the vesicular hand eczema transcriptome showed a high upregulation of IL4R in its lesional transcriptome compared to healthy control skin. This suggests that in vesicular hand eczema, the IL-4 and IL-13 pathway, which dupilumab specifically inhibits, could play a role in the pathophysiology.\(^{27}\) Considering that dupilumab has shown to reduce the expression of K16 and the gene expression of MKi67\(^{26}\), which are upregulated in hyperkeratotic hand eczema\(^5\), dupilumab might have a good effect on hyperkeratotic hand eczema as well. A small case series showed major and rapid improvement in two out of three patients with hyperkeratotic hand eczema due to treatment with dupilumab.\(^{28}\) Since dupilumab reduced the expression of genes involved in a Th2 response and in Th17/Th22 activity, dupilumab might also be effective in allergic contact dermatitis of the hands if it is caused by allergens that induce more of a Th2 pathway such as fragrances. Contrastingly, it is thought that inhibiting the IL-4/IL-13 pathway can lead to a polarization of Th1/Th17, potentially causing more severe reactions to allergens that induce a Th1/Th17 response.
such as nickel. However, treatment with dupilumab has shown good effect on allergic contact dermatitis caused by nickel. At the moment, dupilumab seems to have more potential in treating allergic contact dermatitis caused by allergens that induce more of a Th2 pathway, but more research is needed to clear up the therapeutic action in allergic contact dermatitis. Lastly, since treatment with dupilumab results in an upregulation of epidermal differentiation, barrier and lipid genes, dupilumab might also have an effect on irritant contact dermatitis of the hands.

In this thesis, we have looked into the first clinical results of the biological dupilumab for the treatment of atopic and non-atopic hand eczema (Chapter 5, Chapter 6 and Chapter 7). In an observational daily-practice cohort study at our outpatient clinic, dupilumab showed continuous and long-term improvement of hand eczema severity and quality of life up to 52 weeks, and was well-tolerated in patients with atopic hand eczema (Chapter 5 and 6). Additionally, we studied the efficacy of dupilumab in severe chronic hand eczema in a 16-weeks, randomized, double-blind, placebo-controlled proof-of-concept study (Chapter 7). Treatment with dupilumab showed improvement in severity and patient reported itch scores compared to placebo at as early as four weeks after baseline. Severity and itch scores continued to improve until the end of study visit at 16 weeks. Unfortunately, due to the small sample size of 30 patients, we were not able to perform a sub-analysis between clinical subtypes or etiological diagnoses. Based on the long-term daily practice studies on atopic hand eczema, further improvement and a sustained positive effect on hand eczema could be expected after 16 weeks.

Additionally, dupilumab was well-tolerated by patients and there were no cases of conjunctivitis observed in this study. This is in contrast with the trials that investigated dupilumab for atopic dermatitis, in which conjunctivitis regularly (up to 22.1%) occurred. The pathogenesis behind the high rates of conjunctivitis due to treatment with dupilumab in atopic dermatitis patients specifically, has yet to be fully understood. One of the hypotheses, is that patients with atopic dermatitis have a pre-existing lower rate of conjunctival goblet cells. Inhibition of IL-4 and IL-13 by dupilumab then further decreases the quantity of goblet cells, resulting in low mucin production and irritative conjunctivitis. In Chapter 8, we describe a case report of a patient with a dupilumab-related conjunctivitis in which we took conjunctival biopsies during and after treatment with dupilumab. In that case, we observed goblet cell scarcity during treatment with dupilumab, which fully normalized after discontinuation of dupilumab.

More research on the efficacy of dupilumab on hand eczema is currently being conducted in two multicentre trials. The first multicentre study is a phase III study in which the investigators evaluate the efficacy of dupilumab in severe chronic hand eczema in a sample size of 133 patients with a 1:1 randomization to dupilumab and placebo. In the
other phase III multicentre study, the investigators look into the efficacy of dupilumab in moderate-to-severe atopic hand eczema, while also assessing atopic foot eczema.\textsuperscript{37}

**JAK-inhibitors**

Besides biologicals, JAK-inhibitors might be very promising in the treatment of hand eczema. JAKs are four different intracellular tyrosine kinases: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). JAKs activate signal transducer and activator of transcription (STAT), which then will carry the signal into the nucleus of the cell and result in the activation of downstream proteins.\textsuperscript{38} Type I and type II cytokine receptors lack intrinsic enzyme activity. Because of this, these cytokine receptors need to rely on JAKs for signal transduction and to activate their correlation downstream proteins. Drugs inhibiting the JAK-STAT signalling pathway, inhibit a broad scale of cytokines, including Th1, Th2 and Th17 pathways.\textsuperscript{39} Therefore, JAK-inhibitors can be used in many immune mediated diseases.\textsuperscript{40} Currently, a JAK-inhibitor combined with a spleen tyrosine kinase (SYK) inhibitor is being investigated for atopic dermatitis. SYK is a tyrosine kinase, that mediates the immunoreceptor signalling of immune cell receptors on the surface of immune cells, including macrophages, monocytes, neutrophils, mast cells and B-cells.\textsuperscript{41} After the immune receptors of these cells engage with their ligands, SYK is activated and mediates the cellular responses. For example, SYK mediates the cytokine production and release in T-cells and monocytes, maturation of B-cells, differentiation of dendritic cells, terminal differentiation in keratinocytes and phagocytosis in macrophages.\textsuperscript{41-44} In atopic dermatitis, inhibition of the JAK-STAT pathways leads to the inhibition of the Th1, Th2 and Th17 pathways, since these type II pathways depend on JAK-STAT signalling.\textsuperscript{39} More specifically, JAK1 and JAK3 inhibition leads to inhibition of cytokines within the gamma chain family, including IL-2, IL-4, IL-7, IL-9 and IL-15, and the inhibition of JAK2 and TYK2 leads to the inhibition of IL-12 signalling and Th1 differentiation.\textsuperscript{45,46}

JAK inhibitors have already proven to be effective as a treatment of atopic dermatitis. During the two large phase III randomized controlled trials studying the effect of upadacitinib in patients with atopic dermatitis, the effect of upadacitinib on hand eczema was studied as well. Upadacitinib is a JAK-inhibitor with greater inhibitory potency for JAK1 than JAK2, JAK3 and tyrosine kinase 2. In both trials, patients with atopic dermatitis were randomized to either upadacitinib 15mg, upadacitinib 30mg or placebo once daily.\textsuperscript{47} Patients with all hand eczema severities at baseline were included in the hand eczema analyses. The results showed that both upadacitinib 15mg and 30mg rapidly improved hand eczema compared to placebo through week 16, with respectively 68% and 74% improvement on the Hand Eczema Severity Index (HECSI), compared to 15-18% in the placebo groups.\textsuperscript{47} The sub-analysis, in which patients were stratified according to baseline HECSI, showed that more patients with moderate-to-severe eczema (HECSI >17) achieved at least 75% improvement on the HECSI (HECSI-75) than patients with
'almost clear' hand eczema (HECSI <17). Another randomized, double-blind and placebo-controlled phase IIb trial with gusacitinib, an oral dual pan-JAK/SYK-inhibitor, reported rapid and significant improvement of moderate-to-severe chronic hand eczema up to 16 weeks compared to placebo, with significant improvement as early as two weeks. The 32-weeks, phase II trial has been positively completed early 2020, but until now, results have not been published and phase III is announced in press release. For the use of oral-JAK inhibitors in non-atopic hand eczema, only one case report has been published in which baricitinib, a selective JAK1/JAK2 inhibitor, was used to treat a patient with chronic hand eczema without atopic dermatitis. The patient with severe chronic hand eczema showed significant improvement in both the clinical symptoms of hand eczema as improvement in quality of life after 16 weeks of treatment with baricitinib. At the moment, no clinical trials are planned to investigate the effect of systemic JAK-inhibitors on hand eczema. However, looking at the good efficacy of JAK-inhibitors on atopic dermatitis, and how JAKs broadly inhibit multiple inflammatory pathways, JAK-inhibitors will probably become a therapeutic option for hand eczema in the future.

**Novel topical treatment options**

Currently the topical pan-JAK-inhibitor delgocitinib is being investigated for the treatment of chronic hand eczema. In a randomized phase IIb trial, 258 patients with chronic hand eczema were treated with delgocitinib cream 1, 3, 8 or 20mg/g, or placebo (vehicle cream) twice daily. Treatment success was defined as achieving 'clear' or 'almost clear' with at least two-point improvement from baseline to week 16 on the investigator’s global assessment for chronic hand eczema. Treatment success at week 16 was achieved by 36.5% in the 8mg/g group and 37.7% in the 20mg/g group, versus 8.0% in the vehicle group. Delgocitinib was also very well tolerated by the patients in this study. At the moment, delgocitinib is being investigated in 16-week double-blind, placebo controlled phase III clinical trials with an open-label extension in adult patients with moderate-to-severe hand eczema, and in a 16-week double-blind, placebo controlled phase III clinical trial in adolescents aged 12 to 17 years. Thus far, delgocitinib seems to be the most promising, novel topical drug for hand eczema that will possibly be available in the near future. Besides delgocitinib, another topical JAK-inhibitor, ruxolitinib, is being studied for hand eczema. It has been approved by the Food and Drug Administration (FDA) for short-term treatment of mild-to-moderate atopic dermatitis, based on good results in two eight-week phase III, randomized, double-blind studies. At the moment, one proof-of-concept phase I/II trial for the treatment of hand eczema with 1.5% ruxolitinib cream has been planned to start early 2023.

Apart from topical JAK-inhibitors, phosphodiesterase-4 (PDE4) inhibitors are being investigated for the treatment of chronic hand eczema. PDE4-inhibitors inhibit the enzyme that degrades cyclic adenosine monophosphate (cAMP) in inflammatory cells, therefore
inhibiting T-cell proliferation and suppression of the release of several cytokines.\textsuperscript{57,58} In atopic dermatitis, crisaborole has shown to modulate markers of epidermal proliferation, such as K16, and to inhibit Th1-, Th2- and Th17-associated products, including IL-4R, CCL17/CCL22 and S100As.\textsuperscript{59} Crisaborole is a topical PDE4-inhibitor, and approved in the United States by the FDA for the treatment of mild to moderate atopic dermatitis in patients three months and older.\textsuperscript{60} In a recent review of 18 patients using crisaborole in daily practice for their atopic hand eczema, 11 patients achieved ‘clear or almost clear’ hand eczema.\textsuperscript{61} Among the seven patients who had crisaborole monotreatment, four patients achieved ‘clear or almost clear’. Another topical PDE4-inhibitor, ARQ-252 or roflumilast, has been studied for chronic hand eczema in a phase I/IIb, multiple dose, placebo-controlled 12-week clinical trial.\textsuperscript{62} The study has been completed in the summer of 2022, but results have not been published yet.

CCL2/CCL5 inhibition is also being investigated for chronic hand eczema.\textsuperscript{63} CCL2 and CCL5 are chemokines secreted by keratinocytes and are upregulated in atopic dermatitis,\textsuperscript{64} initiating the migration of Langerhans cells.\textsuperscript{65} This makes it quite promising for hand eczema caused by irritant contact dermatitis especially, since it would cause inhibition of the migration of Langerhans cells after the skin is exposed to irritant factors, that initiate the inflammatory process in irritant contact dermatitis. AFX5931 is a CCL2/CCL5 inhibitor that has been studied for chronic hand eczema in a phase IV, double-blind pilot study including 20 patients.\textsuperscript{63} Results have recently been shared in the Clinicaltrials.gov record of the study, but unfortunately, treatment with AFX5931 did not show any significant results compared to baseline or to placebo. No other clinical trials with a CCL2/CCL5 inhibitor for hand eczema or atopic dermatitis is running or planned.

**Head-to-head trials**

To be able to determine the position of existing and novel treatment options for hand eczema in a guideline in the future, daily practice and head-to-head studies are needed. At the moment, there are three ongoing head-to-head trials for hand eczema. The first one is a head-to-head study comparing the for hand eczema registered treatment option alitretinoin and the off-label treatment option cyclosporine for moderate-to-very severe hand eczema.\textsuperscript{66} The second head-to-head study, the ALPHA trial, compares alitretinoin and PUVA for severe hand eczema, and is almost completed.\textsuperscript{67} The third ongoing head-to-head study is a 24-week, phase III randomized trial comparing the efficacy and safety of delgocitinib cream to alitretinoin in adults patients with severe chronic hand eczema.\textsuperscript{68} As more treatment options are under investigation for the treatment of hand eczema nowadays, these head-to-head trials will hopefully provide more insight into how well these (novel) treatments compare to established hand eczema treatment options.
FUTURE PERSPECTIVES

Gradually, we are learning more and more about various aspects of the pathogenesis of hand eczema. Since most studies have already looked into the pathways for irritant contact dermatitis, atopic dermatitis and allergic contact dermatitis, it would be valuable to focus on investigating clinical subtypes. Pathways between these clinical subtypes appear to be different, with certain subtypes having inflammatory processes as a primary cause of action, and other subtypes having a decreased epidermal barrier function as their primary cause. Future studies might be able to better elucidate the differences between the clinical subtypes. The collection of samples for RNA transcriptome analysis can be facilitated by means of tape stripping.\textsuperscript{22,69,70} Tape stripping, due to it being a non-invasive procedure, can enable easier recruitment of patients for transcriptome studies, leading to larger sample sizes within a shorter time frame. However, it is not clear if tape stripping is a usable method for palmar hyperkeratosis in hyperkeratotic hand eczema. Additionally, linking transcriptome data to drug databases could contribute to the identification of treatments that may be suitable to treat hand eczema, based on the protein products of the differentially expressed genes.\textsuperscript{71}

In regards to research on genetic factors for hand eczema, genome-wide association studies (GWAS) may help to elucidate this part in the pathogenesis of hand eczema, just as GWAS have helped to identify susceptibility loci in atopic dermatitis.\textsuperscript{72,73} Hitherto, two GWAS with a small sample (up to 150 samples) have been performed, but no significant single nucleotide polymorphisms were found in these studies.\textsuperscript{74,75} GWAS with a large sample size, in which an adjustment for atopic dermatitis could be applied, might be able to identify genes associated with hand eczema, independent of atopic dermatitis. If the sample size is large enough, it might even be possible to identify genes associated with certain hand eczema subtypes. Then, clinical examination of all cases should be performed, which might not be feasible in large sample sizes needed for GWAS.

Recent studies on the pathogenesis of hand eczema have provided a better understanding of this heterogeneous skin disease. As these are just the first steps, more studies on the transcriptome and proteome of hand eczema are needed. If we gain more knowledge on the pathogenesis of hand eczema, it might be possible in the future to create a new classification system based on differences in gene and protein expression. This could facilitate in the development of targeted therapies for hand eczema.
REFERENCES


