Discussion

How to treat hand eczema in daily practice?

Wietske Andrea Christoffers

Department of Dermatology, University of Groningen,
University Medical Center Groningen, Groningen, Netherlands
Overview of main findings & general discussion

This thesis discusses the various treatment options for patients with hand eczema. In chapter 2 we reviewed extensively, according to the Cochrane protocol, all the randomized controlled trials (RCT) on interventions for hand eczema. The slightly disappointing conclusion was that, with a few exceptions, the overall quality of the studies is poor and head-to-head trials are lacking. A systematic review published in 2004 came to the same conclusion. In spite of well-designed studies regarding alitretinoin and topical calcineurin inhibitors, the evidence for the efficacy of topical corticosteroids or cyclosporine and acitretin, often used in daily practice, has remained scarce.

Clinicians often wonder what treatment would be best for their specific patient with hand eczema. The choice for an optimal treatment should, ideally, be based on a comparison between different treatment modalities, such as topical corticosteroids versus topical calcineurin inhibitors. In chapter 3 we discussed questions from daily practice. Here the overall conclusion was in line with that of chapter 2: in general, there is insufficient high-quality evidence to recommend one treatment over another. For example, PUVA and UVB are both effective in the treatment of hand eczema, but there is no evidence of a clinical advantage of one over the other. The same is true of topical calcineurin inhibitors; although they are more effective than placebo, their superiority over topical corticosteroids in cases of hand eczema has not been demonstrated. Oral retinoids (alitretinoin), however, do appear to be effective and well tolerated in hand eczema, especially in hyperkeratotic hand eczema. In chapter 2 we included a potentially important study by Schmitt et al. which compared the effectiveness of cyclosporine to alitretinoin. Unfortunately, this investigator-initiated study was ended prematurely due both to an insufficient number of naïve participants and to limited resources. These problems are characteristic for intervention studies with patents: once a drug has been established in daily practice or has received market authorization, there is no financial motivation for pharmaceutical companies to conduct a comparative study. This could explain the scarcity of head-to-head trials.

Besides randomized controlled trials, daily life studies like chapter 4 provide useful information. One advantage is the applicability of their results to daily clinical practice; therefore the external validity is higher in daily life studies than in clinical trials, though the internal validity is lower. Limitations in external validity make it difficult to apply results of clinical trials in daily practice. Trials recruit only ‘perfect patients’ who fulfill strict inclusion and exclusion criteria, are relatively healthy, motivated and adherent to treatment. In daily practice patients are unselected: only patients with true contraindications are excluded from treatment. In general the number of drop-outs due to adverse events is higher in daily practice than in clinical trials. Differences in duration of active treatment may also contribute to the higher...
discontinuation rates. Moreover patients who choose to participate in clinical trials are often very motivated to fulfill the trial period despite adverse events. Finally, artificial endpoints and a fixed duration of treatment might influence the external validity of RCTs. The endpoints might not be relevant for a patient at all: for example, a reduction in erythema after 14 days of using tacrolimus might not be very relevant to a patient with a chronic condition like hand eczema.

For this reason, in chapter 4 we conducted a daily practice study regarding the drug survival of cyclosporine. This study concluded that cyclosporine is a safe treatment for patients with recurrent vesicular hand eczema and patients used it for an average of 10.3 months, which is substantially longer than the average trial.

One of the first steps after diagnosing hand eczema is to provide education regarding the use of emollients, gloves and the avoidance of allergens and irritants. Contact allergens such as thiuram, mercaptams and acrylates are well known for their role in hand eczema. However, the role of contact allergies is an issue of debate in patients with chronic hand eczema.

In chapter 5 we studied the most frequent sensitizers in subjects with hand eczema. We demonstrated that 50.3% of patients with clinical subtype chronic fissured hand eczema were sensitized to at least one allergen in an extended European baseline series. This number was substantially higher than the sensitization rate in the general population, where the median prevalence of contact allergy to at least one allergen is 21.2% (range 12.5–40.6%). In subjects with recurrent vesicular hand eczema this number was even higher: 55.2% of the patients was sensitized to at least one allergen in the extended European Baseline series and 17.0% of this clinical subtype was polysensitized.

In patients with pulpitis, acrylates were frequent sensitizers. Acrylates are in general known to be potent sensitizers. In chapters 6 and 7 we describe two cases of hand eczema due to acrylate contact allergy. In chapter 6 a process operator developed bullae on the hands and knee due to contact with various acrylates, of which 1,6-hexanediol diacrylate and glycidyl methacrylate were, among others, the main sensitizers. Subsequently, in chapter 7 we went on to describe therapy-resistant hand eczema in a printer who worked with acrylates. A rare contact allergy to isobornyl acrylate turned out to be the explanation for his persistent hand eczema. Triggered by these cases we further studied our patients who were sensitized to (meth)acrylates; 87.5% turned out to have a contact allergy of the hands. These findings highlight the importance of (meth)acrylates in (occupational-related) hand eczema.

When conventional therapies do not give desired results, patients tend to search for alternatives. One marketed alternative for the treatment of eczema is tea tree oil (melaleuca alternifolia), a natural oil derived from the Australian Melaleuca Alternifolia. This oil is claimed to have antibacterial, anti-inflammatory properties and to reduce histamine-induced skin
inflammation. Because it is a natural product consumers assume it to be safe. However, when tree tea oil oxidizes, several sensitizing degradation products are formed. Chapters 8 and 9 discussed one of these products, ascaridole; more than one third of our patients who were sensitized to ascaridole suffered from hand eczema.

How to treat hand eczema in daily practice?
In spite of our focus on different interventions for hand eczema, we have not been able to give a one-off recommendation for the treatment of patients with this disease. Although, a Dutch guideline for the treatment of hand eczema does not exist, various well-respected international groups have proposed guidelines, including Canadian, Danish and German guidelines and the British consensus. These all acknowledge the importance of (primary, secondary and tertiary) prevention, avoidance strategies and education and propose that treatment be tailor made to the needs of the specific patient. All guidelines go on to recommend moderate to super potent topical corticosteroids. If the hand eczema is unresponsive to topical corticosteroids, different guidelines give different recommendations, but the potential options are often listed in alphabetic order without clear stratification. In this final chapter of the thesis we aim to provide a clear, stratified, practical tool to treat hand eczema based on current literature, existing guidelines and the findings of this thesis.

In chapter 1 we discussed the steps for diagnosing hand eczema and the differential diagnosis. We later in chapter 5 presented a flow chart to classify the clinical subtypes of hand eczema according criteria of Danish Contact Dermatitis Group. Once the diagnosis of hand eczema and the clinical subtype have been established, the treatment of hand eczema consists of several important steps as displayed in Fig. 1.

Immediate treatment is recommended and watchful waiting should be discouraged, since various studies have demonstrated that the prognosis of chronic hand eczema is poor. Hald et al. found in a 6-month follow up study that fissures and scaling, signs of chronic hand eczema, had a poorer prognosis than, for example, vesicles. Meding demonstrated that the extent of the hand eczema also influences the prognosis negatively. Since patients experience a median patient delay of three months, and 11.2% of the patients wait longer than one year before consulting a physician, physicians should be prompt with proactive treatment.

Basic skin care & protection
The first step in the treatment of hand eczema is education and basic skin care advice. One must emphasize that no quick and easy solution for hand eczema exists. As proper skin care
will not cure the eczema completely patients may fail to see its value, but skin care is vital and patients should continue with it for the rest of their lives. Patients need to know that frequent contact with irritants such as water, detergents and cutting fluids can impair the skin barrier function. This impaired barrier function can evoke or maintain hand eczema. Insight into potential triggers and the mechanism behind the disease makes the patient self-reliant and increases self-management.\(^\text{16}\)

Whenever possible, causative factors should be removed. Chapter 5 demonstrated that about half of hand eczema patients are sensitized to at least one allergen. The clinician and patient should try to establish whether this sensitization is relevant for the hand eczema, though this could be a complex quest. Contact allergens that are clinically relevant for the hand eczema can be present in cosmetic, household and occupational products; these should be checked, and where necessary, avoided. Websites such as www.huidarts.com or www.huidziekten.nl contain extensive lists of allergens with clear information as to potential sources of allergens. The physician ought to provide the patient with specific written information, since it is difficult to remember complex information like names of contact allergens. Unfortunately, the complete elimination of a contact allergen does not guarantee complete healing of the hand eczema, since hand eczema is typically a multifactorial disease.

A silent causative factor in hand eczema is frequent washing of the hands (>20 times a day). If the hands are not visibly dirty but must be cleaned to prevent infection, as in the case of health care workers, the use of alcohol-based disinfectants instead of traditional full hand washing should be encouraged.\(^\text{17,18}\) If hands are visibly dirty, traditional hand washing is necessary.\(^\text{19}\) Therefore lukewarm water and preferably a fragrance-free soap without well-known sensitizers such as MCI/MI should be used. The hands should be dried well, preferably with disposable paper towels, which have higher drying efficiency and are more hygienic than (hot) air dryers or common-use towels.\(^\text{20}\) Subsequently, an emollient should be applied immediately. One should avoid rings, especially when washing the hands, as dirt and soap can get trapped under a ring, causing irritation; the skin underneath a ring is also difficult to dry.\(^\text{21}\)

Wet work in general is an important stressor for the skin and plays a prominent role in the majority of irritant hand eczema cases. Whenever possible, wet work should be avoided, for example by using a washing machine and a dishwasher. Protective (household) gloves can also be worn, but gloves be worn in the correct way. Gloves are essential in the avoidance of contact with allergens and irritants. Different gloves are suitable for different purposes. It is important to select a specific glove for a specific job, since gloves might provide good protection against one substance but be easily penetrated by another.\(^\text{22}\) Moreover, gloves may themselves contain sensitizers which should be avoided.
Nitrile gloves provide good protection against solvents, oils, greases, selected acids and bases. These gloves can contain common sensitizing rubber accelerators such as carbamates, thiurams, and mercaptams.

Vinyl gloves protect against acids, bases, oils, greases, peroxides, and amines. These gloves might contain the rare sensitizers phthalates and bisphenol A and are not very elastic.

Latex gloves provide proper protection against biological and water based materials. These gloves can contain common sensitizing rubber accelerators such as carbamates, thiurams, and mercaptams. Moreover, latex gloves can cause a protein contact dermatitis or an immediate type I allergic reaction.

Polychloroprene gloves protect against acids, bases, alcohols, fuels, peroxides, hydrocarbons, oils, greases, and phenols. Polychloroprene gloves might contain the rare sensitizer thioureas.

Polyvinyl alcohol gloves protect against aromatic and chlorinated solvents, ketones, esters and methacrylate. These gloves are quite expensive.

Butyl gloves protect against ketones, aldehydes and esters. These gloves are also expensive.

Multilayer laminated gloves (laminated gloves of ethylene- vinyl-alcohol-polyethylene, 4H®) protect against practically everything, but their fit is poor. As discussed in chapters 5, 6 and 7, acrylates are well known sensitizers. Multilayer laminated gloves provide the best protection against acrylates, however these gloves have a poor fit and are not practical for fine manual work like that of nail stylists and dental technicians. In such cases thicker nitrile gloves are more effective than latex or vinyl gloves because of their longer breakthrough time for various acrylates. Their elasticity is also superior to that of multilayer laminated gloves.

Not only must patients select the proper gloves, but they must wear gloves only for a short period of time and not re-use them. The barrier function of a glove is impaired after the first contact with an allergen, whether or not the glove has been worn. One should immediately discard gloves with holes and regularly replace all gloves. Moreover, when putting gloves on or off, a subject can come into contact with the, often contaminated, outer lining of the glove and transfer the allergen from the outside to the inside of the glove. Selection of proper gloves remains challenging, since besides exposure to allergens and irritants, one must also consider the risk of latex allergy and sensitization to rubber chemicals. Additional information regarding gloves can be found on http://www.ansell.nl/, http://www.kcl.de/ and http://www.marigoldindustrial.com/. We also recommend contacting the occupational physician. Another point to consider is that although gloves protect the skin from contact with allergens and irritants (especially wet work), the occlusion of the skin caused by the glove
itself is a risk factor for hand eczema. Therefore, cotton linings or inner gloves underneath occlusive gloves are recommended when gloves are worn for longer than 10 minutes. In conclusion, gloves must be worn as long as necessary, but as short as possible.

Patients should be instructed to use emollients frequently. Lipid-rich emollients (ointments) are preferred over creams: because these are more lipid and contain less water, thus there is less evaporation. Moreover, creams more often contain sensitizing preservatives and mildly irritating emulsifiers. The Cochrane review (chapter 2) demonstrated that a petrolatum-based emollient (Vaseline lanette) did not differ from a ceramide-containing emollient (Locobase® Repair). However, one must consider not only the efficacy of an emollient but, even more important, the patients’ preference. Patient-rated factors such as cosmetic acceptability, odor, greasiness and amount of staining should therefore be taken into account. Providing various alternatives during the first visit allows the patient to select the emollient of his personal preference, which could contribute to his adherence. Patients must be instructed to use emollients several times a day, especially after contact with water. Multiple samples should be available in several places in the house, as next to every sink, or in a handbag. The patient must understand the use of emollients and that emollients must be applied to the entire hands, including web spaces, finger tips and the back of the hands.

**Topical treatment**
Topical corticosteroids are the mainstream treatment for hand eczema. The rationale for topical corticosteroids is based largely on pharmacological reasoning and clinical experience; actual evidence is limited. Nine randomized controlled trials with topical corticosteroids were carried out with hand eczema patients. These studies had different designs; different corticosteroids and different vehicles, dosages or application frequencies were used. It is thus difficult to compare and recommend an evidence-based dosing regime. To prevent chronicity of hand eczema, we recommend as first treatment step a potent topical corticosteroid, applied once or twice daily. To treat one entire hand, one fingertip unit (0.5 gram) of topical corticosteroids should be applied. Patients should be instructed not to apply corticosteroids at the same time as their emollients, since this might diminish the total dosage.

If after two to four weeks a potent topical corticosteroid seems to be insufficient, one should evaluate the patient’s adherence to treatment. This should be discussed openly, since treatment adherence to topical therapy is even poorer than to oral therapy. In a small study, 10 patients with moderate to severe atopic dermatitis were instructed to apply fluocinonide 0.1% cream twice daily for 5 days. The median treatment adherence was only 40% (range
0-100). For treatments with longer durations, the adherence might diminish even further. To improve treatment adherence, the dosage schedule should be easy to comprehend and follow. Therefore a once daily application is preferable to a twice daily application, and complex tapering schedules should be avoided. Although little studied, the correct way of tapering is an issue of debate. Given the reservoir function of the epidermis, application every other day might be preferred over application on three or four successive days. During the tapering phase, the patient should be reminded to continue with frequent use of emollients. Lack of information and (irrational) fear of adverse events can diminish treatment adherence. Patients may suffer from corticophobia due to fear of skin atrophy and systemic effects. However, a systematic review of atopic dermatitis reported that randomized controlled trials had shown no evidence for the development of skin atrophy provided that the corticosteroids were used appropriately. Full body application of very potent corticosteroids such as clobetasol propionate does result in inhibited cortisol production in patients with severe atopic dermatitis or bullous pemphigoid; however these effects disappeared with dosages of less than 50 mg a week and with less potent corticosteroids. Thus the risk of systemic effects in the topical treatment of hand eczema was found to be negligible. This, combined with the poor prognosis of chronic hand eczema, should encourage physicians to prescribe potent topical corticosteroids in an early phase. If topical corticosteroids are necessary over a longer time period, for example during the maintenance phase, one can consider rotation with less potent topical corticosteroids or topical calcineurin inhibitors (tacrolimus and pimecrolimus). Other potential explanations for ineffectiveness of topical treatment are contact allergies to lanolin or corticosteroids. This can be the case especially in hand eczema that worsens despite adequate topical treatment, or if the eczema is more active in the borders than in the center of the lesion (after ruling out dermatomycosis). In case of lanolin-sensitizations, one must prescribe lanolin-free emollients (unguentum leniens (koelzalf FNA), paraffin, Vaseline and Vaseline album) and lanolin free corticosteroids (Emovate, Elocon, and Dermovate among others). Diagnosing a contact allergy to corticosteroids can be difficult, since the patch test with corticosteroids suppresses the delayed type reaction by the anti-inflammatory action of the corticosteroids themselves. When patch testing, one should at least test the screening markers tixocortol pivalate, budesonide and hydrocortisone-17-butyrate, along with the patient’s own corticosteroids. A day-7 reading can be introduced to pre-empt late reactions to corticosteroids, but even this cannot exclude false-negative reactions. Corticosteroids are known to cross-react, based on C16-methylated and non-methylated molecules. Recommending a safe topical corticosteroid can be difficult. However, topical calcineurin inhibitors are a valuable treatment alternative for every patient with a sensitization to corticosteroids.
The Cochrane review demonstrated that topical calcineurin inhibitors are comparable to or more effective than placebos, but they are not more effective than mometasone furoate.\(^{44,45}\) Moreover, topical calcineurin inhibitors are almost seven times as expensive as topical corticosteroids (on average €12 versus €80 per 100 gram). Finally, long term adverse events are not yet known, as long-term studies in atopic dermatitis are still in progress. A further suggestion is to add salicylic acid to the treatment for patients with hyperkeratotic hand eczema and water baths for patients with recurrent vesicular hand eczema, though these recommendations are based purely on experience and not on evidence.

If topical treatment is successful after initial crisis intervention, one should switch to the maintenance phase. Frequent application of topical corticosteroids should be tapered in an easy to follow schedule and the patient should be encouraged to continue the application of emollients. If tapering of corticosteroids results in a flare, one can prescribe short bursts of potent topical corticosteroids or longer term continuous application of less-potent corticosteroids. One can also consider using rotation with topical calcineurin inhibitors instead of maintenance therapy with topical corticosteroids.

**Phototherapy**

When potent corticosteroids have failed to help patients with vesicular hand eczema one should, before starting systemic treatment, consider phototherapy. Clinical experience has also shown phototherapy to be effective in treating chronic fissured hand eczema. The effectiveness of topical PUVA in treating hyperkeratotic palmar eczema might be less, however, probably because of the thick hyperkeratotic plaques and the absence of inflammation.

In Chapter 2 we demonstrated that phototherapy was more effective than placebo, but there was little evidence to indicate which method, either UV-B or PUVA was superior. If frequent visits to the hospital are feasible and the travel distance to the hospital is acceptable, one can prescribe phototherapy, although several treatment centers may decide to skip this treatment option. First of all, phototherapy needs to be tailored to specific patients and clinics. Moreover, although it is effective, phototherapy has drawbacks. Studies of psoriasis patients concluded that patients found phototherapy demanding and time consuming and some even doubted the therapeutic value of the time they had invested.\(^{46}\) Moreover, frequent hospital visits resulted in considerable direct and indirect costs and absence from work.\(^{47}\) Phototherapy at home could resolve some of these issues: in patients with chronic hand eczema oral PUVA with a portable tanning unit at home is as effective as hospital-administered bath PUVA and more cost-effective.\(^{48}\) In the Netherlands, the main disadvantage of phototherapy at home is the uncertainty of reimbursement.
Systemic interventions for hand eczema

Before starting systemic therapy for hand eczema, one must re-evaluate the patient’s treatment adherence and reconsider the diagnosis.

The decision to start systemic treatment should be made by both physician and patient, taking into consideration possible adverse events, benefits and costs for the specific patient. Patients should be given verbal and written information regarding the systemic options and offered sufficient time to consider these options.
In the Netherlands, alitretinoin is the only registered systemic treatment option for chronic hand eczema. In well-designed pharmaceutical sponsored trials\textsuperscript{49-51} 30 mg alitretinoin a day resulted in clear or almost clear responses in 48% of the participants, compared to 17% with a placebo.\textsuperscript{50} In the hyperkeratotic subtype 49% reacted, as compared to 12% in the placebo group. However, only one third (33%) of the participants with recurrent vesicular hand eczema (defined in the study as pompholyx) reached clearance or almost clearance, as compared to 16% in the placebo group.

Based on these statistics and the mechanism of alitretinoin, and the fact that alitretinoin is the only registered treatment option for hand eczema, we recommend alitretinoin as the first systemic intervention step for all types of chronic hand eczema, except for recurrent vesicular hand eczema (Fig. 1). A dosage of 30 mg/day should be prescribed. If there is no considerable improvement after 12 weeks, alitretinoin should be stopped. Otherwise it can
be continued until 24 weeks. After 24 weeks of treatment, according to the manufacturer’s guidelines the patient should stop with alitretinoin. In case of an exacerbation, alitretinoin can be restarted.

If alitretinoin is insufficient, acitretin 25 mg/day is a valuable alternative for hyperkeratotic hand eczema. For other clinical subtypes of hand eczema cyclosporine can be considered.

For patients with recurrent vesicular hand eczema a low dose of oral cyclosporine might be preferred over alitretinoin. As demonstrated in chapter 4, the drug survival of cyclosporine was especially long for patients with recurrent vesicular hand eczema, and more than half of the patients achieved an improvement of at least 50%. Meta-analysis in patients with atopic dermatitis demonstrated an efficacy of cyclosporine of 55% after 6 to 8 weeks. In patients with atopic dermatitis, starting with a high dose of cyclosporine (>3.5 mg/kg/day) and subsequent tapering of the dose (drop-down) seemed more effective and resulted in a longer drug survival than starting with a low dose of <3.5 mg/kg/day and slowly increasing the dose to reach the optimum treatment effect (step-up). Moreover, in chapter 4 we demonstrated that cyclosporine can be used safely for several months to years and only one patient discontinued treatment because of an increase in serum creatinine levels. Unpublished data demonstrate the same; atopic dermatitis patients whose median treatment duration was more than one year experienced no substantial influence on renal function. After 6 weeks one should evaluate the effect of cyclosporine; if this is satisfactory, the drug can be continued for 3-6 months as needed. Even longer treatment did not seem to result in more adverse events and can therefore be considered for refractory cases. During treatment with cyclosporine, one must carefully monitor blood pressure and serum creatinine, among others.

If cyclosporine is not effective, one can then consider alitretinoin for patients with recurrent vesicular hand eczema.

If alitretinoin, acitretin and cyclosporine are ineffective, various other off-label treatment options are available. Methotrexate (10-15 mg/week) with folic acid may be beneficial in hyperkeratotic hand eczema, while azathioprine (50-150 mg/day) can be effective in recurrent vesicular hand eczema and chronic hand eczema. For severe refractory chronic or vesicular hand eczema, unresponsive to conventional treatment, mycophenolate mofetil (0.5-3 gram/day), enteric-coated mycophenolate sodium (720 mg twice a day), or a low-dose of prednisolone (5-10 mg/day) with osteoporosis prophylaxes can be prescribed, though there is no evidence for the effects of these treatment options in patients with hand eczema. Furthermore, based on experience, a course of the oral antifungal agent itraconazol occasionally seems effective for recurrent vesicular hand eczema. If a subject is prone to superimposed infections of the skin this may aggravate the hand eczema; long-term treatment with oral claritromycin (500 mg/day) can then be
considered. For hyperkeratotic palmar eczema dithranol and coal tar can be prescribed. Combinations of different oral treatments can be considered in extreme refractory cases, though this should be done with extreme caution and careful monitoring. In the future, biologicals may provide alternative options, though to date no effective biological for (hand) eczema is known.

The ESCD Guideline: Guidelines for diagnosis, prevention and treatment of hand eczema

An expert working group of the European Society of Contact Dermatitis (ESCD) is currently working on a guideline for the diagnosis and treatment of hand eczema, partly based on the findings of the Cochrane review from chapter 2. Overall, the guideline of the ESCD does not differ essentially from our flow chart. The skin protection program of the ESCD with regards to gloves, hand washing and emollients overlaps with the advices described in the text above.

The ESCD strongly recommends quick and vigorous treatment to avoid the development of chronic hand eczema. The use of topical corticosteroids is the first line treatment in the management of hand eczema (evidence of high quality, strong consensus-based recommendation), but states a maximum duration of six weeks. For patients with chronic hand eczema refractory to topical corticosteroids, the ESCD strongly recommends alitretinoin (high quality evidence, consensus-based recommendation) or photo-therapy (UVB, PUVA) (evidence of moderate quality, strong consensus-based recommendation). We have positioned phototherapy at the same level as the ESCD. The ESCD emphasizes that other treatment options are off-label. The off-label use of cyclosporine is recommended as alternative option by the ESCD (evidence of moderate quality, strong consensus-based recommendation). Other options such as azathioprine, acitretin or methotrexate can be considered once other therapeutic options have failed. A substantial difference between the ESCD guideline and our treatment plan is the inclusion of specific subtypes of hand eczema in our treatment plan. The ESCD emphasizes that in research and clinical trials some kind of classification needs to be applied, though current consensus is lacking. Thereupon the ESCD proposes to use the classification system of Diepgen et al. This classification, as discussed in chapter 5, includes a mixture of etiological and clinical types. In the guideline of the ESCD the classification of subtypes is not further incorporated to recommend specific treatment options to specific subgroups of hand eczema. Our flow chart distinguishes clinical subtypes of hand eczema according to classification of the Danish contact Dermatitis Group. Because of this classification, we slightly differ from the guidelines of the ESCD. Alitretinoin is a highly appreciated treatment option for the most
subtypes of hand eczema. However, in our opinion, altretinoin should not be preferred for recurrent vesicular hand eczema, but we recommend the use of cyclosporine. This can be considered as a controversial statement given the level of evidence for altretinoin.\textsuperscript{49-51,61} In addition, cyclosporine is not registered for the treatment of hand eczema, only for the treatment of atopic dermatitis. However, based on clinical experience, the findings in chapter 4 and the limited efficacy of altretinoin in clinical trials in this subtype, we consider this justified. Though, further studies are needed.

**Future perspectives**

This thesis demonstrates various hiatuses in our knowledge regarding hand eczema. First, there is no consensus regarding the definition of hand eczema and the classification of its subtypes. The textbook definition of hand eczema is “noninfectious skin inflammation of the hands”. For chronic hand eczema Diepgen’s definition is widely accepted: “hand eczema which exists for more than three months or which returns twice or more within 12 months despite adequate dermatological therapy and patient compliance.”\textsuperscript{11} In chapter 2 we encountered various time slots for the definition of ‘chronic’, such as six weeks or six months. International consensus regarding this last definition is important in order to improve uniformity in clinical trials. However, the differences in the definition of chronic hand eczema seem relatively insignificant compared to the lack of consensus regarding classification of subtypes of hand eczema. Several contradicting articles have been published.\textsuperscript{10,62,63} Some groups use etiological subtypes, others clinical, and still others a combination of etiological and clinical subtypes. We would like to recommend the clinical classification as described by the Danish Contact Dermatitis Group,\textsuperscript{10,62} though slightly adjusted. We would include a more detailed description of the clinical subtype ‘chronic fissured dry hand eczema’ since, as reported in chapter 5, a wide range of different morphological types can be included under this subtype. The tool in chapter 5 includes the localization on the hand and the morphology, which results in a clinical diagnosis. This tool should be expanded with the factor ‘time’ to distinguish chronic from acute hand eczema and to further determine the nature of recurrent vesicular hand eczema. This could be an important step toward consensus regarding these subtypes.

In the Cochran review we encountered first of all a wide range of systems for scoring severity of the disease, and newer and improved scoring systems are still being developed. Weistenhöfer et al. demonstrated a maze of different, often unvalidated, scoring systems: 45 different methods for quantifying hand eczema were identified in 69 articles.\textsuperscript{64} The different scoring systems included either the extent of the hand eczema, the morphological characteristics, subjective criteria, or a combination of these. Moreover, for the majority of the scoring systems, inter and intra observer reliability were not studied. To reach a consensus regarding the scoring of severity we would advocate the approach
of OMERACT (Outcome Measures in Rheumatology) and HOME (Harmonizing Outcome Measures for Eczema). The HOME initiative aims to facilitate an international, multidisciplinary consensus on core outcome measures to be included in all eczema trials and clinical record keeping: it also aims to identify other relevant issues for eczema outcome research. The use of standardized endpoints in randomized controlled trials and in observational studies is vital in that it facilitates comparisons of outcomes across studies in different study populations, which as we learned in chapter 2 is frankly impossible in current studies. Moreover, a minimal set of outcome measures would improve the quality of studies overall; some studies included in chapter 2 used outcomes which were barely relevant in daily practice.

Consensus regarding the definition of hand eczema and its subtypes, and the development or recommendation of a single severity scoring system are essential for evidence based medicine.

A second important observation of the Cochrane review was the lack of well-designed randomized controlled trials comparing major treatment groups. We therefore present an urgent appeal for such studies. At the time of writing, alitretinoin is, in the Netherlands, the only registered treatment for chronic hand eczema. Other treatment options such as cyclosporine or acitretin are used off-label. In clinical trials alitretinoin was effective in the majority of hand eczema patients, though it is effective only in 33% of patients with vesicular hand eczema. Based on the findings of chapter 4, cyclosporine might be more effective in patients with recurrent vesicular hand eczema. Therefore we would like to propose a clinical trial which compares the efficacy of alitretinoin and cyclosporine. Schmitt designed such a trial and registered it at clinicaltrials.gov. This trial aimed to compare the efficacy and safety of cyclosporine and alitretinoin in the treatment of severe atopic hand dermatitis. Although unfortunately this study was ended prematurely because of the inability to include a sufficient number of patients, the need for such research is obvious.

The perfect study would compare the efficacy of cyclosporine and alitretinoin in different clinical types of chronic hand eczema, starting with recurrent vesicular hand eczema, since a relatively large number of patients suffer from recurrent vesicular hand eczema and this group seems to benefit the least from alitretinoin.

The study should include proper outcome measures. The primary outcome would preferably be an objective observer-rated severity score, such as the HECSI. Patient-rated outcomes should be included prominently in the secondary outcomes. Quality of life is an important subjective outcome parameter. The DLQI seemed to correlate with the HECSI, though a scoring system specific for hand eczema patients would be preferred. Recently, an interna-
tional group of experts developed the German Quality of Life in Hand Eczema Questionnaire (QOLHEQ). The QOLHEQ scores the health related quality of life for hand eczema patients in different domains (symptoms, emotions, functioning, and treatment) and is currently being translated into Dutch. This instrument will be a valuable addition to the existing dermatological quality of life scoring systems such as the SKINDEX and the DLQI. Further, other patient-rated outcomes such as itching, loss of sleep and productivity loss should be included. The number and severity of adverse events should be registered throughout the study. Finally, we highly recommend a cost-effectiveness analysis, including health care costs and patient expenses (absence from work, out-of-pocket expenses). The study would require a minimum duration of 24 weeks, since hand eczema is a chronic relapsing condition. During the study, all participants would be advised to continue the use of emollients.

One of the main difficulties Schmitt encountered in his study was the lack of naïve patients (patients who had never before received alitretinoin or cyclosporine). However, as demonstrated by the multivariate analysis in chapter 4, being naïve does not significantly influence the outcome of the systemic therapy. Moreover, the majority of our patients received multiple episodes of systemic therapy, and the effectiveness during a second or third episode is not necessarily better or worse in the following episodes. The requirement to include naïve patients can therefore be negated, or the study could be conducted in a multicenter setting to achieve a substantial number of patients. Including a sufficient number of patients is important in order to draw valid conclusions with sufficient statistical power. The majority of the studies in the Cochrane review did not, however, include a sample size rationale. The sample size calculation is usually based on the power ($\beta = 80$ or $90\%$), the level of significance ($\alpha = 0.05$) and the expected difference in the primary outcome of the study. To do so, consensus regarding the primary outcome and the clinical relevant difference is necessary. Reports on the study should adhere to the updated CONSORT (Consolidated Standards of Reporting Trials) statement. The CONSORT statement provides a checklist of 25 items which should be reported for each randomized controlled trial. Such reporting facilitates complete and transparent reporting of trials and aids in critical appraisal and interpretation. Observational studies should be reported according to the STROBE (STrengthening the Reporting of OBServational studies in Epidemiology) statement.

Several questions remain unanswered, including: a comparison between alitretinoin and cyclosporine; a comparison of various potencies of topical corticosteroids and the taper regime; a comparison between phototherapy and potent topical therapy; and so on. We are also still waiting for long-term results of studies regarding counseling and education. With regard to intervention studies, much remains to be explored.
Not only interventions, but also the causality of hand eczema needs more attention in the research. Studies of its genetic makeup should be included. Thyssen et al. took the first steps with their research into the association between xerosis, atopic dermatitis, hand eczema and contact sensitization, and filaggrin gene mutations. Filaggrin mutations are known for their role in atopic dermatitis and skin barrier dysfunction, and seemed to be associated with the chronic dry fissured type of hand eczema. Moreover, hand eczema in patients with atopic dermatitis and filaggrin null mutations had an earlier onset and was more persistent (OR 2.98; 95% confidence interval 1.27-7.01) than in controls. We currently lack studies regarding the distinct groups of hyperkeratotic palmar eczema and recurrent vesicular hand eczema; however, since large population based studies are being conducted and gene mapping is a developing area, in the next few years the genes responsible for these specific subtypes may be revealed.

Several times in this thesis we have emphasized the need for better definitions of subtypes; one of these subtypes is hyperkeratotic palmar eczema. Hyperkeratotic eczema could be caused by repeated trauma or a dysfunction in keratinisation, but the exact mechanism is unknown. Further studies into the histology and pathophysiology of this eczema might provide insight into this mechanism and whether hyperkeratotic palmar eczema is truly a form of hand eczema or something entirely different.

In this thesis I would like to advocate setting up well-designed randomized controlled trials of at least 24 weeks in order to compare different treatment groups. The quality of such studies would greatly benefit from more precise definitions of the types of hand eczema and their clinical subtypes. For this purpose international consensus is indispensable.
References


2. Rothwell PM. External validity of randomised controlled trials: “to whom do the results of this trial apply?” Lancet 2005;365:82-93.


47. van Coevorden AM, Coenraads PJ, Stant AD, Duizendstraal A. Thuisbehandeling van handeczema met PUVA (THP). 2002:VAZ/CVZ 99252.


van der Schaft J, Politiek K, Schuttelaar MLA, de Bruin-Weller MS. Drug survival for cyclosporin A in a long-term daily practice cohort of adult patients with atopic dermatitis. manuscript in preparation.


Agarwal US, Besarwal RK. Topical clobetasol propionate 0.05% cream alone and in combination with azathioprine in patients with chronic hand eczema: an observer blinded randomized comparative trial. Indian J Dermatol Venereol Leprol 2013;79:101-103.


