Summary
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Patients suffering from hand eczema, the most common skin disorder of the hands, can experience a significant decrease in quality of life and socio-economic consequences. Treatment options are unfortunately limited, as only the retinoid alitretinoin is a licensed systemic treatment option for those with severe, chronic hand eczema. In order to discover novel treatment targets for this multifactorial skin disease, it is essential to gain more in-depth knowledge of its pathogenesis. This thesis focuses on the epidemiology, pathogenesis and treatment of hand eczema.

Limited data is available on the prevalence and severity of chronic hand eczema in the general population. These data can provide valuable insights into the patient burden of hand eczema. In Chapter 2, we used data from the Lifelines Cohort Study and sent out an additional questionnaire, to study the prevalence and severity of chronic hand eczema in the general population of the Netherlands. 57,798 adult participants of the Lifelines Cohort Study were included in the study. The lifetime prevalence of hand eczema among this population was 15.0%, and the one-year prevalence was 7.3%. Of the subjects with hand eczema, the majority (56.9%) had almost clear hand eczema at its worst. However, a substantial proportion of participants experienced severe to very severe hand eczema, with a 1.9% prevalence of severe to very severe hand eczema at worst ever. Additionally, the majority of subjects with hand eczema in the past year had chronic hand eczema, resulting in a 1-year prevalence of chronic hand eczema of 4.7%, and the severity of hand eczema among those with chronic hand eczema was higher compared to those with hand eczema that was not chronic.

The pathogenesis of hand eczema is not well understood yet. Identifying the involved pathways could potentially reveal novel treatment targets for chronic hand eczema. Therefore, we conducted a transcriptome and proteome analysis of vesicular hand eczema in Chapter 3. This hand eczema subtype is characterized by a pruritic eruption of vesicles on the palm and palmar or lateral aspects of the digits, and can occur without any known etiological factors. It has been suggested in several classifications that vesicular hand eczema can be considered a distinct entity, just as hyperkeratotic hand eczema. To compare the transcriptome and proteome of lesional vesicular hand eczema to non-lesional vesicular hand eczema and healthy control skin, we took biopsies of the skin, isolated ribonucleic acid (RNA) and conducted RNA-sequencing to identify differentially expressed genes between groups. This study revealed that the lesional vesicular hand eczema transcriptome largely overlaps the lesional atopic dermatitis transcriptome, which implies that treatments for atopic dermatitis may be effective in treating vesicular hand eczema as well. This overlap included an upregulation of keratinocyte host defence and inflammation genes (e.g. genes belonging to the S100A family), epidermal...
differentiation genes (e.g. KRT6, KRT16, KRT17), immune signalling genes (e.g. CCL17) and a downregulation of several skin barrier related genes (e.g. FLG, LOR). Additionally, we did not find any significant differences between the non-lesional vesicular hand eczema transcriptome and healthy control skin transcriptome. This is in contrast to the non-lesional atopic dermatitis transcriptome, which is distinguished from healthy skin by delayed and intermittent expression of barrier genes and proteins, and increased expression of immune-related genes. In previous hand eczema studies, it has been suggested that a primary dysfunctional epidermal barrier is one of the key pathways for developing hand eczema, since these studies showed a downregulation of barrier genes and their corresponding proteins. As no significant differences were found between non-lesional vesicular hand eczema and healthy skin, it can be questioned whether a primary dysfunction epidermal barrier is a key pathway in vesicular hand eczema. It is plausible that the lower expression of barrier proteins in lesional vesicular hand eczema is the result of the inflammatory processes.

For patients with severe chronic hand eczema, treatment options are limited. Alitretinoin is the only registered systemic treatment option, but it is less effective in hand eczema subtypes other than hyperkeratotic hand eczema. Therefore, in Chapter 4, we compared the treatments alitretinoin and azathioprine in an open-label, head-to-head study for the treatment of severe hand eczema. In this study, we found that both alitretinoin and azathioprine resulted in improvement of hand eczema severity and hand eczema-specific health related quality of life. Alitretinoin appeared to give more improvement of severity scores and health related quality of life in the analysis of the data. However, due to the limited number of 42 patients and the high drop-out rate, the study was too underpowered to draw any conclusions on differences in efficacy between the two treatments.

Chapter 5, Chapter 6, Chapter 7 and Chapter 8 covered studies regarding the biological dupilumab as a potential treatment for severe chronic hand eczema. In an observational daily practice cohort study at our outpatient clinic in which 72 patients were included, dupilumab had a continuous and long-term improvement in hand eczema severity and quality of life up to 52 weeks and was well-tolerated in patients with atopic hand eczema (Chapter 5 and Chapter 6). At 52 weeks, the majority of patients (87.1%) achieved more than 75% improvement on the Hand Eczema Severity Index (HECSI-75). Additionally, 90.3% of patients achieved the endpoint of ‘clear’ or ‘almost clear’ as determined by a photographic guide. The mean reduction in scores on the Quality of Life in Hand Eczema Questionnaire (QOLHEQ) was -63.5%. These daily-practice results in atopic hand eczema hold promise for dupilumab to be a potential treatment option for patients with isolated chronic hand eczema.
In addition, in Chapter 7, we studied the efficacy of dupilumab in severe chronic hand eczema in a 16-week, randomized, double-blind, placebo-controlled proof-of-concept study, in patients who do not respond to or do not tolerate treatment with alitretinoin. In this phase IIb proof-of-concept trial, 30 patients were randomized, 29 of whom received either dupilumab (n=20) or placebo (n=9). Treatment with dupilumab showed more improvement in severity and patient-reported itch scores compared with placebo as early as four weeks after baseline. Severity and itch scores continued to improve until the end of study visit at 16 weeks. At week 16, more patients in the dupilumab group achieved HECSI-75 than in the placebo group (95.0% vs. 33.3%). Additionally, dupilumab showed a greater improvement in least square mean percentage change from baseline to week 16 in peak pruritus numerical rating scale than in the placebo group (-66.5% versus -25.3%). Adverse events were comparable between the two groups and were primarily mild. No serious adverse events occurred, nor did any of the adverse events lead to discontinuation of the study drug. The results of this trial demonstrate that dupilumab is superior to placebo in treating severe chronic hand eczema and is well-tolerated. However, further research is needed to provide more evidence regarding the efficacy of dupilumab on chronic hand eczema, especially in patients without atopic dermatitis. Additionally, larger studies of longer duration are necessary to compare the efficacy of dupilumab between hand eczema subtypes or etiological diagnoses, such as irritant contact dermatitis.

Lastly, in Chapter 8, we presented a case study of a patient with atopic dermatitis and a dupilumab-related conjunctivitis. Dupilumab-related conjunctivitis is a common side effect of dupilumab treatment in patients with atopic dermatitis. In dupilumab-related conjunctivitis, a reduction or complete depletion of conjunctival goblet cells is observed. To investigate whether this effect is reversible after discontinuation of dupilumab, we took conjunctival biopsies of a patient with dupilumab-related conjunctivitis both during and after treatment with dupilumab. In this case, we observed goblet cell scarcity during treatment with dupilumab, which fully normalized after discontinuation of dupilumab.