Hand eczema
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Chapter 13

General discussion and future perspectives
GENERAL DISCUSSION AND FUTURE PERSPECTIVES

This thesis is focused on three aspects: the impact of hand eczema, the treatment of the disease, and outcome measures used in studies in the hand eczema patient population. Here, these aspects are discussed and suggestions for future research into these topics are provided.

IMPACT

In Section I of this thesis, we focused on the financial and occupational impact of hand eczema. In chapter 2 we presented a literature review on the cost-of-illness of hand eczema, showing the financial impact of the disease. The mean total annual costs per patient ranged from €1311 to €9792, which roughly corresponds to the costs of, for example, psoriasis, another common inflammatory skin disease. As the most recent articles on cost-of-illness of hand eczema were published in the year 2013, there is a need for a new study into this subject. Particularly because the retinoid alitretinoin was recommended for the treatment of hand eczema in the European guideline, published in 2015.

The significant heterogeneity between the six studies that we systematically reviewed is an important reason for the broad range in mean annual costs that was found; which is why we developed a checklist for future studies to improve similarity in study design. This checklist consists of two main groups: direct costs and indirect costs. Direct costs, which are either directly healthcare-related or directly associated with the disease but not medical in nature, are often quite easy to measure and can be estimated with some degree of certainty. Indirect costs are costs that arise as a secondary result of disease or treatment, and these include productivity losses related to the disease of interest. Estimating this in monetary values is much more difficult. Absenteeism (not working because of sickness) can be measured well, but the large issue here is the underestimation of the extent of presenteeism (working while being sick), because it cannot be measured with precision and various definitions have been used. Therefore, until now, financial losses attributed to this phenomenon were included in a hand eczema study just once (using a non-valid measurement instrument), while it may, in fact, have a large contribution on cost-of-illness in hand eczema. Presenteeism in this patient group deserves our interest.

Especially for more severe hand eczema, financial loss because of presenteeism is an issue, because the phenomenon is common in this group. This was shown in chapter 3, in which we focused on the occupational impact of hand eczema. We found that a higher hand eczema severity was associated with a higher presenteeism prevalence, especially when combined with a high-risk of occupational exposure to allergens or irritants. Whether the disease leads to real production losses, and concomitant financial losses, as a cause of presenteeism, will only be determinable when a validated instrument for the measurement of presenteeism can be applied to the population of patients with hand eczema. In the most recent Dutch guidelines for economic evaluation in health care the Productivity Cost Questionnaire (iPCQ), developed by the institute for Medical Technology Assessment (iMTA), is recommended. However, as of yet, this instrument was only partially validated. Also, working while having hand eczema does not always have to be synonym to production loss, certainly not when very mild cases are considered.

Although the exact measurement of presenteeism is currently difficult, it should be given attention in the daily care of patients with hand eczema. Especially because the most often reported reasons for presenteeism are intrinsic (chapter 3), which may require a patient to develop a higher degree of insight in his/her own behavior to be able to achieve a form of behavioral change.
TREATMENT

In Section II of this thesis, we highlighted aspects of the treatment of hand eczema. Proper diagnostics are vital when determining a treatment strategy for a patient with hand eczema. Each patient presenting with the disease should be patch tested for contact allergies. Also, irritant factors need to be identified to be able to provide proper counseling concerning this common etiological factor. Treating a patient who sustains contact with irritants and/or allergens is likely to be of limited, or only temporary, benefit for that patient. For patients who have severe disease, despite avoiding exposure to irritants and/or allergens, systemic treatment is indicated.\textsuperscript{2,10}

Very few placebo-controlled or comparative head-to-head studies with systemic drugs have been performed in hand eczema. Only the retinoid alitretinoin was studied in several large placebo controlled trials, and daily practice-based case series.\textsuperscript{11–17} Because of this, firm recommendations regarding optimal stepwise treatment cannot be provided.\textsuperscript{18} Therefore, we have designed two randomized controlled trials (RCTs) in search of new evidence to support the existing treatment algorithm. One of these is the ALICsA trial – alitretinoin versus cyclosporine in the treatment of severe recurrent vesicular hand eczema – of which in chapter 4 the protocol is presented. The choice to include only patients with the morphological subtype of recurrent vesicular hand eczema in this trial is mainly based on our clinical experience, combined with the results of a retrospective study. In that study, 68% of patients with the recurrent vesicular subtype, who were treated with cyclosporin, showed more than 50% improvement.\textsuperscript{19} Another small study by Grandlund \textit{et al.} also supports this.\textsuperscript{20} Conversely, alitretinoin showed only a small effect on the recurrent vesicular subtype in large trials.\textsuperscript{12} If our study provides evidence for the hypothesis that cyclosporine will have a superior effect over alitretinoin in recurrent vesicular hand eczema, this will definitely have implications for the treatment algorithm.

The second RCT we designed is the ALIAZ trial\textsuperscript{21} – alitretinoin versus azathioprine in the treatment of severe non-hyperkeratotic hand eczema – which was conceived based on our retrospective case review in chapter 5. In this study, we observed that, if patients tolerate azathioprine treatment, their hand eczema often improves. However, the number of patients discontinuing treatment because of subjective, often gastro-intestinal, side-effects was substantial. This is also seen in daily practice in atopic dermatitis patients treated with azathioprine.\textsuperscript{22,23} Possibly, measuring thiopurine metabolites (6-thioguanine nucleotide [6-TGN] and methylated 6-methylmercaptopurine [6-MMP]), optimizing azathioprine dose based on levels of these metabolites, and/or co-prescribing the xanthine oxidase inhibitor allopurinol, may improve clinical outcomes for hand eczema patients, as was reported for atopic dermatitis patients.\textsuperscript{24,25} This should be further investigated in future studies.

For atopic dermatitis, a flood of novel treatments are being developed. It seems a matter of time before these drugs will also be applied to patients with (isolated) hand eczema. We have already taken a small first step by assessing the effect of the biological dupilumab on the hands of patients with atopic dermatitis (chapter 6 and 7). We found that HECSI-75 was achieved by 60% of patients, while EASI-75 was reached by 57% of patients. This observation, implying that the hands responded at least as favorable as the whole body, holds promise for patients with severe isolated hand eczema. The next step will be to design a dupilumab versus placebo RCT, including only these patients. Also, head-to-head trials with dupilumab versus other systemic therapies for hand eczema are necessary. Dupilumab has its drawbacks, mainly in the form of eye-related adverse effects. Whether these effects will also occur in isolated hand eczema patients remains to be seen, as in other diseases for which dupilumab is used,
like asthma, chronic rhinosinusitis with nasal polyps, and eosinophilic esophagitis, eye-related adverse events were, interestingly, not more common in the dupilumab group than in patients who received placebo.26

For the future, it would be recommendable for new atopic dermatitis drug trials, that hand eczema receives increased attention. This will result in the effect of new therapies on the hands being more closely studied in an early phase, with the goal of subsequently assessing the effect of these new drugs in isolated hand eczema.

OUTCOME MEASURES

Section III of this thesis features several studies designed to improve measurement in hand eczema. In quantitative research, proper measurement is of the utmost importance. In hand eczema, well-validated measurement instruments are still scarce. An implication of this, is that conclusions of the majority of studies, which are based on measurements performed with the plethora of non-validated scoring systems currently available, at this point lack validity and a clear meaning.18,27

This issue has long been acknowledged in other fields. For example, in atopic dermatitis an initiative called ‘Harmonizing Outcome Measures for Eczema’ (HOME) was started.28 This group collaborates to define the most important domains, which should always be assessed when studying patients with the disease in clinical trials; the core outcome set (COS). Subsequently, proper measurement instruments are chosen with which best to measure (impairment in) these domains. Such measurement instruments are compared and the best, often most rigorously validated, instruments are chosen; the core set of outcome measurement instruments.29 In accordance with this initiative, a similar program was conceived for hand eczema, called ‘Hand Eczema Core Outcome Set’ (HECOS). The first step in this initiative was already taken, by identifying which outcomes, or domains, have been studied in interventional hand eczema research since the year 2000.30 The HECOS group will proceed to initiate a consensus process to determine the most relevant (core-)domains and subsequently to choose appropriate instruments with which to measure these domains. The studies that we performed in the current thesis should provide a firm basis for the Quality Of Life in Hand Eczema Questionnaire (QOLHEQ) and the HECSI to be considered for incorporation in the future COS for hand eczema. The HECSI should probably be incorporated in a general domain like ‘signs’ or ‘skin’. The QOLHEQ may be incorporated in a general domain like ‘quality of life’, or ‘perceived health status’, and for its subscales in more detailed domains like ‘emotional functioning/wellbeing’ or ‘social functioning’.

Regarding the validation and interpretability studies reported in this thesis, it is important to consider the external criteria based on which validity and meaning was attributed to the measurement instruments under scrutiny. For the QOLHEQ in chapter 9, a construct validity approach had to be used, as there is no gold standard for the measurement of true quality of life impairment in hand eczema. Other, skin-specific and general health measurement instruments were used to test whether the QOLHEQ measures what it purports to measure. For interpretability in chapter 11, the gold standard was approached by asking patients themselves, as experts on their own quality of life status, to provide their external criterion by answering anchor questions. For hand eczema severity, also, no gold standard is available, as we have not yet established a basis on which the true severity of hand eczema can be determined. It is all expert- and consensus-based. However, for the HECSI, in chapter 12, we did use a criterion-based approach with the Photographic guide as proxy for the gold standard. This approach is commonly used.31 Nevertheless, researchers should always be aware
of how validity and interpretability of the measurement instrument they use are determined. The choice of external criterion or anchor is key.32

In case of the Photographic guide as anchor for severity, there is an issue regarding generalizability. The Photographic guide developed by Coenraads et al. is a graphical description of five categories of hand eczema severity, focusing on clinical signs and extent of the disease. These five ordinal categories are ‘clear’, ‘almost clear’, ‘moderate’, ‘severe’, and ‘very severe’.33 In several hand eczema intervention studies performed over the years, a so-called Physician Global Assessment (PGA) (or Investigator Global Assessment [IGA]) is regularly used to grade hand eczema severity, often supported by the Photographic guide.12,14,34,35 However, this PGA often uses the ordinal categories ‘clear’, ‘almost clear’, ‘mild’, ‘moderate’, and ‘severe’. Moreover, the PGA was designed as a verbal description corresponding to the Photographic guide, but the subjective features ‘pain’ and ‘pruritus’ were also added.14 Combining subjective symptoms with clinical signs might cause individual bias by overestimation of self-reports.27 In yet another study, an IGA of six categories was used.36 It should be noted that the interpretability of the HECSI, as presented in this thesis, only corresponds to the physician-rated, Photographic guide, with five categories ranging from ‘clear’ to ‘very severe’, and which does not include patient reported features like ‘pruritis’ and ‘pain’.

Regarding the HECSI, two measurement properties have now been assessed; reliability37 and responsiveness, or sensitivity-to-change (chapter 12). Also, values for interpretability are proposed. However, probably the most important measurement property of the HECSI is yet to be tested: validity, defined as the ability of the instrument to measure what it intends to measure.31 In the first publication on the HECSI, no justification was given as to how the six clinical signs it measures were chosen for this instrument, from the more than thirty visual parameters that were assessed in atopic dermatitis38; or on the basis of which considerations the hands were divided in the five areas that are measured.39 Minimally, a construct validity study should be performed, in which a priori stated hypotheses on the correlation of the HECSI to existing instruments measuring the same or related constructs are tested, similar to what was done for the Dutch QOLHEQ in chapter 9 of this thesis. Aside from this, the reliability of the HECSI is not consistent for all signs.37 This is probably because there is not a clear framework which raters can use to achieve high agreement. Another avenue for further study might therefore be the development of a training manual on how to score the various elements of the HECSI. This will certainly improve reliability and therefore comparability of scores.40

The application of the QOLHEQ and HECSI is currently most suitable for clinical trials, as the completion of both instruments is time-consuming; in clinical trials there is usually more time available for evaluation of a patient compared with daily practice. For severity measuring in this setting, the Photographic guide is easy and fast to use, as it corresponds quite well to a general measure of severity that is normally estimated by a dermatologist. For the QOLHEQ, it might be interesting to investigate whether a short version could be created for application in daily practice. A study to look into this matter can be performed with Rasch analysis, using the framework of item response theory, which was already used in this thesis to validate the full Dutch QOLHEQ in a Dutch population of hand eczema patients (chapter 9), and to assess cross-cultural validity and differential item functioning in an international sample (chapter 10). In dermatology, the reduction of quality of life measurement instruments was performed previously by Nijsten et al., who reduced the number of items of the Skindex and the Impact of Psoriasis Questionnaire respectively from 29 to 17, and from 16 to 11.41,42
FINAL REMARKS
Knowledge in the field of hand eczema moves forward, but progress is mainly hampered by our limited understanding of the pathophysiology of the disease. Much could be gained by identifying endo-phenotypes, like the work that is now being done in the field of atopic dermatitis.⁴³,⁴⁴ Also, instead of just looking at disease-causing or aggravating exogenous factors (irritants and allergens), it may be more meaningful to look into the large variability in susceptibility of patients to these factors. Being able to more accurately diagnose and classify patients with hand eczema, will result in improved treatment strategies, ultimately tailored to the individual patient, and more focused research.

MAIN CONCLUSIONS OF THIS THESIS
The following conclusions can be drawn based on the results of the studies described in this thesis.

SECTION I – IMPACT
- The current literature shows a wide range of cost-of-illness associated with hand eczema, because of the heterogeneous designs used in various studies.
- Indirect costs, and particularly presenteeism, are underestimated in economic evaluations in hand eczema patients.
- Presenteeism is common among patients with a high severity of hand eczema, who have occupational exposure to irritants and allergens.
- The most frequently reported reasons for reporting presenteeism in hand eczema patients are of an intrinsic nature.

SECTION II – TREATMENT
- Azathioprine treatment may be effective in patients with hand eczema, but side effects result in discontinuation of therapy in a considerable number of patients.
- The effectiveness of dupilumab on the hand eczema of atopic dermatitis patients is similar to that on the whole body, suggesting avenues to explore in isolated hand eczema.

SECTION III – OUTCOME MEASURES
- Guidelines on how to perform validation studies on measurement properties should be used, resulting in well-validated measurement instruments to aid the performance of clinical trials.
- The Dutch QOLHEQ is a valid tool to measure disease-specific health-related quality of life impairment in Dutch hand eczema patients.
- The multi-language versions of the QOLHEQ can be used internationally to compare health-related quality of life impairment in hand eczema patients.
- International single-score values of the QOLHEQ can now be interpreted, and an improvement of ≥22 should be interpreted as a minimally important, real change.
- The HECSI shows a good responsiveness, single scores can now be interpreted, and an improvement of ≥41 should be interpreted as a minimally important, real change.
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