SUMMARY
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Hand eczema is considered a common disease. The exact prevalences however, are unknown. Studies estimate a point prevalence of 1 to 5% among adults in the general population, and a one-year prevalence of up to 10%, depending on whether the disease definition includes more pronounced or mild cases. Hand eczema tends to run a long lasting and chronic relapsing course, probably because of the multifactorial origin: atopy, irritant and allergic contact factors all may play a role, alone or in combination. In addition to the obvious itch, the social stigmata associated with a visible skin disease can be a great burden. The skin changes in hand eczema can prevent manual work, leading to significant disability and huge economic loss to both individuals and society.

The above-mentioned characteristics of hand eczema make it an important disease to study from an individual and a societal perspective. The aim of this thesis, stimulated by our randomised controlled trial (RCT), is to clinically reflect on the evidence-base for the treatments of hand eczema. The work focuses on the comparative efficacy of interventions for hand eczema and on the burden of disease associated with it.

In order to improve standards of design and reporting in hand eczema trials, chapter 2 describes the prevalent study designs and comments on the quality of reporting of such studies. Six electronic databases were searched and 21 journals were hand-searched, from the beginning of 1977 to April 2003 for all possible therapeutic studies. Ninety studies reported in 87 papers dealt with 11 different classes of interventions. Forty-four were uncontrolled case studies, and less than a third were RCT. The overall quality of reporting (eligibility criteria, randomisation generation, concealment of allocation, masking, intention-to-treat analysis) was poor. Based on the poor quality of reporting, most studies are not adequate to guide clinical practice. Therefore, future trials of hand eczema should be randomised, using a parallel group or self-controlled design. Further research is needed to develop validated and clinically relevant outcome measures. Most of the remaining issues relating to poor quality of existing evidence can be relatively easily dealt with by following the CONSORT guidelines.

The studies that were identified in chapter 2, were used in chapter 3 to answer 14 clinically relevant questions with regard to the treatment of hand eczema. Only controlled trials were used to answer these questions, unless on a specific subject only uncontrolled case series were available. The following conclusions could be drawn. There is insufficient evidence for a choice between short bursts of potent topical corticosteroids versus continuous application of mild corticosteroids. Although widely prescribed,
there is not much evidence of a corticosteroid-sparing effect of emollients. PUVA and UVB are effective, but there is no evidence of a clinical advantage of one modality over the other. Oral retinoids appear to be effective in hand eczema. There is insufficient evidence of an additive effect of iontophoresis or botulinum injections in dyshidrotic hand eczema. There is insufficient evidence for low-nickel diet or chelating agents in hand eczema accompanied by nickel allergy. There is insufficient evidence of an additive effect of topical antibacterial agents. There is insufficient evidence of superiority of topical calcineurin-inhibitors to topical corticosteroids.

A systematic review is presented in chapter 4. It studied all interventions for hand eczema that had been evaluated by RCTs since 1977, in order to determine which therapy would reflect current standard treatment and to which extent there is evidence for its effectiveness. In addition, the qualitative characteristics of the papers are given. A wide range of treatments was found, reflecting the fact that there seems to be no single candidate for a standard-therapy. Given the number of RCTs, topical corticosteroids and UV-phototherapy may be considered first-choice options. Most trials have either placebo, vehicle or a variant of its intervention as comparator, making it difficult to draw conclusions on the comparative advantage. There was too much heterogeneity in the three ‘major’ treatment categories (topical corticosteroids, UV-phototherapy, X-rays) to attempt any pooling and meta-analysis. Serious limitations in the quality of reporting have been found. Frequent shortcomings were missing information on randomisation and blinding, no justification of the number of participants and no analysis of dropouts. A range of outcome parameters were presented, most of which were not validated. We could not find any evidence that any of the various scoring methods that were used in the trials are relevant to patients, and the interpretation of the changes in scores derived by adding several physical parameters together is obscure even to clinicians. This review is unable to inform clinical practice with regard to the best way of managing hand eczema, especially in the long term. The most important implication is the need to conduct high-quality RCTs of people with hand eczema comparing commonly used interventions using simple outcome measures that can be understood by patients and clinicians. There is currently no consensus on a standard severity scale for hand eczema. A validation of commonly used scoring systems, or of simple global ratings using photographic anchors is needed. Many deficiencies in trial reporting thus far can be avoided if all specialist dermatology journals adopt CONSORT standards.

Chapter 5 describes an open label RCT, with a 10 weeks treatment period and an 8 weeks follow-up period, studying whether oral PUVA with a portable tanning unit at home and 8-methoxypsoralen (8-MOP) capsules is equally
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effective as hospital administered bath PUVA in patients with chronic hand eczema. Patients with moderate to severe chronic hand eczema (more than 1 year duration), n=158, were included. Both groups showed a comparable and substantial decrease in a physician-rated severity score (evaluation of desquamation, erythema, vesiculation, infiltration, fissures, itch and pain, each on a four-point scale), corresponding to a meaningful clinical improvement. This decrease was maintained during the follow-up period.

The patients who were included in the RCT as described in chapter 5, were also asked to complete a burden of disease questionnaire (the Dermatology Life Quality Index: DLQI) and to make a self-assessment of the severity of their hand eczema. Chapter 6 demonstrates how physicians and patients differ in their assessment of the severity of hand eczema as seen in a physician-rated severity score (evaluation of desquamation, erythema, vesiculation, infiltration and fissures), patient-rated severity score (self-assessment) and a burden of disease questionnaire. The correlations between these parameters, both at inclusion and over time, were calculated. Only desquamation and infiltration were significantly correlated with patient-rated severity score. Patient-rated severity score correlated with 7 out of 10 DLQI items, and did not correlate with the items regarding the influence on wearing clothes, impairment of doing any sport, and problems associated with treatment of the skin. The majority of patients showed improvement in all parameters after treatment. However, the improvement in patient-rated severity score was not clearly correlated to changes in physician-rated severity score. Except for DLQI item 1 (itch, soreness, pain, stinging), none of the changes in burden of disease were correlated to changes in patient-rated severity score. For each DLQI item, change over time correlated with a decrease in a component of the physician-rated severity score. Patient satisfaction was not guaranteed when treatment was focused solely on the visible aspects of hand eczema. Instead, burden of disease has a greater impact and for which counselling by other professionals may be required.

The economic impact of a disease is another component of burden of disease. In the first appendix the economic outcomes of oral PUVA at home and hospital administered bath PUVA are presented. This evaluation was based on a socio-economic perspective, i.e. both medical costs and costs outside of the healthcare sector were included. Of the patients who were included in the RCT as described in chapter 5, the costs in both intervention arms were prospectively registered from the time of randomisation until the end of the follow-up period. It showed that the patients who were treated with oral PUVA at home generated significantly lower costs for a number of cost types. These cost types are costs for PUVA-therapy, travel costs, time costs (costs related to the travel and
waiting time for a visit to the hospital) and costs due loss of productivity caused by limitations at work due to hand eczema.

One of the participants of the RCT of chapter 5 who was treated with 8-MOP capsules at home reported unusual adverse events, which are described in appendix 2. Between one and two hours after taking 8-MOP capsules, the patient experienced nausea with vomiting, dyspepsia, severe headache, fatigue, muscle aches and fever of up to 39.0°C, increasing in severity after every subsequent intake, and lasting up to 40 hours. Reintroduction of the 8-MOP along with testing of the patient’s blood and urine samples, monitoring of his temperature and with supervised documentation of his symptoms, led us to conclude that acute severe influenzalike symptoms can be caused by oral 8-MOP; UVA is not required to elicit the symptoms. We assumed that these adverse events were attributable to a hypersensitivity to 8-methoxypsoralen. The rarity of this reaction, with no other published cases, prompted us to report it.

In conclusion, this thesis demonstrates the lack of good quality trials studying the efficacy of hand eczema interventions and it shows that this is partly due to the lack of consensus on severity scoring and definition of realistic outcomes. Topical corticosteroids and UV-phototherapy appear to be the major standard treatment categories; oral PUVA at home is equally effective as hospital administered bath PUVA with lower travel costs and less time off work. Although new treatment options with retinoids and calcineurin inhibitors are emerging, the comparative advantage over topical corticosteroids or UV-phototherapy has not yet been established. Patient satisfaction is not guaranteed when treatment is focused solely on the visible aspects of hand eczema.