University of Groningen

The Challenge of Hand Eczema

Politiek, Klazien

DOI:
[10.33612/diss.133205005](https://doi.org/10.33612/diss.133205005)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):
Politiek, K. (2020). *The Challenge of Hand Eczema: Pathogenesis, Treatment, and Burden of Disease*. [Thesis fully internal (DIV), University of Groningen]. <https://doi.org/10.33612/diss.133205005>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

The Challenge of Hand Eczema

Pathogenesis, Treatment, and Burden of Disease

Klaziene Politiek

2020

ISBN: 978-94-6361-450-4

© Copyright 2020 K. Politiek, The Netherlands

No part of this thesis may be reproduced in any form or by any means, without prior permission of the author. The copyrights of the publications remain with the publisher, unless stated otherwise.

Financial support for the publication of this thesis was provided by:

Sanofi, Almirall, Galderma, LEO Pharma, DermaCura, Eurocept Homecare, La Roche Posay, Eucerin, Researchfonds Dermatologie, Rijksuniversiteit Groningen, Universitair Medisch Centrum Groningen, Vereniging voor Mensen met Constitutioneel Eczeem.

The study in Chapter 2 was supported by Stichting Milieu en Arbeidsdermatologie.

Design:	A.E. Koops
	Source image race bike: Freepik.com
Lay-out:	A.E. Koops
Printed by:	Optima

**rijksuniversiteit
 groningen**

The Challenge of Hand Eczema

Pathogenesis, Treatment, and Burden of Disease

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. C. Wijmenga
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 23 september 2020 om 18.00 uur

door

Klaziena Politiek

geboren op 18 januari 1989
te Sneek

Promotor

Dr. M.L.A. Schuttelaar

Prof. dr. P.J. Coenraads

Beoordelingscommissie

Prof. dr. S.A. Reijneveld

Prof. dr. P. Elsner

Prof. dr. M. Fartasch

Paranimfen

Wianda Christoffers

Marjolein Koldijk

Table of Contents

Chapter 1	General Introduction	11
Part I – Pathogenesis		
Chapter 2	Hyperkeratotic Hand Eczema – Eczema or not?	29
Part II – Treatment of Hand Eczema		
Chapter 3	Alitretinoin and Acitretin in severe chronic Hand Eczema – Results from a retrospective daily practice study	53
Chapter 4	Drug Survival of Cyclosporine in Hand Eczema – A multicentre, daily use study	65
Chapter 5	Drug Survival of Methotrexate Treatment in Hand Eczema Patients – Results from a retrospective daily practice study	75
Chapter 6	Azathioprine Treatment and Drug Survival in Patients with chronic Hand Eczema – Results from daily practice	83
Part III – Burden of Hand Eczema		
Chapter 7	Quality of Life, Treatment Satisfaction, and Adherence to Treatment in Patients with vesicular Hand Eczema – A cross-sectional study	95
Chapter 8	Systematic Review of Cost-of-Illness Studies in Hand Eczema	111
Part IV		
Chapter 9	General Discussion and Future Perspectives	131
Chapter 10	Summary	143
Chapter 11	Samenvatting	149
Appendices		

List of abbreviations

ACD:	allergic contact dermatitis
AD:	atopic dermatitis
AE:	adverse event
AHE:	atopic hand eczema
ARIA:	allergic rhinitis and its impact on asthma
CHE:	chronic hand eczema
COSMIN:	consensus-based standards for the selection of health measurement instruments
CsA:	cyclosporine
CU:	contact urticaria
DLQI:	dermatology life quality index
DSC:	desmocollin
DSG:	desmoglein
DSP:	desmoplakin
ECS:	epidermal cell surface
FLG:	filaggrin
GINA:	global Initiative for asthma
HC:	healthy control
HE:	hand eczema
HECSI:	hand eczema severity index
HHE:	hyperkeratotic hand eczema
HR:	hazard ratio
HRQoL:	health-related quality of life
H&E:	hematoxylin and eosin
ICD:	irritant contact dermatitis
IHC:	immunohistochemistry
IF:	immunofluorescence
IL:	interleukin
INV:	involucrin
JAK:	janus-activated kinases
K:	keratin
KLK:	kallikrein-related peptidase
LOR:	loricrin
MMAS:	morisky medication adherence scale
METc:	medical ethical review board
MTX:	methotrexate
OHI:	occupational health insurance
PCD:	protein contact dermatitis
PG:	plakoglobin
PGA:	physician's global assessment
PKP:	plakophilin

PPK:	palmar plantar keratoderma
PRISMA:	preferred reporting items for systematic reviews and meta-analyses
PUVA:	psoralen and ultraviolet A
QOLHEQ:	quality of life in hand eczema questionnaire
qPCR:	quantitative polymerase chain reaction
RAR:	retinoic acid receptor
RCT:	randomized controlled trial
RXR:	retinoid X receptor
sIgE:	specific inhalant immunoglobulin E
SD:	standard deviation
SF-HLQ:	short version of the health and labour questionnaire
SPINK5:	serine protease inhibitor kazal type 5
TNF:	tumor necrosis factor
TSQM:	treatment satisfaction questionnaire for medication
UMCG:	university medical center Groningen
UMCU:	university medical center Utrecht
UV:	ultraviolet
VHE:	vesicular hand eczema
VOUS:	variants of unknown significance
WES:	whole exome sequencing

Klazien Politek

Department of Dermatology, University Medical Center Groningen,
University of Groningen, Groningen, the Netherlands

Chapter 1

General Introduction

Introduction

Hand eczema is an inflammatory skin disease that tends to run a chronic, relapsing course. It is a common condition in the general population. A review of previous studies in mainly Scandinavian countries showed a lifetime prevalence of about 15%, with an average 1-year prevalence of 6.4% in men and 10.5% in women.¹

A recent study in Norway showed an even higher self-reported hand eczema prevalence of 11.3% in 50,805 respondents; 8.4% in men and 13.8% in women.² It should be noted that these prevalences also include mild cases. Although patients can develop hand eczema at all ages, one-third develop the disease before the age of 20.³ An exception is hyperkeratotic hand eczema, which is most often seen in middle-aged patients.⁴

Pathogenesis

Most cases of hand eczema have a multifactorial etiology, consisting of a combination of endogenous and exogenous factors.⁵ Aspects of these factors will be discussed in the following paragraphs.

Skin barrier function

A skin barrier dysfunction contributes to the pathogenesis of hand eczema. Impairment of the skin barrier due to genetic and exogenous factors allows for easier penetration of irritants, allergens and microorganisms. The cornified envelope, consisting of terminally differentiating keratinocytes in an insoluble protein-lipid matrix, plays an essential role in the skin barrier function. A major component of the cornified envelope is filaggrin. Filaggrin contributes to the structure and function of the stratum corneum. It aggregates intermediate filaments and inhibits transepidermal water loss.⁶ Filaggrin is known to be a strong genetic risk factor in atopic dermatitis (AD), and is therefore the most extensively studied gene in hand eczema. Studies showed that patients with AD and filaggrin gene (*FLG*) mutations had a significantly increased risk of hand eczema, and early-onset and persistent hand eczema.^{7,8} However, there are no independent associations between *FLG* mutations and the risk of hand eczema.⁸⁻¹¹ Another gene associated with the regulation of the skin barrier function is the serine protease inhibitor Kazal type 5 (*SPINK5*) gene. A study in Taiwanese nurses found distinct variants of the *SPINK5* gene to be associated with the development of atopic eczema (including atopic hand eczema, 48%) and non-atopic hand eczema.¹² Besides gene mutations, also expression of epidermal barrier proteins was examined. Molin et al. investigated whole protein expression in lesional skin biopsies of 6 chronic hand eczema patients. They found a downregulation of the barrier proteins filaggrin, filaggrin-2, and hornerin, as well as of the desquamation-related enzymes kallikrein-related peptidase (KLK) 5 and KLK7, and cystatin E/M. The antimicrobial peptides S100A7 and S100A8/A9 and the small proline-rich protein 2B and S100A11 were upregulated in diseased skin, confirming a skin barrier dysfunction.¹³ Another study by Wang et al. examined the expression of caspase-14 in the stratum corneum of 30 patients and 30 healthy controls. Caspase-14 is a protein important in processing filaggrin monomers and producing natural moisturizing factors in the skin. In chronic hand eczema patients the study reported a downregulation of caspase-14.¹⁴ Jungersted et al. investigated skin barrier function in adjacent stratum corneum samples of 2 different conditions (allergic/irritant ($n=23$) and hyperkeratotic hand eczema ($n=15$)). They found no differences between stratum corneum lipids or skin barrier impairment in the non-lesional skin of these different hand eczema subtypes.¹⁵

Genetic susceptibility

The above data confirmed the role of a genetic predisposition in the risk of hand eczema. This influence of genetic factors was supported by studies with twins.^{16,17} Monozygotic twins with a co-twin with hand eczema showed twice as high an incidence of hand eczema as dizygotic twins with a co-twin with hand eczema. Genetic modeling of these data indicated that genetic risk factors have a moderate effect on the liability of developing hand eczema. Forty-one percent of the etiological background of hand eczema could be explained by endogenous (individual) variables and 59% by exogenous exposures.¹⁷

Etiological risk factors

The most important etiological risk factors for developing hand eczema are a history of AD, repeated contact with irritants, and contact allergies (Figure 1).^{18,19}

In patients with hand eczema, irritant contact dermatitis (ICD) is the most frequent etiological diagnosis.²⁰ Irritants induce disruption of the skin barrier and lead to an inflammatory reaction, mediated mainly by the innate immunity.²¹ The risk of developing an ICD involves a complex interaction of endogenous factors that influence skin barrier function (such as AD and/or *FLG* mutations) and exogenous exposures (like wet work, chemical detergents, dust, soil and physical irritants).^{10,21,22} It follows that jobs in healthcare, kitchen work, service and cleaning create more risk, and most likely explain the higher prevalence in women.^{23–25} AD, past or present, is an important endogenous risk factor for the development of ICD.²¹ Patients with AD have a three- to four-fold increased risk of hand eczema compared to controls.²⁶ Moreover, children with persistent or more severe AD have a greater risk of developing atopic hand eczema (AHE) as young adults.²⁷ However, no association exists between hand eczema and other 'atopic' diseases such as asthma, rhinoconjunctivitis and/or positive specific IgE levels.^{3,27,28} Allergic contact dermatitis (ACD) is less common than ICD, although it should always be excluded in case of chronic hand eczema.²⁹ A delayed-type hypersensitive immune response gradually develops after contact with the hapten, and can be diagnosed using epicutaneous patch tests. The characteristic common to ACD and other (etiological) hand eczema subtypes is the skin barrier dysfunction. This results in an easier cutaneous penetration of allergens and irritants, but also induces local immune activation. This may be the reason why an ACD is often preceded by an ICD.³⁰ Finally, a less common etiological cause, which should be considered among workers in the food industry, is a protein-contact dermatitis (PCD). The initial reaction after contact with a protein is caused by a IgE-mediated sensitization and results in a contact urticaria (CU), over time followed by eczema.^{18,31}

In addition to the well-known etiological risk factors mentioned above, the relationship between lifestyle factors and hand eczema has drawn a marked interest in the last decade. In particular, the use of tobacco has been extensively investigated. Recent studies seem to point in the direction of an association between tobacco smoke and an increased prevalence and severity of hand eczema, mainly in occupational hand eczema.^{32–36} However, in previous studies the relation between hand eczema and lifestyle factors like stress, alcohol consumption and obesity were debatable.^{32,37,38} Two previous studies showed that exercise was associated with positive effects on hand eczema. Individuals who have regular endurance and/or high physical exercise reported hand eczema less frequently compared to patients who do little or no exercise.^{35,37} Compared to studies of AD and psoriasis, among others, regarding hand eczema fewer studies about the role of skin microbiome have been published.³⁹ Only colonization of staphylococcus aureus has been examined. Previous

studies showed colonization by staphylococcus aureus bacteria in more than half of the patients, and also reported an association with more chronic and severe hand eczema.^{40–42}

Altogether, the above literature demonstrated a complex interaction between skin barrier function, genetic predisposition, and multiple environmental risk factors. However, an exact pathogenesis of hand eczema remains largely unknown, and has not been elucidated for different hand eczema subtypes.

Figure 1. Multi-factorial pathogenesis of chronic hand eczema, with skin barrier dysfunction seen as common denominator interferes with the most common etiological risk factors: atopic dermatitis, exposure to irritants and exposure to contact allergens.

○ allergen; * irritant; Δ lymphocyte

Histopathology

A few studies focused on the histopathology of hand eczema, dealing mainly with hyperkeratotic and dry fissured forms. These studies reported common histological findings, like spongiotic dermatitis, epidermal hyperplasia and parakeratosis. It can be difficult for clinicians to distinguish hyperkeratotic subtypes from palmar psoriasis, since histological findings have an overlap (among others: confluent parakeratosis, psoriasiform elongated rete ridges, clubbing and anastomosis of the rete ridges).^{43–46} **Chapter 2** evaluates the histopathology of hyperkeratotic hand eczema, and discusses immunofluorescent stainings of different keratins, epidermal barrier proteins and adhe-

sion molecules. In addition, to further elucidate the pathogenesis of hyperkeratotic hand eczema, all patients were screened for variants in genes related to palmoplantar keratoderma.

Diagnosis

Hand eczema is a clinical diagnosis. In daily practice, histopathological examination is rarely necessary. However, one can consider a biopsy when hand eczema is refractory to therapy or when other diagnoses need to be excluded.⁴⁷ The differential diagnosis of hand eczema can, among others, include psoriasis, dermatomycosis, scabies and lichen planus.

No consensus has yet been reached on the classification of hand eczema. The current classification systems include information on etiology (ICD, ACD, AHE, PCD/CU), morphology (e.g. hyperkeratotic, vesicular), location (e.g. pulpitis, interdigital, palmar) and temporal variation (acute, recurrent or chronic).⁴⁸

Two main classification systems have been described. Agner et al. defined a combined etiological/morphological classification system with 6 subgroups: ICD – ACD – AHE – PCD/CU –hyperkeratotic endogenous hand eczema and vesicular endogenous hand eczema.²⁰ Patients were classified into one of the six subgroups and an additional diagnosis could be made if contributing factors were of importance for the diagnosis. Due to the multi-causality of hand eczema, often one or more additional diagnoses were given. For example, ACD was often combined with a sub-diagnosis of ICD. However, some patients could not be allocated to any of the subgroups and were diagnosed as 'unclassified'.

The Danish Contact Dermatitis Group described a classification system using clinical definitions in order to classify each patient under one of the six morphological subgroups (Figure 2). Besides the morphological diagnosis, patients can have one or more etiological diagnoses.³¹ In around 20% of all patients no etiological factor could be found, most frequently among patients with hyperkeratotic hand eczema.⁴⁹ An unresolved problem in both classification systems is that etiological and morphological subgroups overlap (at least partially) and may change significantly over time. In this thesis, for morphological and etiological diagnosis we will further use the classification system from the Danish Contact Dermatitis Group.³¹

Treatment

Non-pharmacological interventions, such as education about exposure to irritants and allergens and use of emollients, are important for every hand eczema patient, since in most cases a skin barrier dysfunction is present.

Along with emollients, the first-line treatment in the management of hand eczema is application of a (potent) topical corticosteroid, often for at least 6 weeks. Other treatments, like tacrolimus ointment and different forms of UV-therapy (local PUVA and UVB), can be considered if topical corticosteroids cannot be reduced or symptoms do not respond to treatment. An estimated 2–4% of hand eczema patients are unresponsive to first-line treatment with topical corticosteroids. This group requires systemic (oral) treatment.^{29,50} Alitretinoin is recommended as second-line treatment. This vitamin A derivative or retinoid, is the only licensed systemic treatment for hand eczema. Alitretinoin was studied in large randomized controlled trials with more than 1600 participants and showed positive effects on all hand eczema subtypes.^{51–53} Treatment with 30 mg/day of alitretinoin resulted in clear or almost clear hand eczema in 48% of the participants, compared

Figure 2. Examples of the morphological subtypes, adapted from Menné et al.³¹

with 17% of those receiving a placebo.⁵² The best therapeutic effects were found for the hyperkeratotic subtypes.^{52–54}

Evidence about effectiveness of other systemic hand eczema treatments is scarce, and large randomized controlled trials are lacking.^{29,54} Regularly used off-label treatment alternatives for severe hand eczema are systemic corticosteroids, azathioprine,⁵⁵ methotrexate,^{56,57} acitretin^{58–60} and, more recently, dupilumab.^{61,62}

In case of acute symptoms, systemic corticosteroids can be considered as treatment (generally for a maximum of three weeks). However, chronic use is not recommended due to potentially harmful long-term effects. Ciclosporin is used to treat chronic severe hand eczema, and may be considered if first- and second-line treatments are insufficient or contra-indicated.^{63,64}

Chapters 3–6 discuss real life effectiveness, using drug survival analyses of the above-mentioned ‘classic’ systemic treatments in a daily practice cohort of hand eczema patients. Drug survival refers to the ‘time on drug’ and is thought to be a comprehensive outcome, covering efficacy, safety, and patients’ and doctors’ preferences.^{65,66} This method was used during the last decades to reflect real life treatment in, among others, dermatology^{67,68} and rheumatology.⁶⁹

Burden of Hand Eczema

Hand eczema is associated with itch, pain, social stigma and impairment in employment. It is one of the most frequent work-related diseases and often has far-reaching personal consequences.^{78,79} Hand eczema patients were found to have a similar degree of impairment of health-related quality of life (HRQoL) and psychological burden as patients with AD and psoriasis.^{62,79–82} This implies that hand eczema, with its involvement of visible parts of the body and often a functional impairment, has an even greater impact on mental health than skin lesions localized elsewhere. Hand eczema severity is negatively associated with HRQoL and also influences the development of mental disorders.^{79,83,84} Furthermore, treatment of chronic hand eczema can be challenging and, at times, insufficient and unsatisfactory.^{85,86} Most literature about treatment effectiveness is based on outcomes reported by physicians, and only few studies evaluate treatment benefit from the perspective of patients. Assessment of patient-reported outcomes better characterize the key symptoms and impact experienced by patients with dermatologic diseases.^{87,88} **Chapter 7** presents an evaluation, during maintenance treatment, of disease-specific health-related quality of life in vesicular hand eczema patients. Treatment satisfaction and treatment adherence were also studied in this subgroup of hand eczema patients.

In addition to affecting patients’ health-related quality of life, chronic hand eczema can limit their ability to carry out some occupations. In particular, hand eczema of occupational origin frequently results in productivity loss, owing to presenteeism (‘attending work despite having hand eczema, which should prompt rest and absence’), absenteeism, or even job loss.^{84,89} Compared to other occupational diseases, hand eczema generally affects younger people. Many patients are in the middle of a busy life phase in terms of work, career and small children. This causes an even greater socio-economic burden.^{83–85} Individual costs-of-illness will differ between patients and depend, among others, on factors like severity and occupational sector, and subsequent consequences like costs of healthcare and treatment.^{78,90–94} **Chapter 8** of this thesis presents a review of the costs of illness in hand eczema.

Table 1. Mode of action of various systemic treatments of hand eczema

Compound	Mode of Action	Most important Adverse Events
Alitretinoin ^{70,71} (9-cis RA)	Vitamin A derivative (retinoid), 1st generation, natural ligand Binds to both retinoic acid receptor (RAR) and retinoid X receptor (RXR) Effects on cell proliferation, cell differentiation, apoptosis, angiogenesis, keratinization and immunomodulation	Teratogenicity Lipid abnormalities Psychiatric effects
Acitretin ⁷²	Synthetic monoaromatic retinoid, 2nd generation Binds selectively to retinoic acid receptor (RAR) Inhibits keratinocyte production of vascular endothelial growth factor and inhibits neutrophil migration	Teratogenicity Lipid abnormalities Psychiatric effects
Azathioprine ^{73,74}	Prodrug of mercaptopurin Interference with purine base production and DNA/RNA synthesis Depression of cell-mediated immunity	Bone marrow suppression Hepatotoxicity Risk of malignancies
Ciclosporin ⁷⁵	Inhibits T-cell activation by interfering with calcium dependent signaling events involved in cytokine transcription Affects interleukin-2 production, B cells and dendritic cells	Nephrotoxicity Hypertension Risk of malignancies
Dupilumab ⁷⁸	Human monoclonal antibody against the interleukin (IL)4 α Inhibits both IL-4 and IL-13 cytokine-induced responses, including proinflammatory cytokines, chemokines and IgE	Conjunctivitis (risk related to underlying atopic dermatitis pathogenesis) Injection-site reaction
Methotrexate ^{73,74}	Anti-inflammatory effects through augmenting concentration of adenosine, which acts as an endogenous anti-inflammatory agent Modulating cytokine release and adhesion molecule expression	Myelosuppression (early phase) Hepatotoxicity Interstitial pneumonitis Risk of malignancies
Oral corticosteroids ⁷⁷	Various immunosuppressive and anti-inflammatory effects Effects on cell migration and phagocytosis by leucocytes and monocytes	Alteration in glucose tolerance High blood pressure Osteoporosis Psychiatric effects

Aim and Outline of the Thesis

The main aims of this thesis are:

1. To gain more insight into the pathogenesis of hyperkeratotic hand eczema by focusing on histopathology, immunofluorescent stainings of important epidermal components, and genetic aspects of palmar hyperkeratosis.
2. To contribute to the knowledge about effectiveness and safety of (off label) use in daily practice of classic systemic treatments for chronic hand eczema
3. To investigate health-related quality of life, treatment satisfaction, and adherence during treatment of patients with chronic recurrent vesicular hand eczema
4. To gain insights into cost-of-illness of patients with chronic hand eczema by reviewing mean direct and indirect costs for patients and society

These aims will be addressed in three parts, consisting of the following chapters:

Part I – Chapter 2 starts with a study regarding the pathogenesis of hyperkeratotic hand eczema. In this study we describe the histopathology and expression of keratins, epidermal barrier proteins, and adhesion molecules in hand eczema. Gene variants of palmar hyperkeratosis will also be discussed.

Part II – Chapters 3–6 focus on drug survival in different systemic treatments of severe hand eczema, providing data on effectiveness and safety in daily practice. The four chapters discuss retrospective studies of various systemic treatments, using data collected in the University Medical Center Groningen and the University Medical Centre Utrecht.

Part III of this thesis explores the impact of hand eczema in terms of health-related quality of life, treatment satisfaction, and cost of illness. **Chapter 7** is a cross-sectional study of health-related quality of life, treatment satisfaction, and treatment adherence in a patient cohort with chronic recurrent vesicular hand eczema. **Chapter 8** provides a systematic review of cost-of-illness in hand eczema, including summary and analysis of the available literature.

The main findings of this thesis are reviewed and discussed in **Chapter 9**, together with our view on future research perspectives.

References

1. Thyssen JP, Johansen JD, Linneberg A, Menné T. The epidemiology of hand eczema in the general population--prevalence and main findings. *Contact Dermatitis*. 2010 Feb;62(2):75–87.
2. Vindenes HK, Svanes C, Lygre SHL, Hollund BE, Langhammer A, Bertelsen RJ. Prevalence of, and work-related risk factors for, hand eczema in a Norwegian general population (The HUNT Study). *Contact Dermatitis*. 2017;77(4):214–23.
3. Meding B, Jarvholm B. Incidence of hand eczema—a population-based retrospective study. *J Invest Dermatol*. 2004 Apr;122(4):873–7.
4. Brans R, John SM. Clinical patterns and associated factors in patients with hand eczema of primarily occupational origin. *J Eur Acad Dermatology Venereol*. 2016;30(5):798–805.
5. Molin S. Pathogenese des Handekzems Pathogenesis of hand eczema. *Der Hautarzt*. 2019;70(10):755–9.
6. Brown SJ, McLean WHI. One remarkable molecule: Filaggrin. *J Invest Dermatol*. 2012;132(3 PART 2):751–62.
7. Thyssen JP, Carlsen BC, Menné T et al. Filaggrin null mutations increase the risk and persistence of hand eczema in subjects with atopic dermatitis: Results from a general population study. *Br J Dermatol*. 2010;163(1):115–20.
8. Visser MJ, Landeck L, Campbell LE et al. Impact of atopic dermatitis and loss-of-function mutations in the filaggrin gene on the development of occupational irritant contact dermatitis. *Br J Dermatol*. 2013;168(2):326–32.
9. Lerbaek A, Bisgaard H, Agner T, Ohm Kyvik K, Palmer CNA, Menné T. Filaggrin null alleles are not associated with hand eczema or contact allergy. *Br J Dermatol*. 2007;157(6):1199–204.
10. Visser MJ, Verberk MM, Campbell LE et al. Filaggrin loss-of-function mutations and atopic dermatitis as risk factors for hand eczema in apprentice nurses: Part II of a prospective cohort study. *Contact Dermatitis*. 2014;70(3):139–50.
11. Palmer CN, Irvine AD, Terron-Kwiatkowski A et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet*. 2006;38(4):441–6.
12. Lan C-CE, Tu H-P, Wu C-S et al. Distinct SPINK5 and IL-31 polymorphisms are associated with atopic eczema and non-atopic hand dermatitis in Taiwanese nursing population. *Exp Dermatol*. 2011;20(12):975–9.
13. Molin S, Merl J, Dietrich KA et al. The hand eczema proteome: imbalance of epidermal barrier proteins. *Br J Dermatol*. 2015;172(4):994–1001.
14. Wang B, Liu LL, Zhao ZT, Tu P. Impaired skin barrier function and downregulated expression of caspase-14 in moderate to severe chronic hand eczema. *Dermatology*. 2018;234(5–6):180–5.
15. Jungersted JM, Høgh JK, Høllgren LI, Wilkinson S, Jemec GBE, Agner T. Hand eczema and stratum corneum ceramides. *Clin Exp Dermatol*. 2015;40(3):243–6.
16. Bryld LE, Agner T, Kyvik KO, Brøndsted L, Hindsberger C, Menné T. Hand eczema in twins: A questionnaire investigation. *Br J Dermatol*. 2000;142(2):298–305.
17. Lerbaek A, Kyvik KO, Mortensen J, Bryld LE, Menné T, Agner T. Heritability of Hand Eczema Is Not Explained by Comorbidity with Atopic Dermatitis. *J Invest Dermatol*. 2007;127(7):1632–40.
18. Coenraads PJ. Hand eczema. *N Engl J Med*. 2012;367(19):1829–37.
19. English J, Aldridge R, Gawkrödger DJ et al. Consensus statement on the management of chronic hand eczema. *Clin Exp Dermatol*. 2009;34(7):761–9.
20. Agner T, Aalto-Korte K, Andersen KE et al. Classification of hand eczema. *J Eur Acad Dermatology Venereol*. 2015;29(12):2417–22.
21. Bains SN, Nash P, Fonacier L. Irritant Contact Dermatitis. *Clin Rev Allergy Immunol*. 2019;56(1):99–109.
22. Behroozy A, Keegel TG. Wet-work Exposure: A Main Risk Factor for Occupational Hand Dermatitis. *Saf Health Work*. 2014;5(4):175–80.
23. Meding B. Epidemiology of hand eczema in an industrial city. *Acta Dermato-Venereologica, Suppl*.
24. Diepgen TL, Andersen KE, Brandao FM et al. Hand eczema classification: A cross-sectional, multicentre study of the aetiology and morphology of hand eczema. *Br J Dermatol*. 2009;160(2):353–8.
25. Carøe TK, Ebbelhøj N, Agner T. A survey of exposures related to recognized occupational contact dermatitis in Denmark in 2010. *Contact Dermatitis*.

- 2014;70(1):56–62.
26. Ruff SMD, Engebretsen KA, Zachariae C et al. The association between atopic dermatitis and hand eczema: a systematic review and meta-analysis. *Br J Dermatol*. 2017;178(4):879–88.
27. Grönhagen C, Lidén C, Wahlgren CF et al. Hand eczema and atopic dermatitis in adolescents: a prospective cohort study from the BAMSE project. *Br J Dermatol*. 2015;173(5):1175–82.
28. Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE. Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. The Odense adolescence cohort study on atopic diseases and dermatitis. *Br J Dermatol*. 2001;144(3):523–32.
29. Diepgen TL, Andersen KE, Chosidow O et al. Guidelines for diagnosis, prevention and treatment of hand eczema--short version. *J Dtsch Dermatol Ges*. 2015;13(1):77–85.
30. Martin SF. New concepts in cutaneous allergy. *Contact Dermatitis*. 2015;72(1):2–10.
31. Menné T, Johansen JD, Sommerlund M, Veien NK. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. *Contact Dermatitis*. 2011;65(1):3–12.
32. Sørensen JA, Fisker MH, Agner T, Clemmensen KK, Ebbelhøj NE. Associations between lifestyle factors and hand eczema severity: are tobacco smoking, obesity and stress significantly linked to eczema severity? *Contact Dermatitis*. 2017;76(3):138–45.
33. Brans R, Skudlik C, Weisshaar E et al. Association between tobacco smoking and prognosis of occupational hand eczema: a prospective cohort study. *Br J Dermatol*. 2014;171(5):1108–15.
34. Sørensen JA, Clemmensen KK, Nixon RL, Diepgen TL, Agner T. Tobacco smoking and hand eczema – is there an association? *Contact Dermatitis*. 2015;73(6):326–35.
35. Olesen CM, Agner T, Ebbelhøj NE, Carøe TK. Factors influencing prognosis for occupational hand eczema: new trends. *Br J Dermatol*. 2019;181(6):1280–6.
36. Zimmer KA, Armbrrecht ES, Burkemper NM. The association of smoking with contact dermatitis and hand eczema – a review. *Int J Dermatol*. 2018;57(4):375–87.
37. Anveden Berglind I, Alderling M, Meding B. Life-style factors and hand eczema. *Br J Dermatol*. 2011;165(3):568–75.
38. Thyssen JP, Linneberg A, Menné T, Nielsen NH, Johansen JD. The effect of tobacco smoking and alcohol consumption on the prevalence of self-reported hand eczema: a cross-sectional population-based study. *Br J Dermatol*. 2010;162(3):619–26.
39. Heidi H. Kong and Julia A. Segre. Skin Microbiome: Looking Back to Move Forward. *J Invest Dermatol*. 2012;132(3):933–9.
40. Wang X, Xu W, Chen Y et al. Staphylococcus aureus colonization and chronic hand eczema: a multicenter clinical trial. *Arch Dermatol Res*. 2019;311(7):513–8.
41. Mernelius S, Carlsson E, Henricson J et al. Staphylococcus aureus colonization related to severity of hand eczema. *Eur J Clin Microbiol Infect Dis*. 2016;35(8):1355–61.
42. Haslund P, Bangsgaard N, Jarlov JO, Skov L, Skov R, Agner T. Staphylococcus aureus and hand eczema severity. *Br J Dermatol*. 2009;161(4):772–7.
43. Hersle K, Mobacken H. Hyperkeratotic dermatitis of the palms. *Br J Dermatol*. 1982;107(2):195–201.
44. Lim KB, Tan T, Rajan VS. Dermatitis palmaris sicca--a distinctive pattern of hand dermatitis. *Clin Exp Dermatol*. 1986;11(6):553–9.
45. Saeki H, Watanabe R, Tsunemi Y, Tamaki K. Severe hyperkeratotic palmoplantar eczema (eczema tylosicum). *J Dermatol*. 2009;36(6):362–3.
46. Park JY, Cho EB, Park EJ, Park HR, Kim KH, Kim KJ. The histopathological differentiation between palmar psoriasis and hand eczema: A retrospective review of 96 cases. *J Am Acad Dermatol*. 2017;77(1):130–5.
47. Diepgen TL, Elsner P, Schliemann S et al. Guideline on the management of hand eczema ICD–10 Code: L20. L23. L24. L25. L30. *J Dtsch Dermatol Ges*. 2009;7 Suppl 3:S1–16.
48. Thyssen JP, I Silverberg J, Guttman-Yassky E. Chronic Hand Eczema Understanding Has Ramifications On Clinical Management. *J Eur Acad Dermatology Venereol*. 2020;34(8):e429–e430.
49. Johansen JD, Hald M, Andersen BL et al. Classification of hand eczema: Clinical and aetiological types. Based on the guideline of the Danish Contact Dermatitis Group. *Contact Dermatitis*. 2011;65(1):13–21.
50. Diepgen TL, Agner T, Aberer W et al. Management

- of chronic hand eczema. *Contact Dermatitis*. 2007;57(4):203–10.
51. Ruzicka T, Larsen FG, Galewicz D et al. Oral alitretinoin (9-cis-retinoic acid) therapy for chronic hand dermatitis in patients refractory to standard therapy: results of a randomized, double-blind, placebo-controlled, multicenter trial. *Arch Dermatol*. 2004;140(12):1453–9.
 52. Ruzicka T, Lynde CW, Jemec GB et al. Efficacy and safety of oral alitretinoin (9-cis-retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: Results of a randomized, double-blind, placebo-controlled, multicentre trial. *The British journal of dermatology*. 2008;158(4):808–17.
 53. Bissonnette R, Worm M, Gerlach B et al. Successful retreatment with alitretinoin in patients with relapsed chronic hand eczema. *Br J Dermatol*. 2010;162(2):420–6.
 54. Christoffers W, Coenraads P, Svensson Å et al. Interventions for hand eczema. *Cochrane Database of Systematic Reviews* 2019, Issue 4. Art. No.: CD004055. DOI: 10.1002/14651858.CD004055.pub2. .
 55. Agarwal US BR. 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;79:101–3.
 56. Egan CA, Rallis TM, Meadows KP, Krueger GG. Low-dose oral methotrexate treatment for recalcitrant palmoplantar pompholyx. *J Am Acad Dermatol*. 1999;40(4):612–4.
 57. Mittal A, Khare A K, Gupta L, Mehta S, Garg A. Use of methotrexate in recalcitrant eczema. *Indian J Dermatol* 2011;56:232.
 58. Thestrup-Pedersen K, Andersen KE, Mennét, Veien NK. Treatment of hyperkeratotic dermatitis of the palms (eczema keratoticum) with oral acitretin. A single-blind placebo-controlled study. *Acta Derm Venereol* 2001;81(5):353–5.
 59. Capella GL, Fracchiolla C, Frigerio E, Altomare G. A controlled study of comparative efficacy of oral retinoids and topical betamethasone/salicylic acid for chronic hyperkeratotic palmoplantar dermatitis. *J Dermatolog Treat*. 2004;15(2):88–93.
 60. Tan J, Maari C, Nigen S, Bolduc C, Bissonnette R. Open-label exploratory study of acitretin for the treatment of severe chronic hand dermatitis. *J Dermatolog Treat*. 2014;26:1–3.
 61. Zirwas MJ. Dupilumab for hand eczema. *J Am Acad Dermatol*. 2018;79(1):167–9.
 62. Oosterhaven JAF, Voorberg AN, Romeijn GLE, de Bruin-Weller MS, Schuttelaar MLA. Effect of dupilumab on hand eczema in patients with atopic dermatitis: An observational study. *J Dermatol*. 2019;April:1346–8138.
 63. Granlund H, Erkkö P, Eriksson E, Reitamo S. Comparison of cyclosporine and topical betamethasone-17,21-dipropionate in the treatment of severe chronic hand eczema. *Acta Derm Venereol*. 1996 Sep;76(5):371–6.
 64. Reitamo S, Granlund H. Cyclosporin A in the treatment of chronic dermatitis of the hands. *Br J Dermatol*. 1994;130(1):75–8.
 65. Gniadecki R, Kragballe K, Dam TN, Skov L. Comparison of drug survival rates for adalimumab, etanercept and infliximab in patients with psoriasis vulgaris. *Br J Dermatol*. 2011;164(5):1091–6.
 66. van den Reek JM, Kievit W, Gniadecki R et al. Drug Survival Studies in Dermatology: Principles, Purposes, and Pitfalls. *J Invest Dermatol*. 2015;135(7):e34.
 67. van Den Reek JMPA, Van Lümig PPM, Driessen RJB et al. Determinants of drug survival for etanercept in a long-term daily practice cohort of patients with psoriasis. *Br J Dermatol*. 2014;170(2):415–24.
 68. van der Schaft J, Politiek K, van den Reek JM et al. Drug survival for cyclosporin A in a long-term daily practice cohort of adult patients with atopic dermatitis. *Br J Dermatol*. 2015;172(6):1621–7.
 69. Wijnands MJH, Van't Hof MA, Van Leeuwen MA, Van Rijswijk MH, Van De Putte LBA, Van Riel PLCM. Long-term second-line treatment: A prospective drug survival study. *Rheumatology*. 1992;31(4):253–8.
 70. Morris M, Schifano L, Fong R, Graff O. Safety of alitretinoin for severe refractory chronic hand eczema: Clinical studies and postmarketing surveillance. *J Dermatolog Treat*. 2015 Apr 17;1–5.
 71. Schmitt-Hoffmann A, Roos B, Schoetzau A et al. Oral alitretinoin: A review of the clinical pharmacokinetics and pharmacodynamics. *Expert Rev Clin Pharmacol*. 2012;5(4):373–88.
 72. Guenther LC, Kunynetz R, Lynde CW et al.

- Acitretin Use in Dermatology. *J Cutan Med Surg*. 2017;21(3):25–125.
73. Sidbury R, Davis DM, Cohen DE et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol*. 2014;71(2):327–49
 74. Schram ME, Roekevisch E, Leeflang MM, Bos JD, Schmitt J, Spuls PI. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. *J Allergy Clin Immunol*.
 75. Schmitt J, Schmitt N, Meurer M. Cyclosporin in the treatment of patients with atopic eczema – a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol*. 2007;21(5):606–19.
 76. Deleuran M, Thaçi D, Beck LA et al. Dupilumab shows long-term safety and efficacy in moderate-to-severe atopic dermatitis patients enrolled in a phase 3 open-label extension study. *J Am Acad Dermatol*. 2020;82(2):377–88.
 77. Schmitt J, Schakel K, Folster-Holst R et al. Prednisolone vs. ciclosporin for severe adult eczema. An investigator-initiated double-blind placebo-controlled multicentre trial. *Br J Dermatol*. 2010;162(3):661–8.
 78. Fowler JF, Ghosh A, Sung J et al. Impact of chronic hand dermatitis on quality of life, work productivity, activity impairment, and medical costs. *J Am Acad Dermatol*. 2006;54(3):448–57.
 79. Boehm D, Schmid-Ott G, Finkeldey F, John SM, Dwinger C, Werfel T, et al. Anxiety, depression and impaired health-related quality of life in patients with occupational hand eczema. *Contact Dermatitis*. 2012;67(4):184–92.
 80. Marron SE, Tomas-Aragones L, Navarro-Lopez J et al. The psychosocial burden of hand eczema: Data from a European dermatological multicentre study. *Contact Dermatitis*. 2018;78(6):406–12.
 81. Barbieri JS, Gelfand JM. Responsiveness of the EuroQol 5–Dimension 3–Level instrument, Dermatology Life Quality Index (DLQI) and DLQI –Relevant for patients with psoriasis in the U.S.A. *Br J Dermatol*. 2019;5–6.
 82. Dalgard FJ, Gieler U, Tomas-Aragones L et al. The Psychological Burden of Skin Diseases: A Cross-Sectional Multicenter Study among Dermatological Out-Patients in 13 European Countries. *J Invest Dermatol*. 2015;135(4):984–91.
 83. Agner T, Andersen KE, Brandao FM et al. Hand eczema severity and quality of life: A cross-sectional, multicentre study of hand eczema patients. *Contact Dermatitis*. 2008;59(1):43–7.
 84. Apfelbacher CJ, Ofenloch RF, Weisshaar E et al. Chronic hand eczema in Germany: 5-year follow-up data from the CARPE registry. *Contact Dermatitis*. 2019;80(1):45–53.
 85. Cazzaniga S, Ballmer-Weber BK, Gräni N et al. Medical, psychological and socio-economic implications of chronic hand eczema: A cross-sectional study. *J Eur Acad Dermatology Venereol*. 2016;30(4):628–37.
 86. Dibenedetti D, Baranowski E, Zelt S, Reynolds M, Sherrill B. Assessing United States Patient and Dermatologist Experiences with Severe Chronic Hand Eczema. *J Clin Aesthet Dermatol*. 2015 Nov;8(11):19–27.
 87. Barrett A, Hahn-Pedersen J, Kragh N, Evans E, Gnanasakthy A. Patient-Reported Outcome Measures in Atopic Dermatitis and Chronic Hand Eczema in Adults. Patient – Patient-Centered Outcomes Res. 2019;12(5):445–59.
 88. Christoffers WA, Coenraads PJ. Cochrane review “Interventions for hand eczema” is published. *Contact Dermatitis*. 2019;81:226.
 89. Oosterhaven JAF, Flach PA, Bultmann U, Schuttelaar MLA. Presenteeism in a Dutch hand eczema population—a cross-sectional survey. *Contact Dermatitis*. 2018 Jul;79(1):10–9.
 90. Cortesi PA, Scalone L, Belisari A et al. Cost and quality of life in patients with severe chronic hand eczema refractory to standard therapy with topical potent corticosteroids. *Contact Dermatitis*. 2014;70(3):158–68.
 91. Augustin M, Purwins S, Diepgen T, Posthumus J, Kuessner D. Cost-of-illness in patients with chronic hand eczema: Results from a multi-centre study in Germany. *Value Heal*. 2010;13(7):A398.
 92. Diepgen TL, Scheidt R, Weisshaar E, John SM, Hieke K. Cost of illness from occupational hand eczema in Germany. *Contact Dermatitis*. 2013 Aug;69(2):99–106.
 93. Diepgen TL, Purwins S, Posthumus J, Kuessner D, John SM, Augustin M. Cost-of-illness analysis of

- patients with chronic hand eczema in routine care in Germany: focus on the impact of occupational disease. *Acta Derm Venereol.* 2013;93(5):538–43.
94. van Gils RF, Bosmans JE, Boot CR et al. Economic evaluation of an integrated care programme for patients with hand dermatitis. *Contact Dermatitis.* 2013;69(3):144–52.

Part I

Pathogenesis

Klaziena Politiek¹

Laura Loman¹

Hendri H. Pas¹

Gilles F.H. Diercks²

Henny H. Lemmink³

Sabrina Z. Jan³

Peter C. van den Akker³

Maria C. Bolling^{1*}

Marie-Louise A. Schuttelaar^{1*}

^{*}Authors contributed equally

¹ Department of Dermatology, University Medical Center Groningen,
University of Groningen, Groningen, The Netherlands

² Department of Pathology, University Medical Center Groningen,
University of Groningen, Groningen, The Netherlands

³ Department of Genetics, University Medical Center Groningen,
University of Groningen, Groningen, The Netherlands

Published in

Contact Dermatitis. 2020;83(3):196–205

Chapter 2

Hyperkeratotic Hand Eczema – Eczema or not?

Abstract

Background

Hyperkeratotic hand eczema (HHE) is a typical clinical hand eczema subtype with a largely unknown pathophysiology.

Objective

To investigate histopathology, expression of keratins (K), epidermal barrier proteins and adhesion molecules in HHE.

Methods

Palmar skin biopsies (lesional and perilesional) were obtained from seven HHE patients and two healthy controls. Moreover, 135 candidate genes, associated with palmoplantar keratoderma were screened for mutations.

Results

Immunofluorescence staining showed a significant reduction of K9 and K14 in lesional skin. Upregulation was found for K5, K6, K16, and K17 in lesional skin compared to perilesional and healthy palmar skin. Further, upregulation of involucrin and alternating loricrin staining, both in an extracellular staining pattern, was found. Filaggrin expression was similar in lesional, perilesional and healthy control skin. No monogenetic mutations were found.

Conclusion

Currently, the phenotype of HHE is included in the hand eczema classification system, however, it can be argued whether this is justified. The evident expression of filaggrin and involucrin in lesional skin does not support a pathogenesis of atopic eczema. The upregulation of K6, K16 and K17 and reduction of K9 and K14 might contribute to the underlying pathogenesis. Unfortunately, comparison with hand eczema studies is not possible yet because similar protein expression studies are lacking.

Introduction

Hyperkeratotic hand eczema (HHE) is defined by sharply bordered areas of hyperkeratosis or thick scaling on the palms, possibly extending to the palmar aspects of the fingers.^{1,2} There is little or no redness and vesicles are absent. Plantar aspects of the feet can be involved as well. There is a male predominance and patients are mainly middle-aged.³ This phenotype is currently included in the classification system of hand eczema. Two classification systems have been described, however no consensus has been reached yet. Agner et al. consider HHE as an endogenous subtype of hand eczema with no identifiable cause.^{4,5} In contrast, Menné et al. use a morphological classification system in which all clinical subtypes, including HHE, could have identifiable causes of hand eczema such as atopic dermatitis, exposure to irritants, or to contact allergens in sensitized persons.² The pathophysiology of this well-described monomorphic subtype is largely unknown and it could be questioned whether it should be classified as eczema.

Palmar hyperkeratosis is seen in other diseases as well, like palmar psoriasis and palmar plantar keratoderma (PPK). Palmar psoriasis resembles hyperkeratotic hand eczema. It was reported that it can be distinguished from psoriasis by lack of psoriasis-type scaling, but the clinical distinction is very problematic.⁶ PPK is an umbrella term for any form of persistent thickening of the epidermis at palmar and/or plantar skin and includes both genetic and acquired conditions. Literature about PPK showed that mutations in several keratin genes can result in a weakened cell cytoskeleton resulting in abnormal thickened and keratotic palmoplantar skin.^{7,8} Similarly, mutations in genes encoding desmogleins (DSG1–4), desmocollins (DSC1–3), desmoplakin (DSP), plakoglobin (PG), plakophilins (PKP1–3) and corneodesmosin are associated with palmar hyperkeratosis as well.^{9,10}

Here we present a case series of patients with a clinical phenotype of HHE. The aim of this study was to gain more insight in the etiology of this phenotype. Therefore, we have investigated the histopathology, the expression of different palmar keratins, epidermal barrier proteins and adhesion molecules in lesional and non-lesional skin of patients with the clinical phenotype of HHE. In addition, we screened all patients for variants in genes-related to PPK.

Methods

Study design and participants

This pilot study was conducted at the Dermatology Department of the University Medical Center Groningen, a tertiary referral center for hand eczema, between August 2018 until December 2018. Inclusion criteria were: adult patients with a clinical phenotype of HHE.¹² Exclusion criteria were: patients with a current diagnosis of atopic dermatitis,¹¹ patients with topical corticosteroids use within the last two weeks, immunosuppressive/immunomodulatory treatment or UV radiation therapy within the last four weeks, contact allergies with clinical relevance to the hands in which exposure to allergens is not avoided, patients with a history of psoriasis or psoriasis lesions elsewhere on the body, patients with other (genetic) skin diseases or infections of the hands.

Clinical characteristics

The following data were collected: age, gender, onset of symptoms, history of atopic dermatitis (AD), history of allergic asthma (regarding Global Initiative for Asthma (GINA) guideline),¹² history of allergic rhinitis (regarding Allergic Rhinitis and its Impact on Asthma (ARIA) guideline),¹³ specific inhalant IgE (sIgE) allergens, atopy score: < 3 points (probability of AD is very small), 3–9 points (possible diagnosis of AD), > 10 points (reliable diagnosis of AD))¹⁴ patch test results, occupation, work related exposure to irritants¹⁵ and foot involvement.

Skin samples

Four biopsies (3 mm) were obtained, two for histopathology and two for immunofluorescence (IF) microscopy from lesional and perilesional (non-inflamed) palmar skin of seven patients. In addition, 3 mm samples from the hypothenar region of the palms of two HCs were taken for comparison. HC were age- and sex-matched. The study was ethically approved by the local review board (M18.228998).

Histopathology/immunohistochemistry

Hematoxylin and eosin (H&E) stained sections were examined for morphologic features. Epidermal proliferation and differentiation were assessed by immunohistochemically staining for Ki-67 positive nuclei using anti-Ki-67 (30-9) Rabbit Monoclonal Primary Antibody (Ventana Roche, Tucson, Arizona, United States). To analyze the Ki-67 positive cells of each section, a line of 1 mm length following the stratum basale was drawn after choosing a representative region. All positive cells above and under the line were counted by two independent observers (LL and KP) and expressed as 'positive cells per mm length of basement membrane'.

Immunofluorescence stainings

Skin biopsies for IF staining were snap-frozen in liquid nitrogen. For IF staining antibodies against K1, K2e, K5, K6, K9, K10, K14, K15, K16, K17, DSG-1, DSG-3, plakophilin-1, plakoglobin, desmoplakin (rod), filaggrin, loricrin, involucrin and corneodesmosin were used (supplement 1, Table S1). Cryosections of 4 μ m thickness were mounted on polysine TM glass slides, air-dried for 20 min before a fan and encircled with a hydrophobic emulsion (PAP pen; Dako, Glostrup, Denmark). The mapping procedure included two consecutive immunostaining steps of 30 min each at ambient temperature, alternating with washing steps with 0.15 mM PBS for 30 min. The first staining step involved binding of the different monoclonal mouse antigens (supplement 1). The second staining step involved fluorescent detection and bound the antibody in step 1. For this purpose we used highly absorbed Alexa 488-onjugated goat antimouse IgG (Molecular Probes Europe, Leiden, The Netherlands). Thereafter, a BB staining for 5-10 minutes to detect the nucleoli and a last washing steps in 0.15 mM PBS for 10-20 min. The sections were coverslipped under SlowFade antifade. The sections were examined with a Leica DMRA fluorescence microscope and images were acquired by a Leica DFC350 FX digital camera (Leica Microsystems Inc., Bannockburn, Illinois, United States). Further image processing was done by Adobe Photoshop software.

The immunostaining pattern and intensity in the epidermis was examined by three independent observers (MB, HP and KP). The intensity was scored semiquantitatively using a global assessment on a continuous scale from 0 (negative) to 4 (1+, 2+, 3+ of 4+). The mean scores of the observers were used for the final conclusion.

Gene analysis

DNA was extracted from peripheral blood leukocytes of all patients. Whole exome sequencing (WES, Agilent SureSelect Human All Exome V6_S07604514) was performed and a panel of 135 candidate genes associated with palmoplantar keratoderma was screened for relevant variants (supplement 2).

Gene variants were identified using a standard diagnostic pipeline and variant classification was performed according to criteria described by Fokkema et al. and guidelines of the American College of Medical Genetics and Genomics 2015.^{16,17} Because no pathogenic or likely pathogenic

mutations were identified in the 135 PPK-related genes that could be associated with the HHE phenotype, a second analysis was done. Since all seven patients shared a strikingly similar clinical phenotype, we hypothesized that all patients might carry a variant in the same, as yet unknown, gene. To test this hypothesis an open-exome cohort analysis was performed. Gene variant analysis was performed using data analysis pipeline filtering out late-onset genes (e.g. *BRCA1*).

Results

Clinical characteristics

All seven patients were male. Patients had a mean age of onset of 50.7 years (range 38–61 years) and a mean disease duration of 6.9 years (range 1.5–20 years) (Table 1).

All patients showed a consistent clinical picture with sharply bordered hyperkeratosis on the palms with painful fissures and no or mild redness (Figure 1). Two patients had concomitant planar involvement consisting of hyperkeratotic plaques without erythema. None of the patients had current atopic dermatitis and one patient had a history of atopic dermatitis in childhood. In four out of seven patients higher levels of specific IgE inhalation allergens were found. Two patients had asthma and four patients had (mild) symptoms of allergic rhinitis. The atopy score showed a possible atopic skin diathesis in three patients. Three out of seven patients had an irritant exposure, mostly due to work-related mechanical stress and/or chemical irritants. None of the patients had a family history of palmoplantar keratoderma or psoriasis. Six patients had a previous history of systemic treatment, frequently alitretinoin, acitretin and methotrexate.

Histopathology

All lesional skin biopsies presented the following histopathologic features in H&E stained sections: confluent parakeratosis, plasma in the parakeratotic foci, presence of the stratum granulosum, epidermal hyperplasia, spongiosis and exocytosis of lymphocytes. Typical characteristics of palmar psoriasis, e.g. neutrophilic granulocytes in parakeratotic foci and absence of a granular layer, were absent in all biopsies. In five out of seven perilesional skin biopsies mild signs of inflammation were found: a sparse superficial perivascular infiltrate of lymphocytes without spongiotic and hyperkeratotic changes.

Epidermal proliferation

Immunohistochemical analysis showed a significantly higher number of Ki-67 positive nuclei per mm basement membrane (mean $\pm$ SD) in lesional skin (279 ± 75) compared to perilesional skin (75 ± 28) (one perilesional Ki-67 staining was missing) and healthy control skin (51 ± 6). The number of Ki-67 positive nuclei in perilesional skin was 27% of that in lesional skin (P -value $< .05$).

Immunofluorescence staining

K5 showed an intense panepidermal staining in six out of seven lesional skin samples. Perilesional and healthy control (HC) skin presented normal K5 basal cell staining. K14 staining was strongly reduced in all lesional skin samples and two out of seven perilesional skin samples. A normal basal K14 staining was found in five out of seven perilesional and both HC skin samples (Figure 2). K15 was negative in palmar lesional, perilesional and HC skin.

The diffuse staining of K1 and K10 in the suprabasal layers was comparable between lesional, perilesional and HC skin. Also K2e staining in the upper spinous layer were similar in all groups. K9 was significantly decreased or even absent in five out of seven lesional skin biopsies compared

Figure 1. In the left column, clinical pictures showing the palms of the 7 patients with a clinical phenotype of hyperkeratotic hand eczema. The two right columns show the K9 immunofluorescence staining patterns of their skin biopsies: reduced or absent staining of keratin 9 in lesional skin (5/7, middle column) and normal K9 staining in perilesional (7/7, right column) and healthy control (HC) skin.

Figure 1 continued

Table 1. Demographic and clinical characteristics

Patient	Sex	Age (years)	Age of onset (years)	Specific IgE inhalant allergens	AD in childhood	Asthma ²	Allergic rhinitis ¹³	Atopic skin diathesis ^{14*}	Positive patch tests	Occupation	Work related exposure to irritants	Foot involvement
HHE-01	M	63	61	-	-	-	-	0	-	Bricklayer	+	-
HHE-02	M	65	56	-	-	-	-	0	-	Technical service operating rooms	-	+
HHE-03	M	52	47	+	+	+	+	4	+	Not working	-	-
HHE-04	M	46	44	+	-	+	+	5	+	Construction worker	+	-
HHE-05	M	45	38	-	-	-	-	0	+	Accountant	-	-
HHE-06	M	75	55	+	-	-	+	2	-	Retired (golf player)	-	-
HHE-07	M	59	54	+	-	-	+	3	+	Process operator chemical factory	+	+
HC-01	M	63	N/A	X	-	-	-	0	X	Photographer	-	-
HC-02	M	61	N/A	X	-	-	-	0	X	Construction worker	+	-

Clinical features of seven patients with a clinical phenotype of hyperkeratotic hand eczema (HHE) and two healthy controls (HC).

M, male; +, yes; -, no; N/A, not applicable; X, not performed; AD, atopic dermatitis.

*Atopy score: - = < 3 points = probability of AD is very small, +/- = $\geq$ 3-9 points = possible diagnosis of AD.

with normal suprabasal staining in all perilesional and HC skin samples (Figure 1). Two patients had normal K9 staining in lesional skin.

An evident panepidermal upregulation of K6 was found in all lesional skin samples. Some patches of positive basal and/or suprabasal staining were found in six of seven perilesional skin samples. Both HC skin samples were negative for K6. K16 staining presented a strong panepidermal staining in five of seven lesional skin samples compared with a basal layer-limited staining in HC. In two of seven lesional and two of seven perilesional skin samples a dubious K16 staining was found. In five of seven perilesional skin samples a mainly basal and some suprabasal staining was seen. K17 was strongly positive in parts of the suprabasal layers in all lesional skin biopsies. Perilesional and HC skin samples were negative for K17 (Figure 2).

DSG-I staining showed a normal epidermal cell surface (ECS) staining in all groups. However, in all lesional and some perilesional skin samples, three out of seven certain keratinocytes were found with a granular intracellular staining in the stratum granulosum. For DSG-3 a more panepidermal ECS pattern was seen in lesional skin compared to perilesional and HC skin (Figure 3). Staining with antibodies against plakophilin-1, plakoglobin and desmoplakin showed normal ECS staining in lesional compared to perilesional and HC skin (data not shown).

Involucrin staining in lesional skin showed an earlier than normal expression in a mainly ECS pattern in the complete spinous layer. Perilesional and HC skin samples showed a granular intracellular reactivity of involucrin in the upper spinous layers which gradually increased in ascending layers. Lesional loricrin staining showed in five out of seven skin samples an alternating pattern of positive patches of loricrin staining in an ECS pattern in the stratum granulosum. In perilesional and HC skin normal cytoplasmic staining was found in the upper spinous layers which gradually increased in ascending layers (Figure 3). Filaggrin staining was found in the horny and granular layers of all skin samples; also lesional skin showed normal levels of filaggrin expression. In lesional skin, the expression of filaggrin was seen in more layers, due to acanthosis. Corneodesmosin showed normal ECS staining in the stratum corneum of all biopsies.

Gene analysis

The 135 PPK-related gene analysis in the seven patients did not identify any pathogenic or likely pathogenic variants that could be associated to the HHE phenotype. In total, three pathogenic mutations and four variants of unknown significance (VOUS) were identified. These heterozygous variants were identified in genes for autosomal recessive skin disorders, and could be easily excluded as causative for the HHE phenotype on the basis of inheritance and absence of related phenotypic features. Particularly, no mutations in epidermal barrier genes as *FLG*, *FLG2* and serine protease inhibitor Kazal type 5 (*SPINK5*) were detected. Additionally, the cohort-analysis did not reveal a single mutated gene (supplement 3).

K16

K17

.....
Figure 2. Immunofluorescence staining pattern of keratin (K) 5, 14, 6, 16, 17 in healthy control (HC), lesional and perilesional skin of hyperkeratotic hand eczema (HHE) patients. K5, K6, K16 and K17 were strongly upregulated in lesional skin compared to perilesional and HC skin.

Figure 3. Immunofluorescence pattern desmoglein (DSG) 1, 3, involucrin (INV), loricrin (LOR) and flaggrin (FLG) in healthy control (HC), lesional and perilesional skin of hyperkeratotic hand eczema patients. DSG-1 staining in lesional skins showed certain keratinocytes with an intracellular staining compared to the normal extracellular staining in perilesional and HC skin. In DSG-3 more panepidermal staining was found in lesional skin. Involucrin showed an extracellular and earlier staining in lesional skin compared to perilesional and HC skin. Loricrin staining showed alternating extracellular staining compared to intracellular stratum granulosum staining in perilesional and HC skin. Flaggrin was similar expressed in the stratum granulosum.

Discussion

In this pilot study we have assessed the underlying etiology of the clinical phenotype of HHE. Our main findings were identical histopathological features in all lesional skin biopsies, an epidermal hyperproliferation and abnormal differentiation with strong K5, K6, K16, K17 and reduced K14 and K9 staining and, altered DSG-1, DSG-3, involucrin and loricrin staining patterns. The main question in this study was whether our findings support a diagnosis of hyperkeratotic hand eczema. Therefore, we will discuss our most evident findings in comparison with literature of hand eczema and hyperkeratotic palmar diseases such as palmar psoriasis and PPK.

In general, the pathogenesis of hand eczema remains largely unclear and is seen as a complex interaction between endogenous and exogenous factors. An exogenous factor for developing hand eczema is repeated contact with irritating agents and factors (friction).¹ Irritants induce a disruption of the skin barrier, and lead to an inflammatory reaction, mainly mediated by the innate immunity.¹⁸ K6/16/17 are early barrier alarmins and upregulation of these keratins is both seen in wounding and exposure to irritants, which results in keratinocyte hyperproliferation and hyperkeratosis.¹⁹ Irritants induce also an early expression of involucrin.^{20,21} Similar results were found in our study. However, this could not sufficiently cover the whole etiology since not all patients with HHE had exposure to irritants. Probably, HHE patients have a pre-existent skin barrier problem where exposure to irritating agents and factors eventually leads to secondary dysregulation of the immune system.²² The skin barrier problem is an underlying etiology in atopic dermatitis.^{22,23} A two- to fourfold increased risk to develop hand eczema was found in patients with a previous or current history of atopic dermatitis.²⁴ However, in the current study only one patient had a history of atopic dermatitis in childhood. Three patients had a possible atopic skin diathesis based on the atopy score.¹⁴ Four patients had mucosal atopy, although previous studies showed no association between mucosal atopy and an increased risk of developing hand eczema.²⁵⁻²⁷ The histopathology of all lesional skin biopsies in this study presented confluent parakeratosis, plasma in the parakeratotic foci, presence of the stratum granulosum, epidermal hyperplasia, and spongiosis. These morphological features were described in HHE before.²⁸ However, Park et al. described the histological changes in biopsies of 25 HHE patients and 16 patients with palmar psoriasis and found no significant differences.²⁹ It is therefore questionable if differentiation based on histopathology is possible. Summarizing, both histopathology and contributing etiological factors, as exposure to irritants and a history of atopic eczema, could not completely explain the pathogenesis of this clinical phenotype.

Circumscribed hyperkeratosis of the palms is also seen in palmar psoriasis. The clinical distinction between HHE and palmoplantar psoriasis is difficult when plaques are only located on the palms.²⁹⁻³¹ Only few studies have investigated both diseases.^{29,30,32,33} Lillis et al. investigated IL-23, which stimulates Th17 cell survival and proliferation, and found a significantly upregulation of IL-23 which did not significantly differ between HHE and (palmar) psoriasis.³⁰ Possibly, the inflammation in the clinical phenotype of HHE is, as psoriasis, more Th17 driven. This is also supported by the strong lesional K17 staining in our study which plays an important role in the pathogenesis of psoriasis.^{19,34,35} K17 is a stimulator of psoriatic T-cells (Th-17) and producer of specific cytokines (IL-17) which in turn stimulate K17 again leading to an 'autoimmune feedback loop'.^{36,37} This 'feedback loop' might explain the persistent palmar hyperkeratosis at the same location of this clinical phenotype. The persistent plaques were also described by Hersle et al., who noticed after a follow-up of 10 year an almost identical clinical monomorphic picture.³¹ Whereas other clinical subtypes of hand eczema, as well as atopic dermatitis, show more polymorphic skin lesions which tend to vary in appearance and location over time.^{1,11,38} Future studies should evaluate whether the

phenotype of HHE is a variant of (localized) psoriasis.

Furthermore, a common denominator in the pathophysiology of chronic inflammatory skin diseases as atopic dermatitis, hand eczema and, psoriasis seems skin barrier impairment.^{39–41} We studied involucrin, loricrin and filaggrin since these proteins have a major role in forming the cornified envelope. Involucrin provides a scaffold to which other proteins, such as loricrin, subsequently crosslink to form the cornified envelope.⁴² Filaggrin contributes herein by among others aggregating keratin filaments and organizing lipid bilayers.⁴³ Mutations in *FLG* are known to be a risk factor for the development of atopic dermatitis. An independent association of *FLG* mutations and hand eczema has not been found.^{44–47} Furthermore, independently of gene mutations, studies in atopic dermatitis showed lower expression levels of filaggrin, involucrin, and loricrin due to proinflammatory cytokines as IL-4.^{48,49} Both *FLG* mutations and decreased filaggrin expression were not found in the current study. In two other studies filaggrin expression in hand eczema biopsies was analyzed. Molin et al. analyzed the whole proteome by using liquid chromatography with tandem mass spectrometry analysis of palmar skin biopsies from six morphologically unclassified hand eczema patients.⁵⁰ Subsequently immunohistochemistry (IHC) was performed in seven other hand eczema patients to confirm the results. Another study in patients with hyperkeratotic fissured hand eczema by Kumari et al. analyzed filaggrin and loricrin by fluorescence-based real-time quantitative polymerase chain reaction (qPCR), and subsequently IHC in 15 skin biopsies.⁴⁰ Both studies showed that filaggrin expression was downregulated. *FLG* mutations were not analyzed in both studies. Morphological subtypes of hand eczema were not clearly described in these studies. A possible explanation for the differences between our study and the previous studies might be the different patient populations with different morphological subtypes of hand eczema. In the current study we included patients with a typical phenotype of HHE with stable plaques and less redness and no other signs of inflammation. Other morphological subtypes of hand eczema with obvious inflammation may lead to a secondary downregulation of filaggrin expression. The question is whether the differences between this studies and the previous two studies, with respect to expression of epidermal barrier proteins, can be explained by different morphological types of hand eczema. It could also be considered whether HHE is a subtype of hand eczema or has another etiology. Besides atopic dermatitis and hand eczema, Kim et al. studied filaggrin, involucrin and loricrin in skin biopsies of 10 adult patients with psoriasis. qPCR and IHC showed significant decreased filaggrin and loricrin expression, however involucrin was not decreased in lesional skin. An interesting finding in above study was that TNF- α stimulated keratinocytes showed only reduced filaggrin and loricrin expression. In contrast to TNF- α , keratinocytes stimulated by Th2 cytokines, showed reduced expression of filaggrin, loricrin and also involucrin.⁴¹ In our study involucrin was strongly presented in an ECS staining pattern through the complete spinous layer. Loricrin was downregulated and alternately presented in an ECS pattern. Perilesional and HC skin showed unaltered cytoplasmic staining for both in the upper stratum spinosum and granular layers. The early expression of involucrin was described in other hyperproliferative diseases, like psoriasis and PPK, but an ECS staining pattern for both proteins has not been described before.^{21,51,52} We hypothesize that the ECS staining pattern of involucrin and loricrin might be explained by an increased keratinocyte proliferation, whereby the cornified envelope is prematurely formed and involucrin and loricrin are earlier attached underneath the plasma membrane instead of the cytoplasm. Another remarkable finding in our study was the upregulation of involucrin, which has not been described in hand eczema before, although sufficient studies are lacking. The opposite, a downregulation of involucrin, is described in atopic dermatitis. Therefore, possibly other cytokine profiles result into palmar hyperkeratosis in HHE.^{40,41,48,50,53}

Hereditary PPK is another group of skin diseases with palmar hyperkeratosis, which provides more insight about the association of different keratins, desmosomal proteins and epidermal barrier proteins to palmo-plantar hyperkeratosis.^{8-10,54-58} In this study no monogenetic mutations related to palmar hyperkeratosis were found. However, a contributing role for one of the VOUS cannot be completely excluded.

Despite not being able to identify gene mutations, this study showed abnormal differentiation in important keratins. K5 was upregulated and K14 and K9 staining were downregulated in lesional skin compared to HCs. Only a few small studies describe keratin expression in other palmar skin diseases and found contradicting results.^{59,60} Normally, K9 is only expressed in healthy ridged skin. In the current study, lesional palmar skin had lost K9 expression, which might indicate that palmar keratinocytes can change their specific pathways to a trunk-type keratinization. Beside keratins, desmosomes have also an important function in epidermal differentiation. Normally, DSG-3 has a strong basal distribution associated with the proliferating cells, while DSG-1 expression increases from the basal to the granular layer. However, DSG-1 and 3 staining in this study were both panepidermally expressed in lesional skin and showed remarkable granular staining for DSG-1. Desmogleins are in continuous turnover in the desmosome and are discarded by cellular uptake to be destroyed or recycled.⁶¹ Perhaps the abnormal differentiation and disturbed forming of the cornified envelope results into a higher DSG-1 turnover and uptake whereby DSG-1 is not only expressed in the membrane but also in the cytoplasm. Further research should elucidate whether the abnormal desmosomal and keratin staining represent a primary defect in the pathophysiology of HHE, or are of secondary nature.

One of the limitations of this study is the relatively small study sample, though clinical presentations were very uniform. Another limitation is that IF staining is a strong diagnostic method in case of evident differences, while smaller differences can be missed. Furthermore, it is difficult to compare our IF data to previous literature on other palmar skin diseases, as most studies focused on non-ridged skin which differs from ridged skin as we did.^{62,63} Finally, we did not include other hyperkeratotic palmar diseases as palmar psoriasis and PPK in this study. Future studies should investigate disease specific biomarkers, such as NOS2 (psoriasis) and CCL27 (eczema) in different palmar skin diseases.⁶⁴

In conclusion, the phenotype of HHE is currently included in the classification system of hand eczema, however, it can be argued whether this is justified. The evident expression of filaggrin and involucrin in lesional skin does not support a pathogenesis of atopic eczema. The upregulation of K6, K16 and K17 and the contrasting reduction or even absence of K9 and K14 might contribute to the underlying pathogenesis. Unfortunately, comparison with hand eczema studies is not possible because similar protein expression studies are lacking. Further studies are necessary to compare our results with other subtypes of hand eczema and other palmo-plantar skin diseases to see which pathways are involved.

Acknowledgements

The authors would like to thank Gonnie Meijer, Marije van der Molen and Duco Kramer for performing sectioning and staining of the skin biopsies.

References

- Coenraads PJ. Hand eczema. *N Engl J Med*. 2012 Nov 8;367(19):1829–37.
- Menné T, Johansen JD, Sommerlund M, Veien NK. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. *Contact Dermatitis*. 2011;65(1):3–12.
- van der Heiden J, Agner T, Rustemeyer T, Clemmensen KKB. Hyperkeratotic hand eczema compared to other subgroups of hand eczema – a retrospective study with a follow-up questionnaire. *Contact Dermatitis*. 2018;78(3):216–22.
- Diepgen TL, Andersen KE, Brandao FM, et al. Hand eczema classification: a cross-sectional, multicentre study of the aetiology and morphology of hand eczema. *Br J Dermatol*. 2009;160(2):353–8.
- Agner T, Aalto-Korte K, Andersen KE, et al. Classification of hand eczema. *J Eur Acad Dermatology Venereol*. 2015;29(12):2417–22.
- Johansen JD, Hald M, Andersen BL, et al. Classification of hand eczema: Clinical and aetiological types. Based on the guideline of the Danish Contact Dermatitis Group. *Contact Dermatitis*. 2011;65(1):13–21.
- Moll R, Divo M, Langbein L. The human keratins: Biology and pathology. *Histochem Cell Biol*. 2008;129(6):705–33.
- Guerra L, Castori M, Didona B, Castiglia D, Zambruno G. Hereditary palmoplantar keratodermas. Part I. Non-syndromic palmoplantar keratodermas: classification, clinical and genetic features. *J Eur Acad Dermatology Venereol*. 2018;32(5):704–19.
- Petrof G, Mellerio JE, McGrath JA. Desmosomal genodermatoses. *Br J Dermatol*. 2012;166(1):36–45.
- Ishida-Yamamoto A, Igawa S. Genetic skin diseases related to desmosomes and corneodesmosomes. *J Dermatol Sci*. 2014;74(2):99–105.
- Williams HC, Burney PG, Pembroke AC, Hay RJ. Validation of the U.K. diagnostic criteria for atopic dermatitis in a population setting. U.K. Diagnostic Criteria for Atopic Dermatitis Working Party. *Br J Dermatol*. 1996 Jul;135(1):12–7.
- Global initiative for asthma. Global Strategy for Asthma Management and Prevention. Available from: www.ginasthma.org assessed: November. 2019.
- Bousquet J, Khaltaev N, Cruz AA, et al. An introduction of allergic rhinitis and its impact on asthma (ARIA) 2008 update. *Allergy*. 2008;63(86):8–160.
- Diepgen TL, Sauerbrei W, Fartasch M. Development and validation of diagnostic scores for atopic dermatitis incorporating criteria of data quality and practical usefulness. *J Clin Epidemiol*. 1996;49(9):1031–8.
- Cazzaniga S, Apfelbacher C, Diepgen T, et al. Patterns of chronic hand eczema: a semantic map analysis of the CARPE registry data. *Br J Dermatol*. 2018;178(1):229–37.
- Fokkema IFAC, Velde KJ, Slofstra MK, et al. Dutch genome diagnostic laboratories accelerated and improved variant interpretation and increased accuracy by sharing data. *Hum Mutat*. 2019;40(12):2230–2238.
- Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405–24.
- Jakasa I, Thyssen JP, Kezic S. The role of skin barrier in occupational contact dermatitis. *Exp Dermatol*. 2018;27(8):909–14.
- Zhang X, Yin M, Zhang L. Keratin 6, 16 and 17 – Critical Barrier Alarmin Molecules in Skin Wounds and Psoriasis. *Cells*. 2019;8(8):807.
- Mai Le TK, Schalkwijk J, van de Kerkhof PCM, van Haelst U, van der Valk PGM. A Histological and Immunohistochemical Study on Chronic Irritant Contact Dermatitis. *Am J contact Dermat*. 1998;9(1):23–8.
- Ekanayake-Mudiyanselage S, Aschauer H, Schmook FP, Jensen JM, Meingassner JG, Proksch E. Expression of epidermal keratins and the cornified envelope protein involucrin is influenced by permeability barrier disruption. *J Invest Dermatol*. 1998;111(3):517–23.
- Kezic S. Atopic dermatitis: risk estimates for hand eczema. *Br J Dermatol*. 2018;178(4):827.
- Han H, Roan F, Ziegler SF. The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines. *Immunol Rev*. 2017;278(1):116–30.

24. Ruff SMD, Engebretsen KA, Zachariae C, et al. The association between atopic dermatitis and hand eczema: a systematic review and meta-analysis. *Br J Dermatol*. 2017 ;178(4):879–88.
25. Grönhagen C, Lidén C, Wahlgren CF, et al. Hand eczema and atopic dermatitis in adolescents: a prospective cohort study from the BAMSE project. *Br J Dermatol*. 2015 ;173(5):1175–82.
26. Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE. Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. The Odense adolescence cohort study on atopic diseases and dermatitis. *Br J Dermatol*. 2001;144(3):523–32.
27. Meding B, Jarvholm B. Incidence of hand eczema—a population-based retrospective study. *J Invest Dermatol*. 2004 ;122(4):873–7.
28. Weedon D. *Weedon's Skin Pathology* 3rd edition. Churchill Livingstone; 2010. 114–115p.
29. Park JY, Cho EB, Park EJ, Park HR, Kim KH, Kim KJ. The histopathological differentiation between palmar psoriasis and hand eczema: A retrospective review of 96 cases. *J Am Acad Dermatol*. 2017;77(1):130–5.
30. Lillis J V, Guo C-S, Lee JJ, Blauvelt A. Increased IL-23 expression in palmoplantar psoriasis and hyperkeratotic hand dermatitis. *Archives of dermatology*. United States; 2010; 146: 918–9.
31. Hersle K, Mobacken H. Hyperkeratotic dermatitis of the palms. *Br J Dermatol*. 1982;107(2):195–201.
32. Errichetti E, Stinco G. Dermoscopy in differential diagnosis of palmar psoriasis and chronic hand eczema. *J Dermatol*. 2016;43(4):423–5.
33. Kolesnik M, Franke I, Lux A, Quist SR, Gollnick HP. Eczema in psoriatico: An important differential diagnosis between chronic allergic contact dermatitis and psoriasis in palmoplantar localization. *Acta Derm Venereol*. 2018;98(1):50–8.
34. Leigh IM, Navsaria H, Purkis PE, McKay IA, Bowden PE, Riddle PN. Keratins (K16 and K17) as markers of keratinocyte hyperproliferation in psoriasis in vivo and in vitro. *Br J Dermatol*. 1995;133(4):501–11.
35. Bovenschen HJ, Seyger MMB, Van De Kerkhof PCM. Plaque psoriasis vs. atopic dermatitis and lichen planus: A comparison for lesional T-cell subsets, epidermal proliferation and differentiation. *Br J Dermatol*. 2005;153(1):72–8.
36. Yang L, Zhang S, Wang G. Keratin 17 in disease pathogenesis: from cancer to dermatoses. *J Pathol*. 2019;247(2):158–65.
37. Shi X, Jin L, Dang E, et al. IL-17A upregulates keratin 17 expression in keratinocytes through STAT1-and STAT3-dependent mechanisms. *J Invest Dermatol*. 2011;131(12):2401–8.
38. Guttman-Yassky E, Krueger JG. Atopic dermatitis and psoriasis: two different immune diseases or one spectrum? *Curr Opin Immunol*. 2017;48:68–73.
39. Molin S. Pathogenese des Handekzems [Pathogenesis of hand eczema]. *Hautarzt*. 2019;70(10):755–9.
40. Kumari V, Timm K, Kühl AA, Heine G, Worm M. Impact of systemic alitretinoin treatment on skin barrier gene and protein expression in patients with chronic hand eczema. *Br J Dermatol*. 2016;175(6):1243–50.
41. Kim BE, Howell MD, Guttman E, et al. TNF- α downregulates filaggrin and loricrin through c-Jun N-terminal kinase: Role for TNF- α antagonists to improve skin barrier. *J Invest Dermatol*. 2011;131(6):1272–9.
42. Candi E, Schmidt R, Melino G. The cornified envelope: A model of cell death in the skin. *Nat Rev Mol Cell Biol*. 2005;6(4):328–40.
43. Brown SJ, McLean WHI. One remarkable molecule: Filaggrin. *J Invest Dermatol*. 2012;132(3 PART 2):751–62.
44. Lerbaek A, Bisgaard H, Agner T, Ohm Kyvik K, Palmer CNA, Menné T. Filaggrin null alleles are not associated with hand eczema or contact allergy. *Br J Dermatol*. 2007;157(6):1199–204.
45. Visser MJ, Verberk MM, Campbell LE, et al. Filaggrin loss-of-function mutations and atopic dermatitis as risk factors for hand eczema in apprentice nurses: Part II of a prospective cohort study. *Contact Dermatitis*. 2014;70(3):139–50.
46. Visser MJ, Landeck L, Campbell LE, et al. Impact of atopic dermatitis and loss-of-function mutations in the filaggrin gene on the development of occupational irritant contact dermatitis. *Br J Dermatol*. 2013;168(2):326–32.
47. Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet*.

- 2006;38(4):441–6.
48. Kim BE, Leung DJM, Boguniewicz M, Howell MD. Loricrin and involucrin expression is downregulated by Th2 cytokines through STAT-6. *Clin Immunol*. 2008;126(3):332–7.
 49. Bao L, Mohan GC, Alexander JB, et al. A molecular mechanism for IL-4 suppression of loricrin transcription in epidermal keratinocytes: implication for atopic dermatitis pathogenesis. *Innate Immun*. 2017;23(8):641–7.
 50. Molin S, Merl J, Dietrich KA, et al. The hand eczema proteome: imbalance of epidermal barrier proteins. *Br J Dermatol*. 2015 ;172(4):994–1001.
 51. Wan H, Dopping-Hepenstal PJ, Gratian MJ, et al. Striate palmoplantar keratoderma arising from desmoplakin and desmoglein 1 mutations is associated with contrasting perturbations of desmosomes and the keratin filament network. *Br J Dermatol*. 2004;150(5):878–91.
 52. Chen JQ, Man XY, Li W, et al. Regulation of Involucrin in Psoriatic Epidermal Keratinocytes: The Roles of ERK1/2 and GSK-3 β . *Cell Biochem Biophys*. 2013;66(3):523–8.
 53. Danso MO, Van Drongelen V, Mulder A, et al. TNF- α and Th2 cytokines induce atopic dermatitis-like features on epidermal differentiation proteins and stratum corneum lipids in human skin equivalents. *J Invest Dermatol*. 2014;134(7):1941–50.
 54. Shemanko CS, Mellerio JE, Tidman MJ, Lane EB, Eady RAJ. Severe palmo-plantar hyperkeratosis in Dowling-Meara epidermolysis bullosa simplex caused by a mutation in the keratin 14 gene (KRT14). *J Invest Dermatol*. 1998;111(5):893–5.
 55. Livingston RJ, Sybert VP, Smith LT, Dale BA, Presland RB, Stephens K. Expression of a truncated keratin 5 may contribute to severe palmar-plantar hyperkeratosis in epidermolysis bullosa simplex patients. *J Invest Dermatol*. 2001;116(6):970–4.
 56. Ishida-Yamamoto A. Loricrin keratoderma: A novel disease entity characterized by nuclear accumulation of mutant loricrin. *J Dermatol Sci*. 2003;31(1):3–8.
 57. Liu X. Keratin 9 L164P mutation in a Chinese pedigree with epidermolytic palmoplantar keratoderma , cytokeratin analysis , and literature review. 2019;(August):3–9.
 58. Fu DJ, Thomson C, Lunny DP, et al. Keratin 9 is required for the structural integrity and terminal differentiation of the palmoplantar epidermis. *J Invest Dermatol*. 2014;134(3):754–63.
 59. Peryassu MA, Cotta-Pereira G, Ramos-E-Silva M, Filgueira AL. Expression of keratins 14, 10 and 16 in marginal keratoderma of the palms. *Acta Dermatovenerologica Croat*. 2005;13(4):206–11.
 60. Tanioka M, Miyagawa-Hayashino A, Manabe T, Toichi E, Miyachi Y, Takahashi K. Circumscribed palmo-plantar hypokeratosis: A disease with two subtypes. *J Invest Dermatol*. 2009;129(4):1045–7.
 61. Otkarina DAM, Van Der Wier G, Diercks GFH, Jonkman MF, Pas HH. IgG-induced clustering of desmogleins 1 and 3 in skin of patients with pemphigus fits with the desmoglein nonassembly depletion hypothesis. *Br J Dermatol*. 2011;165(3):552–62.
 62. Swensson O, Eady RAJ. Morphology of the keratin filament network in palm and sole skin: evidence for site-dependent features based on stereological analysis. *Arch Dermatol Res*. 1996 ;288(2):55–62.
 63. Vela-Romera A, Carriel V, Martín-Piedra MA, et al. Characterization of the human ridged and non-ridged skin: a comprehensive histological, histochemical and immunohistochemical analysis. *Histochem Cell Biol*. 2019;151(1):57–73.
 64. Garzorz-Stark N, Eyerich K. Molecular diagnostics of hand eczema. *Hautarzt*. 2019;70(10):760–5.

Supplement 1

Table S1. Antibodies against keratins, desmosome and cornified cell envelop proteins used in this study

Antigen	Antibody	Dilution	Supplier
Keratin 1	34bB4	1/20	Novo Castra Laboratories Ltd, Newcastleupon-Tyne, U.K
Keratin 2e	Ks2.398.3.1	1/100	Progen, Heidelberg, Germany
Keratin 5	CK-5	1/200	Biolegend, San Diego, U.S.A
Keratin 6	Ks6-KA12	1/10	Progen, Heidelberg, Germany
Keratin 9	CK9	1/10	Origene, Herford, Germany
Keratin 10	LHP1	1/200	Santa Cruz biotechnology inc.
Keratin 14	LLO01	1/20	Gift from Dr B. Lane, Dundee, U.K.
Keratin 15	LHK15	1/100	Santa Cruz Biotechnology, Dallas, U.S.A
Keratin 16	LL025	1/10	Gift from Dr B. Lane, Dundee, U.K.
Keratin 17	E3	1/30	Novo Castra Laboratories Ltd, Newcastleupon-Tyne, U.K
DSG1	27B2	1/20	Santa Cruz Biotechnology, Dallas, U.S.A
DSG1	DSG1-P23	1/10	Progen, Heidelberg, Germany
DSG-3	G194	1/40	Progen, Heidelberg, Germany
Plakophilin-1	PP1-5C2	1/2	MyBioSource, San Diego, U.S.A
Plakoglobin	15F11	1/1000	Sigma-Aldrich, Saint-Louis, U.S.A
Desmoplakin (rod)	DP2.17	1/200	MyBioSource, San Diego, U.S.A
Filaggrin	15C10	1/50	Monosan, Uden, Netherlands
Loricrin	Loricrin	1/1200	Biolegend, San Diego, U.S.A
Involucrin	SY5	1/100	Sigma-Aldrich, Saint-Louis, U.S.A
Corneodesmosin	P-20	1/50	Santa Cruz Biotechnology, Dallas, U.S.A

Supplement 2

The following 135 candidate genes were analyzed with next-generation sequencing:

AAAS, AAGAB, ABCA12, ABHD5, ACD, ADAM10, ALDH3A2, ALOX12B, ALOXE3, APIS1, AQP5, ATP2A2, BRAF, C16orf57, CAPN12, CARD14, CASP14, CAST, CDSN, CERS3, CHST8, COG6, COL14A1, COL17A1, CSTA, CTC1, CTSC, CYP4F22, DKC1, DSC1, DSC2, DSC3, DSG1, DSG3, DSP, DST, EBP, EDA1, EDAR, EDARADD, ENPPI, ERCC2, ERCC3, ERCC4, ERCC5, ERCC6, ERCC8, EXPH5, FAM83G, FERMT1, FLG, FLG2, GJA1, GJB2, GJB3, GJB4, GJB6, GTF2E2, GTF2H5, HPGD, HRAS, IL-36RN, ITGA6, ITGB4, JUP, KANK2, KDSR, KLHL24, KRAS, KRT1, KRT2, KRT5, KRT6A, KRT6B, KRT6C, KRT9, KRT10, KRT14, KRT16, KRT17, KRT83, LAMA3, LAMB3, LAMC2, LIPN, LOR, MAP2K1, MAP2K2, MBTPS2, MPLKIP, NEMO, NIPAL4, NLRP1, NOLA2, NOLA3, NSDHL, PARN, PERP, PIGO, PKP1, PLEC, PNPLA1, POMP, PVRL1, RHBDF2, RNFI13A, RSPO1, RTEL1, SASH1, SDR9C7, SERPINB7, SERPINB8, SLC27A4, SLCO2A1, SLURP1, SLURP2, SMARCA1, SNAP29, SPINK5, SR-DSA3, ST14, STS, SULT2B1, TAT, TERC, TERT, TGM1, TGM5, TINF2, TP63, TRPV3, TUFT1, VPS33B, WNT10A, WRAP53.

Supplement 3

Table S3. Heterozygous Gene variants in patients with hyperkeratotic hand eczema

Patient	Heterozygous gene variants	Classification	Interpretation
HHE-01	<i>c.35delG p.(Gly12Valfs*2)</i> <i>GJB2 (NM_004004.5)</i>	P	Autosomal recessive focal palmoplantar keratoderma with severe hearing impairment (OMIM #615028) A ~0,95% % in European population
	<i>c.2303delA p.(Lys768Serfs*66)</i> <i>EXPH5 (NM_015065.2)</i>	P	Autosomal recessive nonspecific Epidermolysis Bullosa (OMIM #615028) *Not present
HHE-02	<i>c.1709T>C p.(Val570Ala)</i> <i>ALOX12B (NM_001139.2)</i>	VOUS	Autosomal recessive congenital ichthyosis with PPK (OMIM #242100) *Not present
HHE-03	<i>c.2257G>A, p.(Val753Ile)</i> <i>COL14A1 (NM_021110.3)</i>	VOUS	Autosomal recessive punctate PPK, type IB ¹ *Not present
HHE-04	<i>c.1946A>G p.(His649Arg)</i> <i>ERCC6 (NM_001346440.1)</i>	VOUS	Autosomal recessive Cockayne Syndrome Type B (OMIM#133540) *Very low (only 1 individual) ~0,0009%
HHE-05	<i>c.2413G>A p.(Gly805Arg)</i> <i>ERCC5 (NM_000123.3)</i>	P	Autosomal recessive xeroderma pigmentosum complementation group G (XPG) and Cockayne syndrome ² *Very low (only 3 individuals) ~ 0,0012%
HHE-06	<i>c.989A>T, p.(Asp330Val)</i> <i>CYP4F22 (NM_173483.3)</i>	VOUS	Autosomal recessive congenital ichthyosis (OMIM# 604777) *Low (26 individuals) ~0,02% in European population
HHE-07	No (likely) pathogenic or VUS mutations		

AR: autosomal recessive inheritance; AD: autosomal dominant inheritance; Het: heterozygous; P: Pathogenic; PPK : palmoplantar keratoderma; VOUS: variant of unknown significance. Gene variant classification was based upon criteria as described by Fokkema et al.³
¹Percentage of healthy control individuals carrying this gene variant in the gnomAD database (<http://gnomad.broadinstitute.org/>)
 No pathogenic or likely pathogenic mutations were identified in the 135 PPK-related genes that could be associated with the hyperkeratotic hand eczema phenotype.

References

- Guo BR, Zhang X, Chen G, et al. Exome sequencing identifies a COL14A1 mutation in a large Chinese pedigree with punctate palmoplantar keratoderma. J Med Genet. 2012;49(9):563–8.
- Schäfer A, Schubert S, Gratchev A, et al. Characterization of three XPG-defective patients identifies three missense mutations that impair repair and transcription. J Invest Dermatol. 2013;133(7):1841–9.
- Fokkema IFAC, Velde KJ, Slofstra MK, et al. Dutch genome diagnostic laboratories accelerated and improved variant interpretation and increased accuracy by sharing data. Hum Mutat. 2019; Available from: <http://dx.doi.org/10.1002/humu.23896>

Part II

Treatment of Hand Eczema

**Klaziena Politiek
Wietske A. Christoffers
Pieter-Jan Coenraads
Marie-Louise A. Schuttelaar**

Department of Dermatology, University Medical Center Groningen,
University of Groningen, Groningen, the Netherlands

**Published in
Dermatologic Therapy. 2016;29(5):364-371**

Chapter 3

Alitretinoin and Acitretin in severe chronic Hand Eczema –
Results from a retrospective daily practice study

Abstract

Acitretin has been used off-label for years to treat chronic hand eczema, but acitretin is less often prescribed as alitretinoin was approved. This study evaluates both retinoids in a daily practice cohort of patients with severe chronic hand eczema in terms of drug survival and reasons for discontinuation. Patients using alitretinoin or acitretin between 01-01-1994 and 01-08-2015 were included in this retrospective daily practice study and analyzed by Kaplan-Meier drug survival curves. Potential determinants were analyzed by Cox regression analyses. Ninety-five patients were treated with alitretinoin and 109 patients with acitretin. The main reasons for discontinuation were adverse events and cleared hand eczema, 29.5% and 27.4% in alitretinoin versus 43.1% and 23.9% in acitretin. Patients with hyperkeratotic hand eczema had most often a good effect of treatment: 68.3% in alitretinoin and 50.7% in acitretin treatment. The drug survival rates of alitretinoin and acitretin after 12, 24, 36, and 52 weeks were 69.3%, 45.1%, 19.6%, 7.0% and 74.3%, 45.5%, 33.8%, 23.2%, respectively. Alitretinoin and acitretin are effective treatment options for patients with hand eczema. However, both treatments were more effective in patients with hyperkeratotic hand eczema. Fewer patients discontinued alitretinoin compared with acitretin due to adverse events.

Introduction

Treatment of chronic hand eczema is often a therapeutic challenge. An estimated of 2–4% of the hand eczema patients suffers of chronic hand eczema unresponsive to topical corticosteroids with a significant loss of quality of life.¹ The retinoid acitretin has been prescribed off-label for decades to treat chronic hand eczema. Alitretinoin was approved in 2008 for severe chronic hand eczema and at the moment it is available in several countries in Europe, Israel, South Korea, and Canada. Alitretinoin was approved in the Netherlands in September 2013. Subsequently, acitretin was prescribed less often to treat severe chronic hand eczema.

Both, alitretinoin and acitretin are vitamin A derivatives, but their target profile is different. Alitretinoin works as a pan-retinoid-receptor agonist, activating both retinoic acid receptors and retinoid X receptors (RAR a, b, c and RXR a, b, c). Acitretin is a retinoid which activates only the retinoic acid receptors (RAR a, b, c). Pharmacological the binding to specific nuclear receptors of genes results among others in cellular differentiation, proliferation, and reduction of inflammation and keratinisation.^{2,3} However, the exact mechanism of both treatments in chronic hand eczema is not completely clear.

The efficacy of alitretinoin was studied in large, well-conducted, though pharmaceutical sponsored randomized controlled trials with more than 1600 participants.^{4–6} Alitretinoin 30 mg a day resulted in clear or almost clear hand eczema in 48% of the participants, compared with 17% in placebo.⁵ Acitretin was previously studied in three small trials with a total of 80 hand eczema patients.^{7–9} Thestrup-Pedersen et al. demonstrated in a randomized controlled trial a 51% reduction on severity in 29 patients with hyperkeratotic hand eczema after 4 weeks of treatment with acitretin (30 mg/day) compared with a 9% reduction in the placebo group (n515).⁷

This retrospective study shows a detailed drug survival analysis of both retinoids in a daily practice cohort of severe chronic hand eczema patients. Drug survival is an outcome measure to evaluate drugs in an extensive way covering effectiveness, safety, patients', and doctors' preference.¹⁰ In addition, adverse events, reasons for discontinuation of treatment and relapse rates were studied.

Material and Methods

Patient and treatment characteristics

This retrospective study was conducted at the Dermatology Department of the University Medical Center Groningen (UMCG) in the Netherlands. All patients were registered according to the 10th edition of the International Statistical classification of Diseases and Related Health Problems (ICD–10).¹¹ Study subjects were identified by cross combining morbidity (XII–L20, L23, 24, 25 and L30) and laboratory monitoring. Laboratory monitoring is mandatory in all patients during treatment with oral retinoids and blood lipids and liver function parameters were used to identify the subjects. Subsequently, we preserved the following inclusion criteria: adult patients having a clinical diagnosis of chronic hand eczema, treated with acitretin between 01-01-1994 and 01-08-2015 (data-lock) and/or alitretinoin between 01-09-2013 and 01-08-2015 (data-lock). Chronic hand eczema was defined as hand eczema which lasted for at least three months. The exclusion criteria were patients with psoriasis palmoplantaris, psoriasis elsewhere on the body or patients with predominantly atopic dermatitis. When patients had received both, acitretin and alitretinoin, they were analyzed in both groups.

In case of alitretinoin, patients were treated according to the Summary of Product Characteristics.² The recommended start and maintenance dose of alitretinoin was 30 mg/day. If adverse events

occurred, a dose reduction to 10 mg/day was allowed. The registered treatment period is 12–24 weeks depending on the response. Treatment should be stopped if no effect has occurred after 12 weeks.² In case of a relapse after discontinuation of alitretinoin, patients do benefit from restart of treatment.^{2,12} For acitretin treatment, the start and maintenance dose varied between 20–30 mg daily. Patients were allowed to use medium potent topical corticosteroids and emollients during both treatments.

Data collection

Prespecified medical charts for hand eczema were retrospectively analyzed with regards to patient and treatment characteristics including start and stop dates, effectiveness of treatment, adverse events, laboratory parameters, contact sensitizations according to the guidelines of the International Contact Dermatitis Research Group (ICDRG), clinical diagnosis of hand eczema according to the Danish Contact Dermatitis Group¹³ and previous systemic treatments (such as acitretin, alitretinoin, cyclosporine, azathioprine, methotrexate, or mycophenolatemofetil).

The effectiveness of treatment was retrospectively assessed after three months according to the clustered physician's global assessment (PGA) score.¹⁴ This clustered PGA ranges from 1 to 3: PGA-1: good effect of treatment, PGA-2: moderate effect, PGA-3: failure of treatment (no improvement or worse). Treatment episodes less than 8 weeks were excluded from PGA scoring.

The median time to relapse was measured in patients after discontinuation due to cleared hand eczema, defined as the time until retreatment or the time until severe signs and symptoms of hand eczema reoccured.

Statistical analyses

Data analyses were performed with IBM SPSS Statistics (SPSS, Chicago, IL, USA) for Windows (version 22.0). Duration of drug survival was defined as the number of days which an individual continued the first treatment episode. Treatment interruptions up to 21 days were allowed and considered as one continuous treatment episode. Reasons for drug discontinuation were registered. For each subject only the first treatment episode with alitretinoin or acitretin was analyzed. Drug survival was descriptively analyzed using Kaplan–Meier survival curves. Four events for drug survival were defined and analyzed separately: (a) discontinuation overall, (b) discontinuation due to clear/almost clear hand eczema, (c) discontinuation due to adverse events, and (d) discontinuation due to ineffectiveness. In the overall analysis (a), subjects were censored when still active at the moment of data lock or lost to follow-up. In sub analyses (b, c, d) subjects were censored for all other reasons than the reason of interest. Subjects that discontinued because of both adverse events and ineffectiveness were considered to have an event in both sub analyses (c, d). Graphpad prism version 5.04 was used to create Kaplan Meier survival curves.

In addition, the influence of the following potential determinants was analyzed by a univariate Cox-regression model: gender, age and clinical diagnosis hyperkeratotic hand eczema versus nonhyperkeratotic hand eczema. Determinants in the univariate analysis with a p -value of <0.2 were entered in a multivariate Cox-regression model. By backward selection, a full model was built to identify independent determinants which influence the drug survival curves for alitretinoin and acitretin. Hazard ratios (HRs) for age were categorized in 5-year intervals. In the multivariate analysis, p -values <0.05 were considered statistically significant.

Results

Patient characteristics

A first episode of alitretinoin was prescribed to 95 hand eczema patients and acitretin was prescribed to 109 hand eczema patients. Characteristics of both groups are described in Table 1.

Treatment characteristics

The total included treatment years of alitretinoin was 39.5 years, and for acitretin 89.8 years, respectively. The shortest duration of alitretinoin treatment was 1 day, the longest 1.8 years. The treatment duration of acitretin ranged from 3 days to 10.3 years. In August 2015, the moment of data lock, 11 patients (11.6%) were still actively using alitretinoin and none of the included patients was using acitretin. Reasons for discontinuation were described in Table 1.

Adverse events occurred in 62 alitretinoin users (65.3%), which led in 23 patients (24.2%) to a dose reduction to 10 or 20 mg/day. In 28 patients (29.5%) the occurrence of adverse events was a reason to discontinue therapy (Table 2), of which nine patients had reduced the dose previously. Headache (14.7%), gastro intestinal symptoms (9.5%) and hypertriglyceridemia (3.2%) were the most frequent reported adverse events leading to discontinuation of alitretinoin. Overall eight patients (8.4%) encountered depression or related symptoms during alitretinoin treatment. One patient suffered of suicidal behavior, which disappeared after discontinuation of alitretinoin. Adverse events occurred in 59 acitretin users (54.1%), which resulted for 22 patients (20.2%) in a dose reduction. In total 47 (43.1%) of the acitretin users discontinued treatment due to adverse events (Table 2) in which nine patients had reduced the dose previously. Dry mucosa (12.8%), headache (7.3%) and hair loss (4.6%) were the most frequent reported adverse events which resulted in discontinuation of acitretin treatment. Depression or related symptoms were reported in 4 patients (3.7%).

Nine patients had received acitretin and subsequently received alitretinoin. These subjects were analyzed in both groups. Looking into detail to reasons for discontinuation of acitretin, adverse events ($n=4$), nonresponsiveness ($n=4$) and both reasons ($n=1$) led to discontinuation. Alitretinoin was started nine months till 10 years afterwards. Reasons for discontinuation of alitretinoin were cleared hand eczema at 24 weeks ($n=5$), noncompliance ($n=1$), nonresponsiveness ($n=1$) and two patients were still using alitretinoin at the moment of data lock.

Twenty-six patients (27.4%) discontinued alitretinoin treatment because of cleared hand eczema (clear/almost clear). In this group, two patients (7.7%) had no follow-up. Nine patients (34.6%) had a relapse, which resulted in retreatment with alitretinoin in six patients. The median duration till relapse and/or retreatment was 3 months. Five patients (19.2%) relapsed before 3 months. In fourteen patients (53.8%) hand eczema was controlled during a follow-up duration ranging from 2 months to more than one year. In the group of active users, four patients could not discontinue alitretinoin treatment because of a quick aggravation of their hand eczema. Their mean treatment duration was 1.5 year (± 0.3 SD).

In the patient group treated with acitretin, 26 patients (23.9%) discontinued treatment because of cleared (clear/almost clear) hand eczema. Eight patients (30.8%) were lost to follow-up; seven patients had a relapse (26.9%) which occurred after a median duration of 4 months. Ten patients (38.5%) remained free of hand eczema with a follow up ranging from 1 month to more than one year.

Effectiveness of treatment based on the PGA score after 3 months is shown in Table 1. In addition to the overall effectiveness, PGA scores of the different clinical subgroups are depicted.

Table 1. Demographic and treatment characteristics of included patients

	Alitretinoin <i>n</i> = 95			Acitretin <i>n</i> = 109		
Female gender, <i>n</i> (%)	37	(38.9)		71	(65.1)	
Mean age male, mean $\pm$ SD	50.5	$\pm$ 15.2		47.9	$\pm$ 12.1	
Mean age female, mean $\pm$ SD	52.8	$\pm$ 12.2		55.8	$\pm$ 11.6	
A history of atopic dermatitis, <i>n</i> (%)	42	(44.2)		22	(20.2)	
Contact allergy to one or more allergens, <i>n</i> (%)	45 ^a	(47.4)		42 ^b	(38.5)	
Start dose (mg), mean $\pm$ SD	29.4	$\pm$ 3.2		24.7 ^c	$\pm$ 10.8	
Mean dose (mg), mean $\pm$ SD	26.2	$\pm$ 7.2		24.9	$\pm$ 15.0	
Prior systemic treatment, <i>n</i> (%)	33	(34.7)		10	(9.2)	
Clinical subtypes, <i>n</i> (%)						
- Hyperkeratotic palmar eczema	41	(43.2)		73	(67.0)	
- Recurrent vesicular hand eczema	27	(28.4)		15	(13.8)	
- Chronic fissured dry hand eczema	20	(21.1)		8	(7.3)	
- Pulpitis	4	(4.2)		12	(11.0)	
- Nummular hand eczema	0			0		
- Nonclassifiable	3	(3.2)		1	(0.9)	
Status at the moment of data lock, <i>n</i> (%)						
- Active	11	(11.6)		0		
- Discontinued	81	(85.3)		101	(93)	
- Loss to follow up	3	(3.2)		8	(7.3)	
Reason for discontinuation, <i>n</i> (%)						
- Ineffectiveness	18	(18.9)		19	(17.4)	
- Adverse events	24	(25.3)		41	(37.6)	
- Adverse events and ineffectiveness	4	(4.2)		6	(5.5)	
- Cleared hand eczema	26	(27.4)		26	(23.9)	
- Other stop reason (patients decision, noncompliance, pregnancy wish)	9	(9.5)		9	(8.3)	
Physician's global assessment score (%)	1	2	3	1	2	3
- Hyperkeratotic palmar eczema ^d	68.3	7.3	24.4	50.7	16.4	8.2
- Recurrent vesicular hand eczema ^d	25.9	33.3	14.8	26.7	40.0	20.0
- Others ^d	51.9	22.2	14.8	52.4	28.6	9.5
- All types of hand eczema ^d	51.6	18.9	8.4	47.7	22.0	10.1

^a17 patients were not patch tested, ^b20 patients were not patch tested, ^c5 missing start doses, ^dTreatment episodes less than 8 weeks were excluded from PGA scoring; therefore, total percentages does not add up to 100%.

SD, standard deviation; PGA, physician's global assessment score; PGA-1, good effect of treatment; PGA-2, moderate effect; PGA-3, failure of treatment (no improvement or worse).

Table 2. Overview of the adverse events during treatment of alitretinoin and acitretin

Adverse event	During alitretinoin treatment n = 95 (%)		Stop reason alitretinoin n = 28 (%)		During acitretin treatment n = 109 (%)		Stop reason acitretin n = 47 (%)	
Investigations								
Cholesterol, high (>7.77 mmol/l)	5 ^a	(5.3)	0 ^a		4 ^c	(3.7)	3 ^c	(2.8)
Triglycerides, high (>5.66 mmol/l)	10 ^a	(10.5)	3 ^a	(3.2)	5 ^b	(4.6)	1 ^b	(0.9)
Skin, mucosa, subcutaneous tissue								
Dry mucosa (eyes, mouth, lips)	13	(13.7)	2	(2.1)	47	(43.1)	14	(12.8)
Epistaxis	1	(1.1)	1	(1.1)	6	(5.5)	2	(1.8)
Rash/itch	2	(2.1)	0		11	(10.1)	2	(1.8)
Hair loss	2	(2.1)	1	(1.1)	10	(9.2)	5	(4.6)
Edema	1	(1.1)	0		2	(1.8)	1	(0.9)
Gastrointestinal disorders								
Gastrointestinal symptoms	18	(18.9)	9	(9.5)	7	(6.4)	3	(2.8)
Dysgeusia	4	(4.2)	1	(1.1)	0		0	
Psychiatric								
Mood changes	5	(5.3)	2	(2.1)	3	(2.8)	2	(1.8)
Depressive symptoms	2	(2.1)	1	(1.1)	1	(0.9)	1	(0.9)
<i>Suicidal behaviour</i>	1	(1.1)	1	(1.1)	0		0	
Nervous system								
Headache	33	(34.7)	14	(14.7)	12	(11.0)	8	(7.3)
Vision changes	5	(5.3)	1	(1.1)	8	(7.3)	2	(1.8)
Fatigue	2	(2.1)	1	(1.1)	7	(6.4)	2	(1.8)
Vertigo	2	(2.1)	1	(1.1)	2	(1.8)	0	
Concentration problems	2	(2.1)	1	(1.1)	2	(1.8)	1	(0.9)
Peripheral neuropathy	1	(1.1)	1	(1.1)	0		0	
Vascular								
Flushing	6	(6.3)	2	(2.1)	0		0	
Palpitation	0		0		1	(0.9)	1	(0.9)
Aggravation of rosacea	1	(1.1)	0		1	(0.9)	1	(0.9)
Musculoskeletal								
Muscle pain	5	(5.3)	2	(2.1)	2	(1.8)	1	(0.9)
Arthralgia	3	(3.2)	0		4	(3.7)	3	(2.8)
Infections								
Paronychia	0		0		2	(1.8)	2	(1.8)
Folliculitis	1	(1.1)	0		0		0	
Other								
Malaise	4	(4.2)	2	(2.1)	4	(3.7)	3	(2.8)
Weight gain	2	(2.1)	0		0		0	
Insomnia	1	(1.1)	0		1	(0.9)	1	(0.9)
Lower libido	1	(1.1)	0		0		0	
Dyspnea	1	(1.1)	0		0		0	
Haematuria	0		0		1	(0.9)	1	(0.9)

Multiple adverse events can occur in one patients and the combination of adverse events can lead to discontinuation of the treatment. Missing laboratory assessment of triglycerides and/or cholesterol was mostly due to discontinuation before the first control visit. ^aMissing 17 patients, ^bMissing 15 patients, ^cMissing 14 patients. Bold italic = serious adverse event.

Drug survival analysis

The number of patients using alitretinoin and acitretin after 12, 24, 36 weeks and 1 year was 69.3, 45.1, 19.6, 7.0%, respectively, for alitretinoin and 74.3, 45.5, 33.8, 23.2%, respectively, for acitretin (Figure 1a). The median "overall" drug survival duration was 0.38 year (95%CI: 0.30–0.47) for alitretinoin. Acitretin treatment had a median "overall" drug survival duration of 0.40 year (95%CI: 0.29–0.51). Figures 1b–d show the split curves for the events of interest.

Determinants of drug survival

Determinants during treatment which could influence the drug survival of alitretinoin and acitretin were tested with a univariate Cox regression analysis. The multivariate Cox regression analysis identified male sex (HR: 0.34, 95%CI 0.14–0.81) and hyperkeratotic hand eczema (HR: 0.06, 95%CI 0.01–0.48) as independent determinants associated with a longer drug survival for alitretinoin related to ineffectiveness. Meaning males and patient with hyperkeratotic hand eczema discontinued alitretinoin treatment less often because of ineffectiveness. For acitretin univariate Cox regression analysis did not result in determinants which could be entered in a multivariate analysis.

Discussion

Alitretinoin and acitretin both had median drug survival duration of approximately 0.4 years, though substantial differences between the drug survival curves were found. In alitretinoin treatment a steep drop in drug survival rates was seen after 24 weeks (Figure 1a), which mainly represents patients dropping out due to cleared hand eczema (Figure 1b). This is in line with the registration of alitretinoin up to 24 weeks. However, various patients used alitretinoin for a substantial longer period. Extended use of alitretinoin is supported by Lynde et al. who encouraged the use of alitretinoin up to 48 weeks.¹⁵ Acitretin on the other hand is off label and recommendations regarding duration do not exist. After 1 year, one in five patients was still using acitretin. A considerable number of the patients discontinued treatment with alitretinoin or acitretin in the first months. The main reason was adverse events, mainly in patients treated with acitretin (43.1%). For alitretinoin fewer patients discontinued due to adverse events (29.5%), however this percentage was much higher compared to a previous daily practice study of Diepgen et al. (6.2%).¹⁶ They conducted an observational study with structural daily life conditions over a period of 24 weeks. Probably the stricter treatment conditions, the patient motivation to participate in a study and the shorter duration of follow up resulted in these differences. In our study a minority of the patients discontinued treatment of alitretinoin after 24 weeks due to adverse events.

Some differences in adverse events profile were found between both treatments. In acitretin treatment, frequently reported adverse events such as dry mucosa and hair loss were insurmountable for various patients. These adverse events played a minor role in treatment of alitretinoin. Headache was frequently reported for both retinoids, however for alitretinoin this percentage was significantly higher and was the most important adverse event leading into discontinuation. Another important finding during treatment, mainly in alitretinoin, was the percentage of patients with mood changes or even suicidal behavior (8.4%). This was reported previously in a postmarketing surveillance of 1,124 alitretinoin patients, in which depression or related symptoms were found in 147 patients (13.1%) and suicidal ideation in 20 patients (1.8%).¹⁷ In randomized controlled trials lower percentages were found (3.1%), although one patient did commit suicide.¹⁷ In this study the percentages of patients with mood changes were lower in acitretin treatment compared to alitretinoin treatment. However, this number might be biased since nowadays physicians are more

Figure 1. Drug survival rates of alitretinoin and acitretin split in four events of drug survival: a) discontinuation overall, b) discontinuation due to cleared hand eczema, c) discontinuation due to adverse events, and d) discontinuation due to ineffectiveness.

focused on possible psychiatric symptoms during retinoid therapy. Nevertheless, it is important for treating physicians and patients to discuss the mental state before and during treatment and be aware of this potential side effect of retinoids. As expected, from previous studies increased serum lipids were found in both treatments. During alitretinoin treatment hypertriglyceridemia was the most limiting abnormality in laboratory assessments, which resulted occasionally into dose reductions or discontinuation of treatment. An important advantage of alitretinoin over acitretin is the shorter period of compulsory use of contraception: 2 years after acitretin treatment compared to only 1 month for alitretinoin. However, in this study most patients were not of childbearing age.

Both treatments are known to have therapeutic effects on hyperkeratotic hand eczema.^{5,7} This was confirmed by our evaluation of the PGA scores (Figure 1), which showed especially in hyperkeratotic hand eczema a good treatment response. Moreover, in alitretinoin treatment hyperkeratotic hand eczema was associated with a significant longer drug survival duration related to ineffectiveness compared with patients with nonhyperkeratotic hand eczema, meaning less patients with hyperkeratotic hand eczema discontinued treatment because of ineffectiveness. In the nonhyperkeratotic subgroups, less favorable responses to alitretinoin were found, which is comparable to

results of previous studies.^{5,16} No data in nonhyperkeratotic hand eczema for acitretin exist. In this study, recurrent vesicular hand eczema showed the lowest response, reaching a PGA-1 in only 26% of the patients during alitretinoin treatment and 27% during acitretin treatment.

A positive reason for discontinuation was cleared hand eczema in both treatments. In alitretinoin treatment this was expected around 24 weeks, given the registration. Follow-up after discontinuation due to cleared hand eczema in our study showed a relapse rate of 19.6%. Ruzicka et al. found a relapse rate of 26% of the patients after 3 months.⁶ However, in daily life the use of topical medication was not restricted in contrary to Ruzicka et al. Moreover, in our patient cohort, in four patients a rapid aggravation developed after decreasing the dose or discontinuation for a few days and alitretinoin was therefore restarted. Retreatment with alitretinoin is known to have a beneficial effect in most patients.¹² For acitretin only Capella et al. described a follow-up up to 5 months, in which improvement significantly persisted after discontinuation acitretin compared to conventional topical treatment.⁹ No data on relapse rates was given. In this study, a quarter of the acitretin patients relapsed.

Drug survival does not depict quality of life directly, though it does contain components such as patient satisfaction and the impact of adverse events on daily life. Various studies on alitretinoin showed an improvement in quality of life during treatment.^{6,7} However, to the best of our knowledge, the impact of acitretin in terms of quality of life has not been studied for hand eczema. For psoriasis, recent studies investigated patients' satisfaction and showed varying outcomes for acitretin treatment.¹⁸ However, the quality of life for patients with hand eczema is negatively affected by the severity of hand eczema,¹⁹ and therefore an effective treatment is expected to improve the quality of life.

This study was specifically not designed to compare acitretin to alitretinoin, but to evaluate the use of both retinoids in daily practice. Comparison of both retinoids is not possible based on the included data as the characteristics of the study population, the treatment periods, attitudes toward treatment of patients and physicians and the treatment alternatives were significantly different for both retinoids. The retrospective nature of this study is one of the major limitations. However, the medical records were prespecified and a clustered global PGA score was used based on the dermatological examination. Another pitfall in this study is the difference in treatment period; alitretinoin was only prescribed between 2013 and 2015, while the data on acitretin date back to 1994. This could have resulted in bias due to, for example, physician experiences or patients' attitudes. Over the years the experience of dermatologists in prescribing systemic therapies has increased, although not much documented. This study describes the largest number of hand eczema patients treated with acitretin.

In conclusion, alitretinoin and acitretin are effective treatment options for patients with different types of hand eczema. For both treatments the highest efficacy was found in patients with hyperkeratotic hand eczema. Fewer patients discontinued alitretinoin due to adverse events compared to acitretin. Alitretinoin is approved in several countries, nevertheless acitretin can be considered as an adequate treatment option in countries where alitretinoin is not yet available.

References

1. Diepgen TL, Agner T, Aberer W, et al. Management of chronic hand eczema. *Contact Dermatitis* 2007; 57: 203–210.
2. Basilea Pharmaceutica. ToctinoVR (alitreinoin): UK summary of product characteristics. <https://www.medicines.org.uk/emc/medicine/21177>. Accessed September 04, 2014.
3. Genus Pharmaceuticals, Acitretin: UK summary of product characteristics. <https://www.medicines.org.uk/emc/medicine/28610>. Accessed August 11, 2015.
4. Ruzicka T, Larsen FG, Galewicz D, et al. Oral alitreinoin (9-cis-retinoic acid) therapy for chronic hand dermatitis in patients refractory to standard therapy: results of a randomized, double-blind, placebo-controlled, multicenter trial. *Arch Dermatol* 2004; 140: 1453–1459.
5. Ruzicka T, Lynde CW, Jemec GB, et al. Efficacy and safety of oral alitreinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebocontrolled, multicentre trial. *Br J Dermatol* 2008; 158: 808–817.
6. Fowler JF, Graff O, Hamedani AG. A phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of alitreinoin (BAL4079) in the treatment of severe chronic hand eczema refractory to potent topical corticosteroid therapy. *J Drugs Dermatol* 2014; 13: 1198–1204.
7. Thestrup-Pedersen K, Andersen KE, Menné T, Veien NK. Treatment of hyperkeratotic dermatitis of the palms (eczema keratoticum) with oral acitretin. A single-blind placebo-controlled study. *Acta Derm Venereol* 2001; 81: 353–355.
8. Capella GL, Fracchiolla C, Frigerio E, Altomare G. A controlled study of comparative efficacy of oral retinoids and topical betamethasone/salicylic acid for chronic hyperkeratotic palmoplantar dermatitis. *J Dermatolog Treat* 2004; 15: 88–93.
9. Tan J, Maari C, Nigen S, Bolduc C, Bissonnette R. Openlabel exploratory study of acitretin for the treatment of severe chronic hand dermatitis. *J Dermatolog Treat* 2014; 26: 1–3.
10. van den Reek JM, Kievit W, Gniadecki R, et al. Drug survival studies in dermatology: principles, purposes, and pitfalls. *J Invest Dermatol* 2015; 135: e34.
11. World Health Organization. International Statistical Classification of Diseases and Related Health Problems 10th Revision, 2015. <http://apps.who.int/classifications/icd10/browse/2015/en>. Accessed August 20, 2015.
12. Bissonnette R, Worm M, Gerlach B, et al. Successful retreatment with alitreinoin in patients with relapsed chronic hand eczema. *Br J Dermatol* 2010; 162: 420–426.
13. Menné T, Johansen JD, Sommerlund M, Veien NK, Danish Contact Dermatitis Group. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. *Contact Dermatitis* 2011; 65: 3–12.
14. Hijnen DJ, ten Berge O, Timmer-de Mik L, Bruijnzeel-Koomen CA, de Bruin-Weller MS. Efficacy and safety of long-term treatment with cyclosporin A for atopic dermatitis. *J Eur Acad Dermatol Venereol* 2007; 21: 85–89.
15. Lynde C, Cambazard F, Ruzicka T, Sebastian M, Brown TC, Maeres J. Extended treatment with oral alitreinoin for patients with chronic hand eczema not fully responding to initial treatment. *Clin Exp Dermatol* 2012; 37: 712–717.
16. Diepgen TL, Pfarr E, Zimmermann T. Efficacy and tolerability of alitreinoin for chronic hand eczema under daily practice conditions: results of the TOCCATA open study comprising 680 patients. *Acta Derm Venereol* 2012; 92: 251–255.
17. Morris M, Schifano L, Fong R, Graff O. Safety of alitreinoin for severe refractory chronic hand eczema: clinical studies and postmarketing surveillance. *J Dermatolog Treat* 2015; 17: 1–5.
18. Callis DK, Yeung H, Takeshita J, et al. Patient satisfaction with treatments for moderate-to-severe plaque psoriasis in clinical practice. *Br J Dermatol* 2014; 170: 672–680.
19. Agner T, Andersen KE, Brandao FM, et al. Hand eczema severity and quality of life: a cross-sectional, multicentre study of hand eczema patients. *Contact Dermatitis*. 2008; 59: 43–47.

Wietske.A. Christoffers¹
Klaziena Politiek¹
Pieter-Jan. Coenraads¹
Jorien van der Schaft²
Marjolein S. de Bruin-Weller²
Marie-Louise A. Schuttelaar¹

¹ Department of Dermatology, University Medical Center Groningen,
University of Groningen, Groningen, the Netherlands

² Department of Dermatology & Allergology, University Medical Center Utrecht,
Utrecht, the Netherlands

Published in
Journal of European Academy of Dermatology and Veneorology. 2016;30(1):63-6

Chapter 4

Drug Survival for Cyclosporine in Hand Eczema –
A multicentre, daily use study

Abstract

Background

Hand eczema is a common condition; it is often chronic and can be difficult to treat. Cyclosporine is used off-label to treat severe hand eczema; however, the evidence for this treatment is scarce.

Objective

To examine the drug survival of cyclosporine in a daily practice cohort of patients with chronic hand eczema.

Methods

This retrospective daily use study included hand eczema patients who were treated with cyclosporine between 01-06-1999 and 01-06-2014 in two Dutch university hospitals. Patient and treatment characteristics were retrospectively collected from medical charts. First treatment episodes were analysed by means of Kaplan–Meier drug survival curves. Possible determinants of drug survival were analysed by Cox regression models. Treatment effectiveness was analysed with a retrospective physician's global assessment.

Results

A total of 102 patients were treated with cyclosporine. The median drug survival rate was 0.86 years (10.3 months). The overall drug survival rate after 6 months, 1, 2 and 3 years were 61.7%, 45.2%, 18.6% and 13.9% respectively. Main reasons for discontinuation were adverse events, especially early in treatment, and ineffectiveness. After 3 months, a good response to treatment was recorded in 62.9% of the patients.

Conclusion

Cyclosporine had a median drug survival of 10.3 months. Especially patients with recurrent vesicular hand eczema showed a good treatment response.

Introduction

Hand eczema is a common condition affecting approximately 10% of the population.¹ An estimated 3–5% of hand eczema patients is unresponsive to topical treatment and requires systemic immunosuppressive therapy.² However, except for alitretinoin,^{3–5} the evidence for systemic therapy is limited^{6–8} Cyclosporine is off-label prescribed to treat hand eczema.

In this retrospective daily practice study the treatment of cyclosporine in patients with chronic hand eczema was investigated by means of drug survival. Drug survival is the period of time during which a patient remains on a specific treatment.⁹ This depends on a combination of factors such as drug effectiveness, occurrence of adverse events, patient satisfaction and availability of alternative treatments.^{9,10}

Material and Methods

Subjects and treatment

This retrospective study was conducted at the Dermatology Departments of the University Medical Center Groningen (UMCG) and the University Medical Center Utrecht (UMCU). Patients with a clinical diagnosis of chronic hand eczema treated with cyclosporine between 01-06-1999 and 01-06-2014 were included. Patients with predominantly atopic dermatitis in which the hands were also involved were excluded.

Two different dosages schedules were used: step-up (start with ≤ 3.5 mg/kg/day and gradually increased in weeks to months to a maximum of 5 mg/kg), and step-down regime (start with > 3.5 –5 mg/kg and slowly tapered). During treatment with cyclosporine, patients were allowed to use topical emollients and/or topical corticosteroids.

Data collection

Medical records were retrospectively analysed with regard to patient characteristics, subtype of hand eczema,¹¹ start and stop dates, dosages (< 3.5 or > 3.5 mg/kg/day), adverse events, laboratory parameters, comedication, previous therapies, contact sensitizations among others.

The effectiveness of treatment was retrospectively assessed after 3 months of treatment according to the clustered physician's global assessment (PGA) score¹²: PGA-1: good effect; more than 50% improvement, PGA-2: moderate effect; less than 50% improvement, PGA-3: failure of treatment; no improvement or worse.

Drug survival and statistical analyses

Duration of drug survival was defined as the number of days which an individual continued the first treatment episode. For each subject only the first treatment episode was analysed with Kaplan–Meier survival curves. Separate analyses were conducted for discontinuation in general (a), discontinuation due to adverse events (b) and discontinuation due to ineffectiveness (c). In the overall analysis (a), subjects were censored when still active at the moment of data lock or when lost to follow-up. In subanalyses (b, c) subjects were censored for all other reasons than the reason of interest. Subjects that discontinued because of both adverse events and ineffectiveness were considered to have an event in both subanalyses (b, c).

The influence of the following determinants was analysed by univariate Cox regression models: gender, age, prior immunosuppressive drugs, dosage, comedication and clinical type of hand eczema. Determinants with P-values < 0.2 were entered in a multivariate Cox regression model. By backward selection, a full model was built to identify independent determinants which influence

the overall drug survival for cyclosporine. Missing values were excluded from analyses.

Results

Patient and treatment characteristics

Cyclosporine was prescribed to 102 hand eczema patients, of whom 71 patients were treated in the UMCG and 31 patients in the UMCU. Cyclosporine was often prescribed to patients with recurrent vesicular hand eczema (64.7%) and 42.2% had a physician-diagnosed history of atopic dermatitis (Table 1).

The duration of cyclosporine treatment ranged from 6 days to 13.7 years, in which adverse events were the main reason for discontinuation of therapy (48.0%) (Table 2). The most frequent adverse events which were a reason to discontinue therapy were hypertension (20.6%), gastrointestinal complaints (7.8%), headache (5.9%), fatigue (5.9%) and a serum creatinine increase of >30% compared to baseline (5.9%). Another important reason for discontinuation of therapy was ineffectiveness in 23 patients (22.5%).

After 3 months of treatment 62.9% of the patients improved at least 50% in their hand eczema (PGA-1) (Table 2). In the subgroup of 66 patients with vesicular hand eczema 67.7% achieved a PGA-1 score after 3 months. Gender, age, being naive, clinical type of hand eczema and comedication did not influence PGA scores of cyclosporine after 3 months (data not shown).

Drug survival rates

Figure 1 shows the drug survival for cyclosporine in patients with hand eczema. The overall drug survival rates after 6 months, 1, 2 and 3 years were 61.7%, 45.2%, 18.6% and 13.9% respectively. The median survival duration for cyclosporine in hand eczema was 0.86 year (10.3 months).

With regard to adverse events as reason to discontinue cyclosporine treatment, the drug survival rates were 28.6%, 40.8%, 59.1% and 62.2% after 6 months, 1, 2 and 3 years respectively (Figure 1b). Ineffectiveness was a reason to discontinue cyclosporine treatment in 11.1%, 18.0%, 40.9% and 52.2% of the patients after 6 months, 1, 2 and 3 years respectively (Figure 1c).

Table 3 shows potential determinants associated with the overall drug survival from the univariate Cox regression analyses. However, in the multivariate Cox regression analysis only male sex was an independent determinant associated with a longer overall drug survival for cyclosporine (HR 0.536, 95%CI 0.334–0.861).

Table 1. Demographical characteristics of included patients

	<i>n</i> (%)
Male gender	57 (55.9)
Age over 40 years	62 (60.8)
Mean age (SD)	44.7 (13.7)
Prior systemic therapy ^a	21 (20.6)
At least 1 positive patch test reaction	64 (62.7) ^b
A history of atopic dermatitis	43 (42.2) ^c
Concomitant potent topical corticosteroids	78 (76.5)
Start dosages <3.5 mg/kg/day	50 (49.0) ^d
Recurrent vesicular hand eczema	66 (64.7)

^aNon-naïve patients were treated with another systemic agent in the past, such as acitretin or azathioprine.

^bTwelve patients were not patch tested.

^cThe atopic status was unclear for one patient.

^dSeventeen start dosages in mg/kg/day were missing.

Table 2. Treatment characteristics

	<i>n</i> (%)
Status at the moment of data lock	
Active	13 (12.8)
– Stop due to ineffectiveness	18 (17.6)
– Stop due to adverse events	44 (43.1)
– Stop due to adverse events & ineffectiveness	5 (4.9)
– Stop due to disease control	11 (10.8)
– Other stop reason (pregnancy wish, non-adherence, other compound)	3 (2.9)
– Lost to follow-up	8 (7.6)
Effectiveness after 3 months ¹²	
– PGA-1	61 (62.9)
– PGA-2	20 (20.6)
– PGA-3	16 (16.5)
– Missing PGA	5

Figure 1. Overall drug survival rates for cyclosporine over a period of 3 years (a). The median overall drug survival rate was 0.86 years. Survival rates divided into reasons for discontinuation including adverse events (b) and ineffectiveness (c).

Table 3. Determinants of overall drug survival determined by univariate Cox regression analyses

	Overall drug survival event = discontinuation Hazard ratio [CI95%]
Increasing age every 5 years	1.015 [0.927–1.113]
Male sex	0.641 [0.412–0.996] ^a
Atopic dermatitis	0.929 [0.597–1.446] (1 missing)
Positive patch test	1.457 [0.852–2.492] [†] (12 missing)
Recurrent vesicular hand eczema	0.722 [0.459–1.136] ^b
Prior systemic therapy	1.453 [0.866–2.436] ^b
Concomitant potent topical corticosteroids	0.596 [0.354–1.003] ^b
Start dosage >3.5 mg/kg/day	0.877 [0.535–1.438] (17 missing)

^aP < 0.05.

[†]P < 0.2.

Discussion

Although cyclosporine is not registered for the treatment of hand eczema, extensive clinical experience exists. This is the first study which includes this clinical experience with focus on drug survival in more than 100 patients with hand eczema.

Drug survival as outcome parameter

One of the major limitations of this study is the retrospective nature. However, start and stop dates were adequately registered, which makes drug survival a valuable outcome in a retrospective design.

As expected, a substantial number of patients discontinued cyclosporine treatment in the first

months. The majority of these patients discontinued treatment because of insurmountable adverse events early in treatment, as represented by the steep curve in Figure 1b. The effectiveness of cyclosporine is reached after several weeks: this is shown by the small plateau, followed by a steep drop in Figure 1c. Drop-outs due to ineffectiveness occurred after the first weeks. Later on in treatment other reasons, such as patients wish or pregnancy wish were more often reasons to discontinue therapy.

The drug survival could have been even longer, as 12.8% of the patients were still active user at the moment of data lock. Furthermore, patients which discontinued treatment due to controlled disease were considered as an event as well in the general analysis, though they discontinued therapy for a positive reason instead of a negative reason such as adverse events or ineffectiveness.

Daily life vs. clinical trial

Difference in drop-out rates between clinical trials and daily practice is a well-known phenomenon.¹³ Clinical studies investigate the efficacy of a drug under 'ideal' study conditions, whereas daily practice data study the effectiveness of a drug under the 'usual' conditions. Trial patients are overall 'perfect' patients who fulfil strict in- and exclusion criteria and follow a strict trial protocol towards a fixed end goal. Moreover, they may be more motivated to continue treatment. Because of this, the internal validity is higher in clinical trials, but the external validity may be lower compared to daily use studies.

Disadvantages of daily use studies are the lack of randomization and lack of blinding. Selection bias might have occurred since physicians might have prescribed cyclosporine more often to patients with vesicular hand eczema compared to hyperkeratotic hand eczema.

Cyclosporine treatment for hand eczema is studied in one randomized controlled trial and some case series.^{7,8,14} Granlund et al.^{7,15} compared cyclosporine to topical 0.05% betamethasone-17,21-dipropionate cream in 41 patients with chronic hand eczema for 6 weeks: both gave significant improvement, without significant differences between the groups. A decrease in severity of hand eczema of at least 50% in half of the patients using cyclosporine was found.⁷ These results are consistent with our results: more than half of the patients (62.9%) in our cohort achieved an improvement of at least 50% of their eczema after 3 months.

For cyclosporine the tendency exists to give the drug for short crisis interventions and to taper as soon as possible and only experience up to 16 weeks was described. However, this study demonstrated a median survival for cyclosporine of 10.3 months. The major limiting factor for treatment with cyclosporine was the occurrence of adverse events as reason for discontinuation of treatment. This was also reported by Schmitt et al.¹⁶, who conducted an extensive meta-analysis of 602 atopic dermatitis patients in clinical trials of cyclosporine.

Alitretinoin

In September 2013 the retinoid alitretinoin was registered for the Dutch market. In large, well-conducted trials 30 mg alitretinoin a day resulted in clear or almost clear hand eczema in 48% of the participants.³⁻⁵ However, of the participants with vesicular hand eczema only one-third (33%) achieved clearance or almost clearance. In our study, cyclosporine gave a PGA-1 score in 67.9% of the patients with vesicular hand eczema. Based on these retrospective results, a head-to-head trial comparing cyclosporine to alitretinoin is highly recommended, especially in patients with vesicular hand eczema.

Conclusion

This retrospective study demonstrated a median drug survival of 10.3 months for cyclosporine. Especially patients with vesicular hand eczema showed favourable PGA scores after 3 months and cyclosporine should be considered in this subgroup as one of the first treatment options, though head-to-head trials with alitretinoin are highly recommended.

Acknowledgements

We thank Raisa Thybaut and Anna Brandsma for their help with data collection, Wietske Kievit, Elke de Jong and Juul van den Reek for their support with the statistical analyses and finally Tanja Vogel for her input in the manuscript.

References

1. Meding B, Jarvholm B. Incidence of hand eczema – a population-based retrospective study. *J Invest Dermatol* 2004; 122: 873–877.
2. Soost S, Abdollahnia M, Kostev K, Worm M. Topical therapy of hand eczema – analysis of the prescription profile from dermatologists in private practice. *J Dtsch Dermatol Ges* 2012; 10: 180–184.
3. Ruzicka T, Larsen FG, Galewicz D et al. Oral alitretinoin (9-cis-retinoic acid) therapy for chronic hand dermatitis in patients refractory to standard therapy: results of a randomized, double-blind, placebo-controlled, multicenter trial. *Arch Dermatol* 2004; 140: 1453–1459.
4. Ruzicka T, Lynde CW, Jemec GB et al. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, doubleblind, placebo-controlled, multicentre trial. *Br J Dermatol* 2008; 158: 808–817.
5. Bissonnette R, Worm M, Gerlach B et al. Successful retreatment with alitretinoin in patients with relapsed chronic hand eczema. *Br J Dermatol* 2010; 162: 420–426.
6. Thestrup-Pedersen K, Andersen KE, Menné T, Veien NK. Treatment of hyperkeratotic dermatitis of the palms (eczema keratoticum) with oral acitretin. A single-blind placebo-controlled study. *Acta Derm Venereol* 2001; 81: 353–355.
7. Granlund H, Erkkö P, Eriksson E, Reitamo S. Comparison of cyclosporine and topical betamethasone-17,21-dipropionate in the treatment of severe chronic hand eczema. *Acta Derm Venereol* 1996; 76: 371–376.
8. Reitamo S, Granlund H. Cyclosporin A in the treatment of chronic dermatitis of the hands. *Br J Dermatol* 1994; 130: 75–78.
9. Burden AD. Drug survival rates for tumour necrosis factor- α antagonists in psoriasis. *Br J Dermatol* 2011; 164: 940–941.
10. Gniadecki R, Kragballe K, Dam TN, Skov L. Comparison of drug survival rates for adalimumab, etanercept and infliximab in patients with psoriasis vulgaris. *Br J Dermatol* 2011; 164: 1091–1096.
11. Menné T, Johansen JD, Sommerlund M, Veien NK, Danish Contact Dermatitis Group. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. *Contact Dermatitis* 2011; 65: 3–12.
12. Hijnen DJ, ten Berge O, Timmer-de Mik L, Bruijnzeel-Koomen CA, de Bruin-Weller MS. Efficacy and safety of long-term treatment with cyclosporin A for atopic dermatitis. *J Eur Acad Dermatol Venereol* 2007; 21: 85–89.
13. Martin K, Begaud B, Latry P, Miremont-Salame G, Fourier A, Moore N. Differences between clinical trials and postmarketing use. *Br J Clin Pharmacol* 2004; 57: 86–92.
14. Petersen CS, Menné T. Cyclosporin A responsive chronic severe vesicular hand eczema. *Acta Derm Venereol* 1992; 72: 436–437.
15. Granlund H, Erkkö P, Reitamo S. Comparison of the influence of cyclosporine and topical betamethasone-17,21-dipropionate treatment on quality of life in chronic hand eczema. *Acta Derm Venereol* 1997; 77: 54–58.
16. Schmitt J, Schmitt N, Meurer M. Cyclosporin in the treatment of patients with atopic eczema – a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 2007; 21: 606–619.

Klaziena Politiek¹
Jorien van der Schaft²
Wietske A. Christoffers¹
Pieter-Jan Coenraads¹
Juul M.P.A. van den Reek³
Eelke M.G. de Jong³
Marjolein S. de Bruin-Weller²
Marie-Louise A. Schuttelaar¹

¹ Department of Dermatology, University Medical Center Groningen,
University of Groningen, Groningen, The Netherlands

² Department of Dermatology & Allergology, University Medical Center Utrecht,
Utrecht, The Netherlands

³ Department of Dermatology, Radboud University Nijmegen Medical Centre,
Nijmegen, The Netherlands

Published in
Journal of European Academy of Dermatology and Venerology. 2016;30(8):1405-7

Chapter 5

Drug Survival of Methotrexate Treatment in
Hand Eczema Patients –
Results from a retrospective daily practice study

Methotrexate is an off-label treatment option for chronic hand eczema, although the effectiveness is only discussed in two small case series of, respectively, five and six patients.¹² To gain more insight in the drug survival rates and effectiveness of methotrexate in daily practice a retrospective study was conducted at the Dermatology departments of the University Medical Center Groningen and the University Medical Centre Utrecht. Adult patients with chronic hand eczema, treated with methotrexate between 1997 and December 2014 were included. Patients with predominantly atopic dermatitis were excluded. Treatment dose was initiated with 5–10 mg per week and gradually increased based on clinical signs (maximum total dose 20 mg/week). A physician global assessment (PGA) score³ was assessed at 8–12 weeks. Treatment episodes <8 weeks were excluded. The PGA score ranged from 1 to 3: PGA-1, good effect; PGA-2, moderate effect; PGA-3, failure of treatment.

The duration of drug survival was measured as the number of days in which patients continued their first treatment episode with methotrexate. Treatment interruptions up to 14 days were considered as an uninterrupted treatment episode. The drug survival was analyzed by Kaplan–Meier survival curves in which three ‘events’ for drug survival were analyzed: discontinuation overall; discontinuation due to adverse events; and discontinuation due to ineffectiveness. Patients lost to follow up, discontinued due to another event than the event of interest or active users at data lock were censored.⁴⁵

A total of 42 patients was included (Table 1) with a total of 39.3 patient years. The median treatment duration was 139.5 days (range: 6 days–8.9 years). After 8–12 weeks of treatment, 36.8% of the patients showed a good effect of treatment. Regarding the subtypes, in hyperkeratotic hand eczema 47.6% achieved a good effect compared to 25.0% in the non-hyperkeratotic subgroup (not statistically significant). Five patients discontinued treatment due to controlled hand eczema, all patients had hyperkeratotic hand eczema. In this subgroup, the median treatment duration was 1.5 years (range: 0.9–6.4 years).

As shown in Figure 1, 45.5%, 28.4% and 12.2% of the patients still used methotrexate after 6 months, 1 and 2 years respectively. The median survival duration was 5.2 (95% CI: 2.5–7.9) months. After 6 months, 1 year and 2 years, treatment was discontinued in 33.3%, 46.9% and 46.9% of the patients due to ineffectiveness, and in 19.2%, 34.4% and 34.4% due to adverse events. Age (in 5-year intervals), gender, prior use of systemic therapies, higher maintenance dose, concomitant use of oral corticosteroids, history of atopic dermatitis and hyperkeratotic hand eczema did not significantly influence the duration of drug survival in the univariate Cox regression analysis, therefore no determinants could be entered in a multivariate analysis.

Drug survival curves showed that after 1 year none of the patients dropped out because of ineffectiveness and adverse events and 28.4% of the patients still used methotrexate.

Seven patients discontinued treatment after 8–10 weeks of treatment, with a stop dose varying from 10 to 15 mg. Perhaps the dose was too low in these patients or the treatment period too short, since methotrexate is known for a slow onset of action. Three patients using oral methotrexate, discontinued treatment due to gastrointestinal intolerance, without altering the administration route.

In conclusion, clinical effectiveness for methotrexate therapy in hand eczema under daily life conditions seems to be favorable after 8–12 weeks of treatment. However, the median drug survival was only 5.2 months and ineffectiveness and adverse events were the most important reasons for discontinuation. Increasing the dose, continuing treatment after 8 weeks and changing the administration from oral to subcutaneous are possibilities that could have led to longer drug survival rates

Table 1. Patient and treatment characteristics

	Hand eczema (total group) (n = 42)	Hyperkeratotic hand eczema (n = 23)	Non- hyperkeratotic hand eczema ^a (n = 19)
Age (years), mean $\pm$ SD	53.2 $\pm$ 11.8	53.6 $\pm$ 10.2	52.8 $\pm$ 13.7
Male gender, n (%)	29 (69)	17 (73.9)	12 (63.2)
History of atopic dermatitis, n (%)	14 (33.3)	7 (30.4)	7 (36.8)
History of other systemic therapies ^b , n (%)	36 (85.7)	19 (82.6)	17 (89.5)
Maintenance dose (mg/week), mean $\pm$ SD	12.9 $\pm$ 3.7	12.0 $\pm$ 3.1	13.9 $\pm$ 4.1
Subcutaneous administration ^c , n (%)	4 (9.5)	1 (4.3)	3 (15.8)
Concomitant use of oral corticosteroids	7 (16.7)	–	7 (36.8)
– Median duration of treatment episode ^d , % (range)	95.4 (1–100)		95.4 (1–100)
– At discontinuation due to ineffectiveness, n (%)	1 (2.4)		1 (2.4)
– At discontinuation due to adverse events, n (%)	1 (2.4)		1 (2.4)
– At the moment of data lock, n (%)	3 (7.1)		3 (7.1)
Status of use at the moment of data lock ^e			
– Active user, n (%)	6 (14.3)	1 (4.3)	5 (26.3)
– Discontinued, n (%)	32 (76.2)	19 (82.6)	13 (68.4)
– Lost to follow-up, n (%)	4 (9.5)	3 (13.0)	1 (5.2)
Reasons for discontinuation, n (%)			
– Ineffectiveness	14 (33.3)	7 (30.4)	7 (36.8)
– Adverse events	10 (23.8)	5 (21.7)	5 (26.3)
– Controlled hand eczema	5 (11.9)	5 (21.7)	–
– Other (non-compliance, choice of patient)	3 (7.2)	2 (8.7)	1 (5.2)
Effectiveness after 3 months, n (%)	n = 37	n = 21	n = 16
– PGA-1	14 (36.8)	10 (47.6)	4 (25.0)
– PGA-2	14 (36.8)	5 (23.8)	9 (56.2)
– PGA-3	9 (23.7)	6 (28.6)	3 (18.8)
Excluded <8 weeks or missing PGA (n = 1)	5	2	3
Adverse events as reason for MTX discontinuation ^f			
– Gastro-intestinal complaints, n (%), flu-like symptoms, n (%)	3 (7.1)		
– Headache, n (%)	2 (4.8)		
– Urinary tract infection n (%), hematoma n (%), fatigue n (%), suspicion of an allergic reaction to folic acid or MTX n (%)	1 (2.4)		

SD, standard deviation; MTX, methotrexate; PGA, physician global assessment.

^aNon hyperkeratotic hand eczema included: recurrent vesicular hand eczema, pulpitis and chronic dry fissured hand eczema^g^bSystemic therapies included: alitretinoin, cyclosporine, acitretin, azathioprine.^cOne patient with subcutaneous administration at start, three patients changed to subcutaneous injections (two because of gastrointestinal intolerance and one because of ineffectiveness).^dThe percentage of total treatment episode is the duration of concomitant therapy divided by the duration of total MTX treatment episode.^eData lock: December 15, 2014.^fOne person might have more than one adverse events as reason for discontinuation.

Figure 1. Overall drug survival rate of methotrexate in hand eczema patients with separate curves for discontinuation due to adverse events and ineffectiveness. The median drug survival overall (discontinuation due to controlled hand eczema, adverse events, ineffectiveness and other reasons) was 52 months. The median drug survival with respect to adverse events and ineffectiveness could not be estimated, in these groups >50% still used methotrexate after 1 year.

References

1. Egan CA, Rallis TM, Meadows KP, Krueger GG. Low-dose oral methotrexate treatment for recalcitrant palmoplantar pompholyx. *J Am Acad Dermatol* 1999; 40: 612–614.
2. Mittal A, Khare AK, Gupta L, Mehta S, Garg A. Use of methotrexate in recalcitrant eczema. *Indian J Dermatol* 2011; 56(232–5154): 80434.
3. Hijnen DJ, ten Berge O, Timmer-de Mik L, Bruijnzeel-Koomen CA, de Bruin-Weller MS. Efficacy and safety of long-term treatment with cyclosporin A for atopic dermatitis. *J Eur Acad Dermatol Venereol* 2007; 21: 85–89.
4. Christoffers WA, Politiek K, Coenraads PJ, van der Schaft J, de Bruin-Weller MS, Schuttelaar ML. Drug survival of cyclosporine in the treatment of hand eczema: a multicentre, daily use study. *J Eur Acad Dermatol Venereol* 2015. [e-pub ahead of print]
5. Bissonnette R, Worm M, Gerlach B et al. Successful retreatment with alitretinoin in patients with relapsed chronic hand eczema. *Br J Dermatol* 2010; 162: 420–426.
6. van der Schaft J, Politiek K, van den Reek JM et al. Drug survival for cyclosporin A in a long-term daily practice cohort of adult patients with atopic dermatitis. *Br J Dermatol* 2015; 172: 1621–1627.
7. Menné T, Johansen JD, Sommerlund M, Veien NK, Danish Contact Dermatitis Group. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. *Contact Dermatitis* 2011; 65: 3–12.

**Jart A.F. Oosterhaven
Klaziena Politiek
Marie-Louise Schuttelaar**

Department of Dermatology, University Medical Center Groningen,
University of Groningen, Groningen, The Netherlands

**Published in
Contact Dermatitis. 2017;76(5):304-307**

Chapter 6

Azathioprine Treatment and Drug Survival in Patients with
chronic Hand Eczema – Results from daily practice

Introduction

Azathioprine is an off-label treatment for chronic hand eczema. A few small studies have found a positive effect of azathioprine on this disease, with few side-effects.¹⁻³ More data are needed in order to optimize treatment strategies. Therefore, our aim is to present our experience with azathioprine in the treatment of hand eczema in daily practice.

Methods

We retrospectively reviewed patient records between January 2000 and 16 December 2015 (data lock). Patients were identified according to the International Classification of Disease (10th edition) diagnoses L20, L23-25, and L30. We included adult patients with severe chronic hand eczema who were treated with azathioprine. Patients with concomitant mild atopic dermatitis on other body areas were also included. Many of our patients had recurrent vesicular hand eczema. Because of the treatment-refractory nature of this subtype, these patients had often been treated with cyclosporine (20/26, 76.9%). If this failed, azathioprine was used as a third-line alternative. Most patients were thus not immunosuppressant-naïve. Only first episodes of azathioprine treatment were included in the analyses.

Results

Table 1 shows individual patient data. For effectiveness, a Physician Global Assessment (PGA) after 3 months of treatment was estimated retrospectively from patient records. Patients were scored as follows: good improvement (PGA-1); moderate improvement (PGA-2); and no change or worsening (PGA-3).⁴ Seventeen of 30 patients discontinued treatment prior to the 3-month assessment: 15 because of adverse effects, and 2 because they were lost to follow-up before this time. Five of the remaining 13 patients discontinued treatment at some point following the 3-month assessment, because of insufficient responsiveness or non-responsiveness. Three patients were lost to follow-up, and 2 patients discontinued treatment because they were worried about possible long-term adverse effects of immunosuppressive therapy. These patients all had moderate to good improvement of their hand eczema. One patient discontinued treatment with azathioprine because of remission after 13.6 months. Two patients, who had used azathioprine for approximately 3 and 6 years, were still treated at data lock. Their hand eczema was in full remission at that time. Concomitant treatment with oral corticosteroids at the start of azathioprine treatment was given in 13 of 30 patients (43.3%), to decrease symptoms during the first weeks of treatment. We found no difference between patients with or without oral corticosteroid treatment at the start of azathioprine treatment, and good improvement at 3 months ($p>0.99$, Fisher's exact test). Also, no difference was found between patients who used oral corticosteroids at the start of treatment and patients who did not regarding the adherence to azathioprine at 3 months (Chi²: $p=0.79$). Finally, in the first 3 months, non-responsiveness was never a reason for discontinuing azathioprine treatment, regardless of whether or not oral corticosteroids were concomitantly given. This means that, regarding the long-term effectiveness and drug survival (the time for which patients remain on a drug) of azathioprine, it might be unnecessary to co-prescribe oral corticosteroids. However, despite these observations, a valid reason for co-prescribing oral corticosteroids at the start of azathioprine treatment could be their rapid onset of action, leading to a decrease in symptoms in the short term. Figure 1 shows the drug survival flow diagram of azathioprine.

No differences were found between patients with or without a history of atopic dermatitis and

Table 1. Individual data of patients treated with azathioprine

Patient no	Sex	Age at start of therapy (years)	HE morphological subtype	History of AD	Immunosuppressant/immunomodulant-naïve	Polysensitized ^a	Duration of therapy (months)
1	M	48	Recurrent vesicular	No	No (CsA)	No	0.46
2	F	63	Recurrent vesicular	Yes	No (CsA, Aci)	Yes	0.59
3	M	56	Recurrent vesicular	Yes	No (CsA)	Yes	0.69
4	F	55	Recurrent vesicular	No	No (CsA)	No	0.69
5	F	80	Hyperkeratotic	No	No (Aci)	No	0.72
6	F	56	Recurrent vesicular	No	No (CsA)	No	0.76
7	M	33	Recurrent vesicular	Yes	No (CsA)	No	0.89
8	F	55	Recurrent vesicular	Yes	Yes	No	0.89
9	F	51	Recurrent vesicular	No	No (Ali)	Yes	0.92
10	M	42	Recurrent vesicular	Yes	No (CsA)	Yes	1.02
11	F	58	Recurrent vesicular	No	No (Ali)	Yes	1.15
12	M	66	Recurrent vesicular	Yes	No (MTX)	^d	1.22
13 ^e	M	59	Recurrent vesicular	No	No (CsA)	No	1.22
14	M	46	Pulpitis	No	No (CsA, Aci)	No	1.58
15 ^e	M	64	Recurrent vesicular	Yes	No (CsA)	No	1.84
16	F	60	Recurrent vesicular	Yes	No (CsA)	No	2.14
17	F	33	Pulpitis	Yes	No (CsA)	No	2.30
18	M	31	Recurrent vesicular	Yes	No (CsA)	Yes	3.88
19	F	53	Recurrent vesicular	No	Yes	No	4.40
20	M	22	Recurrent vesicular	No	No (CsA)	No	4.53
21	M	71	Recurrent vesicular	Yes	No (CsA)	No	4.73
22	M	41	Recurrent vesicular	No	No (CsA)	Yes	6.18
23	M	43	Recurrent vesicular	No	No (CsA)	Yes	7.36
24	F	60	Recurrent vesicular	Yes	No (MTX)	No	11.17
25 ^e	F	54	Chronic fissured	No	Yes	No	13.60
26	M	32	Recurrent vesicular	No	No (CsA)	No	20.90
27	F	54	Recurrent vesicular	Yes	No (CsA)	No	28.12
28	F	24	Recurrent vesicular	Yes	No (CsA)	No	34.96
29	F	40	Recurrent vesicular	Yes	No (CsA)	No	60.94
30	M	34	Recurrent vesicular	Yes	No (CsA)	Yes	70.18
		500 ± 142					198 (7.43)

Aci, acitretin; AD, atopic dermatitis; AE, adverse effect; Ali, alitretinoin; Aza, azathioprine; CsA, cyclosporine A; F, female; Hb, haemoglobin; HE, hand eczema; GI, gastrointestinal; LTFU, lost to follow-up; M, male; MTX, methotrexate; NA, not applicable; OC, oral corticosteroid; PGA, Physician Global Assessment; SD, standard deviation.

Mean ± SD or Median (interquartile range). Thiopurine methyltransferase activity was measured in 17 patients. No low activity (or inactivity) was found. The table is arranged according to Aza treatment duration.

^aPolysensitization was defined as three or more positive patch test reactions to allergens in the European baseline series.⁵

^bThirteen patients were still being treated at 3 months (43%).

^cSix more patients reported adverse effects that did not lead to discontinuation.

^dNo patch test.

^eThese 3 patients were retreated with Aza. For details, see text.

Table 1 continued

Aza dose at start (mg/day)	Aza dose at discontinuation (mg/day)	Concomitant OCs. Fraction of Aza treatment duration (OC starting dose)	PGA at 3 months ^b (OC dose at 3 months)	Event(s) leading to discontinuation ^c
50	50	1.0 (10 mg)	NA	AE: GI, flu-like symptoms, arthralgia
50	50	-	NA	AE: flu-like symptoms
50	50	-	NA	AE: headache, arthralgia
50	50	-	NA	LTFU
50	50	-	NA	AE: increased liver enzymes
50	50	-	NA	AE: GI
50	100	1.0 (30 mg)	NA	AE: GI, increased liver enzymes
50	100	1.0 (10 mg)	NA	AE: GI, tiredness
125	125	1.0 (20 mg)	NA	AE: GI
50	100	1.0 (10 mg)	NA	AE: increased liver enzymes
50	100	-	NA	AE: GI
50	150	-	NA	AE: GI
50	125	-	NA	AE: increased liver enzymes
50	100	0.2 (10 mg)	NA	LTFU
50	100	0.1 (?)	NA	AE: tiredness, lowered Hb
50	50	-	NA	AE: increased liver enzymes
100	100	-	NA	AE: Not specified
50	250	0.8 (30 mg)	2 (20 mg)	Non-resp
50	100	-	3	Non-resp
50	100	-	2	Non-resp, AE: GI
50	150	0.8 (30 mg)	2 (5 mg)	Non-resp
50	300	0.7 (10 mg)	2 (10 mg)	Non-resp
50	100	0.2 (10 mg)	1	LTFU
75	50	-	2	LTFU
50	50	-	1	Remission
50	100	-	1	Personal concern
50	100	-	1	LTFU
50	50	-	1	
50	125	<0.01 (5 mg)	1	Personal concern
50	125	0.1 (10 mg)	1 (10 mg)	
50 (0)	100 (75)			

an outcome of good improvement at 3 months ($p>0.99$, Fisher's exact test). Furthermore, we did not find a difference between patients with or without polysensitization and good improvement at 3 months: ($p>0.99$, Fisher's exact test). Polysensitization was defined as having three or more positive patch test reactions to allergens in the European baseline series.⁵ Three of the 30 patients (2 males and 1 female; age range 56–64 years) were retreated with azathioprine at a median dose of 100mg daily. No oral corticosteroids were given at the start of re-treatment. One patient discontinued treatment after 2.5 months because of insufficient response; 2 patients continued treatment for 1 year, and discontinued treatment because of remission of their hand eczema. No severe harmful effects occurred in the studied population. Considering first episodes and retreatments, 7 of 15 (46.7%) patients who used azathioprine at 3 months were still being treated at 1 year.

Figure 1. Azathioprine drug survival flow diagram.
aThe censored patient was still using azathioprine at data lock, and had full clearance of hand eczema during the third year of treatment.

Discussion

Discontinuation of azathioprine treatment was often caused by subjective adverse effects. This occurred mainly during the first 3 months. In this timeframe, patients frequently experienced no change or worsening, probably because of the delayed onset of action of azathioprine (8–12 weeks). Treating patients who indicate subjective adverse effects can therefore be difficult, and it is vital to critically weigh subjective adverse effects against the possible benefit of azathioprine in the long term. In several of our cases, treatment might have been discontinued too soon. Physicians should motivate patients with mild subjective adverse effects to continue treatment for at least 8–12 weeks, when the clinical effect of azathioprine becomes apparent.

Limitations of this study were the small sample size, a probably highly treatment-refractory study group, the lack of a controlled design, and the fact that data on effectiveness were collected retrospectively. Unfortunately, the weight of patients was not documented, so dosage could not be calculated in relative terms (mg/kg).

Our data support the notion that azathioprine can be effective in the treatment of hand eczema. On the other hand, a considerable number of patients experienced adverse effects, leading to early discontinuation of treatment. Prospective studies comparing treatment modalities (especially systemic drugs) in hand eczema are needed to determine more adequate management strategies.

References

1. Scerri L. Azathioprine in dermatological practice. An overview with special emphasis on its use in non-bullous inflammatory dermatoses. *Adv ExpMed Biol* 1999; 455: 343–348.
2. Pearce V J, Mortimer P S. Hand dermatitis and lymphoedema. *Br J Dermatol* 2009; 161: 177–180.
3. Agarwal U S, Besarwal R K. 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.
4. Hijnen D J, ten Berge O, Timmer-de Mik L et al. Efficacy and safety of long-term treatment with cyclosporin A for atopic dermatitis. *J Eur Acad Dermatol Venereol* 2007; 21: 85–89.
5. Carlsen B C, Andersen K E, Menné T, Johansen J D. Patients with multiple contact allergies: a review. *Contact Dermatitis* 2008; 58: 1–8.

Part III

Burden of Hand Eczema

Klaziena Politiek¹
Robert F. Ofenloch²
Marius J. Angelino¹
Ewoud van den Hoed¹
Marie-Louise A. Schuttelaar¹

¹ Department of Dermatology, University Medical Center Groningen,
University of Groningen, Groningen, The Netherlands

² Department of Occupational and Environmental Dermatology,
University Hospital Heidelberg, Heidelberg, Germany

Published in
Contact Dermatitis. 2020;82(4):201-210

Chapter 7

Quality of Life, Treatment Satisfaction, and Adherence to
Treatment in Patients with vesicular Hand Eczema –
A crosssectional study

Abstract

Background

Recurrent vesicular hand eczema frequently has a chronic course and needs long-term treatment.

Objective

To evaluate health-related quality of life (HRQoL), treatment satisfaction, and adherence in patients with vesicular hand eczema.

Methods

Patients using one main treatment for at least three months were included. Data on HRQoL (Quality of Life in Hand Eczema Questionnaire [QOLHEQ]), treatment satisfaction (Treatment Satisfaction Questionnaire for Medication, version II), and treatment adherence (4-item Morisky Medication Adherence Scale) were collected. Univariate and multivariate regression analysis were used to predict variables associated with HRQoL.

Results

HRQoL was moderately impaired, with the highest impact in the QOLHEQ subdomain symptoms. Female sex, more severe hand eczema, and lower treatment satisfaction were associated with more impairment in HRQoL. Patients with severe/ very severe hand eczema had significant lower “global satisfaction” scores compared with the other severity groups. The “global satisfaction” and treatment adherence in patients using systemic treatment were significantly higher compared with those with only topical treatment.

Conclusion

In patients with vesicular hand eczema disease severity affects both HRQoL and treatment satisfaction. Systemic treatment of severe hand eczema could improve the severity and as a result also HRQoL, treatment satisfaction, and medication adherence.

Introduction

Hand eczema can be classified into different clinical subtypes. Recurrent vesicular hand eczema is a typical clinical subtype that is characterized by development of small (1–2 mm) vesicles most often interdigitally or on the palms. The patient experiences episodes of vesicles mostly at unpredictable intervals, which can result in a chronic course of recurrent vesicular hand eczema. In addition to a clinical diagnosis, it is important to classify hand eczema etiologically. The cause of hand eczema is often multifactorial. It can be classified into one or more of the following etiological diagnoses: allergic contact dermatitis, irritant contact dermatitis (ICD), protein contact dermatitis, and atopic hand eczema.¹

The treatment of chronic hand eczema is often challenging and at times insufficient and unsatisfactory.^{2,3} Studies on treatment effectiveness are mainly based on physician-reported outcomes. Fewer studies have actually evaluated treatment benefit in terms of patient-reported outcomes.^{4,5} However, chronic hand eczema can have a remarkable impact on quality of life.^{2,6}

To evaluate the impact of disease and treatment on physical, psychological, and social functioning, the Quality of Life in Hand Eczema Questionnaire (QOLHEQ) was recently developed. It measures overall health-related quality of life (HRQoL) impairment in four domains: “symptoms,” “emotions,” “functioning,” and “treatment and prevention.”^{7,8} Other patient-reported outcomes are treatment satisfaction and treatment adherence.^{9,10} Previous studies in several therapeutic areas demonstrated a positive association between treatment satisfaction and adherence to therapy.¹¹ In this study we aimed to examine HRQoL, treatment satisfaction, and treatment adherence in patients with recurrent vesicular hand eczema.

Material and Methods

Study design and participants

This cross-sectional study was conducted at the Dermatology Department of the University Medical Center Groningen (Groningen, The Netherlands), a tertiary referral center for hand eczema, between December 2016 and May 2019. Patients were recruited while they were on a routine visit at the outpatient clinic. Despite the fact that some patients had mild contributing atopic dermatitis, hand eczema was the main reason for consultation. Inclusion criteria were adult age (>18 years old), diagnosis of chronic (>3 months) vesicular hand eczema (classification of Menné et al.¹), and use of at least one main treatment for at least three months. Patients concomitantly treated with bursts of oral corticosteroids in the last 3 months were excluded. Included patients needed to be able to read and understand the Dutch language. Patients were interviewed according to a structured questionnaire. The study was reviewed and approved by the Medical Ethical Review Board of the University Medical Center Groningen (reference METc M17.207552).

Clinical characteristics

Data collected were basic characteristics (age, sex, education [low/middle vs high]), employment status (low- vs high-risk occupation for hand eczema¹²), and elevated total and specific immunoglobulin E inhalant allergens. Etiological hand eczema diagnosis was based on fixed criteria (see Data S1 – <https://doi.org/10.1111/cod.13459>)

Data on current (topical, UV, and systemic treatment) and previous (topical, UV, systemic treatment, and hospitalization) treatments for hand eczema were collected. All patients with vesicular hand eczema were treated according to the Dutch guidelines of hand eczema.^{13,14} Previous treatment with oral corticosteroids for over 2 weeks was counted as a history of systemic treatment.

The current treatment was based on the most potent medication (systemic treatment vs non-systemic treatment). Patients with systemic treatment may have used concomitantly topical corticosteroids. Disease severity was assessed by the physician with the photographic guide of Coenraads et al.¹⁵ For a complete overview of all variables, see the questionnaire in Data S1.

Quality of life, treatment satisfaction, and adherence

To evaluate the HRQoL, the Dutch translation of the QOLHEQ was used, range 0–89. This disease-specific questionnaire consists of 30 questions covering four subdomains: “symptoms” (7 questions), “emotions” (8 questions), “functioning” (8 questions), and “treatment and prevention” (7 questions). Response categories are never, rarely, sometimes, often, and always.^{7,8} For the recently validated Dutch language version, these are scored as 0, 1, 1, 2, and 3, respectively. The severity band for the QOLHEQ overall score for Dutch patients is as follows: not at all, 0–13; slightly, 14–28; moderately, 29–44; strongly, 45–64; and very strongly, ≥65.¹⁶

Satisfaction was assessed with the Dutch version of the Treatment Satisfaction Questionnaire for Medication, version II (TSQM-II), range 0–100.⁹ The TSQM-II is an 11-item validated questionnaire comprising three domains: “effectiveness” (2 questions), “side effects” (4 questions), and “convenience” (3 questions). Moreover, “global satisfaction” (2 questions) was measured. Response categories are as follows: 1, extremely dissatisfied; 2, very dissatisfied; 3, dissatisfied; 4, somewhat satisfied; 5, satisfied; 6, very satisfied; and 7, extremely satisfied. The score per domain can be calculated with an algorithm ranging from 0 to 100, where higher scores equate to better outcomes. To evaluate treatment adherence four dichotomous questions (yes [1]/no [0]), the 4-item Morisky Medication Adherence Scale was used, range 0–4. A sum score of 0 represents a high patient adherence, a score of 1 or 2 represents a medium adherence, and a score of 3 or 4 represents a low adherence.¹⁰

Statistical analyses

Data analyses were performed using IBM SPSS Statistics version 23.0 for Windows (SPSS/IBM, New York, New York). Descriptive statistics were presented as mean together with median and range for interval-scaled variables, and as relative frequency together with absolute numbers for categorical variables. The four QOLHEQ and TSQM subdomains were analyzed separately for the group of patients with nonsystemic therapy and for the group with systemic therapy. After controlling for normal distribution, the independent sample t test was used to analyze the differences in treatment satisfaction and HRQoL between both treatment groups. Fisher’s exact test was used to test difference in nominal variables between the nonsystemic and systemic groups. Univariate regression analysis included as independent variables age, gender, level of education (high vs middle/low), duration of hand eczema (years), the current treatment (nonsystemic vs systemic treatment), hand eczema severity, treatment adherence, and “global satisfaction,” which were suitable for inclusion ($P < .2$) into the multivariate regression model. Afterwards, multivariate linear regression was used including clinical characteristics associated with treatment satisfaction. P-values less than .05 were considered statistically significant in all analyses. Standardized β -coefficients were presented, with strong correlation defined as $\beta > 0.7$, moderate correlation as $0.7 > \beta > 0.4$, and weak correlation as $0.4 > \beta > 0.2$.¹⁷ The interpretability of the Dutch and International QOLHEQ (subdomain and overall) scores was published by Oosterhaven et al.^{8,16} See Data S3 for the Dutch (Table S3.3) and International (Table S3.4) single score bands. In this publication Dutch scores were presented; the International scores can be found in Data S3.

Results

In total, 168 (56.0% female) participants were included in this study. Sociodemographic and clinical characteristics are outlined in Table 1. The mean duration (median [range]) of a diagnosis of hand eczema was 9.2 (11.3 [0.3–65]) years. The severity grades were pooled for the total group ($n = 168$) because of the small numbers, clear ($n = 6$) and almost clear ($n = 74$); severe ($n = 31$) and very severe ($n = 9$; Table 1). Female patients had more often clear/almost clear hand eczema compared with male patients, although this was only borderline significant ($P = .06$).

Patch tests were performed in most patients (91.9%, $n = 154$). Of the patch-tested patients 69.5% ($n = 107$) had at least one positive patch test reaction to an allergen from the European baseline series. Most patients were patch tested with additional series; 79.2% ($n = 122$) had at least one positive reaction to allergens from all series tested. Polysensitization was found in 24.0% ($n = 37$). Of all patients, 37.5% ($n = 63$) had a high-risk occupation for developing hand eczema. See Data S2 for the list of these occupations. The median (range) treatment duration for nonsystemic and systemic treatments was 0.5 (0.3–32) years and 0.8 (0.3–7) years, respectively.

Health-related quality of life

The overall QOLHEQ scores indicated no impairment of HRQoL in 15.0% of patients ($n = 25$), slight impairment in 29.8% ($n = 50$), moderate impairment in 38.1% ($n = 64$), strong impairment in 12.5% ($n = 21$), and a very strong impairment in 4.2% ($n = 7$; Table 2). The mean overall QOLHEQ scores and the mean QOLHEQ subdomain scores are presented for the total group in Table 3, stratified by sex and type of treatment (systemic vs nonsystemic). The mean overall QOLHEQ score was 31.2, representing a moderately impaired HRQoL. The most affected subdomain was “symptoms”; the mean score was 9.1, representing a moderately impaired HRQoL. The other mean QOLHEQ subdomains scores represented slightly impaired HRQoL.

Differences in HRQoL impairment were evaluated for sex and treatment groups. The overall QOLHEQ score and subdomain “functioning” showed moderate impairment in females and slight impairment in males. The HRQoL impairment because of “symptoms” was significantly lower in the group with systemic treatment compared with the group with topical treatment. However, the mean scores in both treatment groups represented moderately impaired HRQoL.

The QOLHEQ overall scores were significantly different between each of the severity groups ($P < .001$). In the pooled group of patients with severe/very severe hand eczema (mean QOLHEQ overall score 41.1) and the group with moderate hand eczema (mean QOLHEQ overall score 33.3) a moderate impairment of HRQoL was found. The pooled group with clear/almost clear hand eczema (mean QOLHEQ overall score 25.3) showed a slight impairment (Table S3.1,S3.2).

Treatment satisfaction

TSQM subdomain scores are presented in Table 3. Patients were most satisfied about the TSQM subdomain “side effects” and least satisfied about “effectiveness.” Patients receiving systemic treatment had significantly higher TSQM treatment satisfaction scores for “effectiveness” and “global satisfaction” compared with patients receiving nonsystemic treatment (Table 3). “Global satisfaction” scores for nonsystemic vs different individual systemic treatments are presented in Figure 1. Significantly higher “global satisfaction” scores were found for ciclosporin, alitretinoin, and dupilumab compared with nonsystemic treatment. Figure 2 shows the mean TSQM subdomain scores in different severity groups. Patients with severe/very severe hand eczema had significantly lower subdomain satisfaction scores in “effectiveness” (TSQM score: 47.3, standard deviation [SD]: 14.9) compared with patients with moderate (TSQM score: 55.4, SD: 15.0) or clear/almost clear hand

Table 1. Patient characteristics

Characteristics	All patients	Male	Female	Nonsystemic treatment ^a	Systemic treatment ^b
Number of patients, <i>n</i> (%)	168 (100)	74 (44.0)	94 (56.0)	112 (100)	56 (100)
Age (years), mean SD	43.1 (15.7)	44.4 (14.4)	42.0 (16.6)	67 (59.8)	27 (48.2)
High education, <i>n</i> (%)	35 (20.8)	15 (20.3)	20 (21.3)	40.0 (56.6)*	49.3 (14.1)*
High-risk occupation, <i>n</i> (%)	63 (37.5)	30 (40.5)	33 (35.1)	27 (24.1)*	8 (14.3)*
Duration of hand eczema (years), mean (SD)	9.2 (11.3)	10.1 (11.8)	8.5 (10.9)	48 (42.9)	17 (30.4)
Elevated total IgE level (>115 kU/L), <i>n</i> (%)	41 (37.6) ^d	21 (41.2) ^e	20 (34.5) ^f	7.5 (9.9)*	12.5 (13.3)*
Elevated serum-specific IgE inhaled allergens, <i>n</i> (%)	52 (50.0) ^g	30 (60.0) ^h	22 (40.7) ⁱ	27 (39.7) ^j	14 (34.1) ^k
Etiological diagnosis ^c , <i>n</i> (%)					
- Atopic hand eczema	91 (54.2)	38 (51.4)	53 (56.4)	56 (50.0)	35 (62.5)
- Irritant contact dermatitis	81 (48.2)	36 (48.6)	45 (47.9)	57 (50.9)	24 (42.9)
- Allergic contact dermatitis	61 (39.6) ^d	26 (35.1) ^m	35 (37.2) ⁿ	42 (42.0) ^o	19 (35.2) ^p
- Protein contact dermatitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
- Etiologically unclassifiable hand eczema	20 (11.9) ^h	8 (10.8) ^r	12 (12.8)	16 (14.3) ^s	4 (7.1)
Current treatment, <i>n</i> (%)					
- Only topical treatment ^a	111 (66.1)	45 (60.8)	66 (70.2)	111 (99.1)	-
- Systemic treatment	56 (33.3)	29 (39.2)	27 (28.7)	-	56 (100)
- Ciclosporin	25 (14.9)	25 (14.9)	14 (14.9)	-	25 (44.6)
- Alitretinoin	12 (7.1)	7 (9.5)	5 (5.3)	-	12 (21.4)
- Methotrexate	7 (4.2)	3 (4.1)	4 (4.3)	-	7 (12.5)
- Dupilumab	7 (4.2)	4 (5.4)	3 (3.2)	-	7 (12.5)
- Azathioprine	4 (2.4)	3 (4.1)	1 (1.1)	-	4 (7.1)
- Tacrolimus	1 (0.6)	1 (1.4)	0 (0)	-	1 (1.8)
- UV therapy	1 (0.6)	0 (0)	1 (1.1)	1 (0.9)	-

Previous treatment, n (%)					
- Prior systemic treatment ^b	65 (38.7)	25 (33.8)	40 (42.5)	24 (21.4)*	41 (73.2)*
- One prior systemic treatment	30 (17.9)	9 (12.2)	21 (22.3)	14 (12.5)*	16 (28.6)*
- More than one prior systemic treatment	35 (20.8)	16 (21.6)	19 (20.2)	10 (8.9)*	25 (44.6)*
- Oral corticosteroids (<2 weeks)	60 (35.5)	29 (39.2)	31 (33.0)	32 (28.6)*	28 (50.0)*
- UV therapy	58 (34.3)	23 (31.1)	35 (37.2)	44 (39.3)	14 (25.0)
- Previous hospitalization	8 (4.8)	3 (4.1)	5 (5.3)	1 (0.9)*	4 (7.1)*
Disease severity, n (%)					
- Clear	6 (3.6)	2 (2.7)	4 (4.3)	3 (2.7)	3 (5.4)
- Almost clear	74 (44.0)	26 (35.1)	48 (51.1)	45 (40.2)	29 (51.8)
- Moderate	48 (28.6)	26 (35.1)	22 (23.4)	35 (31.3)	13 (23.2)
- Severe	31 (18.5)	14 (18.9)	17 (18.1)	22 (19.6)	9 (16.1)
- Very severe	9 (5.4)	6 (8.1)	3 (3.2)	7 (6.3)	2 (3.6)

^aNonsystemic treatments included UV therapy, topical corticosteroids always combined with neutral emollients, occasionally with concomitant use of calcineurin inhibitors or tar preparations.

^bSystemic treatment included alitretinoin, acitretin, azathioprine, ciclosporin, dupilumab, methotrexate, mycophenolic acid/mycophenolate mofetil, oral corticosteroids (>2 weeks), and tacrolimus.

^cPatients can have one or more etiological hand eczema diagnoses.

^d59 patients were not tested.

^e23 patients were not tested.

^f36 patients were not tested.

^g64 patients were not tested.

^h24 patients were not tested.

ⁱ40 patients were not tested.

^j43 patients were not tested.

^k33 patients were not tested.

^l14 patients were not patch tested, necessary for allergic contact dermatitis classification.

^mNine patients were not patch tested, necessary for allergic contact dermatitis classification.

ⁿFive patients were not patch tested, necessary for allergic contact dermatitis classification.

^o12 patients were not patch tested, necessary for allergic contact dermatitis classification.

^pTwo patients were not patch tested, necessary for allergic contact dermatitis classification.

^qThree patients were not patch tested, necessary for allergic contact dermatitis classification.

^rThree patients were not patch tested, necessary for allergic contact dermatitis classification.

^sThree patients were not patch tested, necessary for allergic contact dermatitis classification.

*P < .05; nonsystemic vs systemic treatment.

Abbreviations: IgE, immunoglobulin E; SD, standard deviation.

Figure 1. Treatment satisfaction scores (TSQM, range 0–100) for nonsystemic treatment vs different individual systemic treatments. A higher score of the TSQM subdomain “global satisfaction” indicates higher levels of treatment satisfaction. * $P < .05$. Other treatments are azathioprine, tacrolimus, and UV therapy. TSQM, Treatment Satisfaction Questionnaire for Medication

Figure 2. Treatment satisfaction domain scores (TSQM, range 0–100) in different hand eczema severity groups. Higher scores in the TSQM domains (bars) indicate higher levels of treatment satisfaction. Error bars represent standard deviation. * $P < .05$ between groups. TSQM, Treatment Satisfaction Questionnaire for Medication

Table 2. Health-related quality of life impairment assessed with the Quality of Life in Hand Eczema Questionnaire (QOLHEQ) in patients with vesicular hand eczema: interpretation of the overall QOLHEQ score and the QOLHEQ subdomain scores

	Health-related quality of life impairment ^a (n = 167)				
	Not at all (n, %)	Slightly (n, %)	Moderately (n, %)	Strongly (n, %)	Very strongly (n, %)
QOLHEQ overall score	25 (15.0)	50 (29.9)	64 (38.3)	21 (12.6)	7 (4.2)
Symptoms	2 (12)	60 (35.9)	48 (28.7)	45 (26.9)	12 (7.2)
Emotions	67 (40.1)	59 (35.3)	30 (18.0)	4 (2.4)	7 (4.2)
Functioning	17 (10.2)	77 (46.1)	34 (20.4)	26 (15.6)	13 (7.8)
Treatment and prevention	60 (35.9)	48 (28.7)	39 (23.4)	8 (4.8)	12 (7.2)

^aOne patient missing.

Table 3. Means for health-related quality of life impairment (QOLHEQ), treatment satisfaction (TSQM), and treatment adherence (MMAS) for the total group and stratified by sex and type of treatment (systemic vs nonsystemic)

Characteristics	All patients			Non-systemic treatment ^a (n = 112)	Systemic treatment ^b (n = 56)
	Male (n = 74)	Female (n = 94)	All		
HRQoL impairment (QOLHEQ Dutch subscales), mean (SD) ^c					
– Overall score (0–89)	28.3 (14.4)**	33.6 (17.8)**	31.2 (16.5)	32.5 (16.0)	28.9 (17.4)
– Symptoms (0–21)	8.4 (3.7)*	9.6 (4.4)*	9.1 (4.2)	9.8 (3.8)*	7.6 (4.5)*
– Emotions (0–24)	6.9 (4.7)	7.8 (5.1)	7.4 (4.9)	7.7 (5.0)	6.9 (4.9)
– Functioning (0–24)	6.5 (4.3)**	8.2 (5.6)**	7.4 (5.1)	7.6 (5.0)	7.1 (5.3)
– Treatment and prevention (0–20)	7.3 (4.0)*	8.8 (4.7)*	8.1 (4.5)	8.3 (4.3)	7.8 (4.7)
Treatment satisfaction (TSQM sub-scale), mean (SD)					
– Effectiveness (0–100)	57.2 (17.7)	60.0 (19.0)	58.7 (18.4)	55.9 (17.9)*	64.4 (18.4)*
– Side effects (0–100)	87.0 (21.1)	88.9 (19.1)	88.1 (19.9)	89.3 (20.2)	85.7 (19.4)
– Convenience (0–100)	64.3 (17.1)	66.7 (12.5)	65.6 (14.7)	64.4 (13.0)	68.1 (17.5)
– Global satisfaction (0–100)	61.0 (18.0)	64.2 (16.2)	62.7 (17.1)	60.8 (14.7)*	66.8 (20.6)*
Treatment adherence (MMAS-4), n (%)					
– High	18 (24.3)*	40 (42.6)*	58 (34.5)	31 (27.7)*	27 (48.2)*
– Medium	41 (55.4)	43 (45.7)	84 (50.0)	58 (51.8)	26 (46.4)
– Low	15 (20.3)	11 (11.7)	26 (15.5)	23 (20.5)	3 (5.4)

HRQoL, health-related quality of life; MMAS-4, 4-item Morisky Medication Adherence Scale; QOLHEQ, Quality of Life in Hand Eczema Questionnaire; SD, standard deviation; TSQM, Treatment Satisfaction Questionnaire for Medication.

^aNonsystemic treatments included UV therapy, topical corticosteroids always combined with neutral emollients, occasionally with concomitant use of calcineurin inhibitors or tar preparations.

^bSystemic treatment included alitretinoin, azathioprine, ciclosporin, dupilumab, methotrexate, and tacrolimus.

^cOne patient missing.

*P < .05 (male vs female and systemic vs nonsystemic treatment), **P < .05 and different severity band.

eczema (TSQM score: 66.4, SD: 18.4), $P < .001$. Furthermore, TSQM subdomain scores of “global satisfaction” were significantly lower for severe/very severe hand eczema (TSQM score: 50.4, SD: 14.6) compared with patients with moderate (TSQM score: 61.1, SD: 15.8) or clear/almost clear hand eczema (TSQM score: 69.9, SD: 15.2), $P < .001$. No significant association between age, hand eczema duration, previous history of systemic treatment, and treatment satisfaction was found.

Adherence

About 50% of the patients had a medium treatment adherence. In the group of patients with high treatment adherence there were significantly more females than males and significantly more patients using systemic therapy compared with nonsystemic therapy (Table 3). The QOLHEQ and TSQM subdomains scores for different adherence groups are presented in Table 4. A high adherence was significantly associated with a lower QOLHEQ overall score and the QOLHEQ subdomain “emotions.” Moreover, high adherence was associated with higher TSQM “global satisfaction” scores and a higher satisfaction about “effectiveness.”

Regression analysis

In the univariate analysis (see Data S4), taking the QOLHEQ domain score as the dependent variable, age, duration of hand eczema, education, and adherence were not associated with HRQoL. The multivariate regression model (Table 5) showed that female sex, more severe hand eczema, and lower treatment satisfaction were associated with more impairment of HRQoL (overall QOLHEQ score). This model explained 37% of the variance of the total HRQoL score (R^2). Severity was strongly associated with the QOLHEQ subdomain “symptoms.” For the association of “global satisfaction,” the standardized beta was similar for all QOLHEQ subdomains. Female sex was not associated with the QOLHEQ subdomain “emotions.”

Discussion

Overall, vesicular hand eczema patients showed a moderately impaired HRQoL, with the highest impairment noted in the QOLHEQ subdomain “symptoms.” We demonstrated that more severe hand eczema was associated with more impairment in HRQoL. The association between severity and HRQoL is in line with previous studies that used the Dermatology Life Quality Index to assess HRQoL and included all types of hand eczema.^{6,18} Female sex was associated with more impairment in HRQoL. Female sex is a well-known demographic factor affecting HRQoL. Other studies showed that female patients experienced more HRQoL impairment compared with male patients, or had similar impairment with less severe hand eczema.^{2,6,7} In the current study “functioning” was particularly affected in females. Female patients probably had more distress related to limitations in work, leisure time, or domestic activities. Previous studies showed a considerable psychosocial burden of hand eczema and underline that anxiety and depression are more common in female patients.^{2,19} In this study we did not find an association between female sex and impairment of HRQoL in the QOLHEQ subdomain “emotions.” The regression analyses showed that lower “global satisfaction” was associated with more impairment of HRQoL; the standardized beta was -0.44 , which indicates a moderate correlation. In previous studies in patients with gout and hypertension a correlation was also found between these outcomes.^{20,21}

For the total group we have shown that patients were least satisfied with “effectiveness” of treatment. In patients with severe and very severe hand eczema significantly lower satisfaction scores were found for the TSQM subdomains “effectiveness” and “global satisfaction” compared with the

Table 4. Means of health-related quality of life (HRQoL) impairment and treatment satisfaction in different groups of treatment adherence

Characteristics	Treatment adherence (MMAS-4)		
	Low (n = 26)	Medium (n = 84)	High (n = 58)
HRQoL impairment (QOLHEQ Dutch subdomains), mean (SD) ^a			
- Overall score (0-89)	32.5 (15.1)*	34.2 (15.0)*	26.6 (18.4)*
- Symptoms (0-21)	10.0 (3.2)	9.5 (3.7)	8.0 (4.9)
- Emotions (0-24)	7.5 (4.6)*	8.4 (4.8)*	5.9 (4.9)*
- Functioning (0-24)	7.4 (4.9)	8.2 (4.9)	6.2 (5.4)
- Treatment and prevention (0-20)	8.4 (4.1)	8.8 (4.1)	7.1 (5.0)
Treatment satisfaction (TSQM subscale), mean (SD)			
- Effectiveness (0-100)	52.2 (17.2)*	57.7 (17.7)*	63.1 (19.1)*
- Side effects (0-100)	85.9 (24.6)	87.1 (21.1)	67.9 (13.7)
- Convenience (0-100)	61.3 (14.6)	65.3 (15.2)	67.9 (13.7)
- Global satisfaction (0-100)	56.1 (13.4)*	60.9 (16.8)*	68.5 (17.5)*

MMAS-4, 4-item Morisky Medication Adherence Scale; QOLHEQ, Quality of Life in Hand Eczema Questionnaire; SD, standard deviation; TSQM, Treatment Satisfaction Questionnaire for Medication.

^aOne patient missing.

* $P < .05$.

other severity groups. Satisfaction about "side effects" and "convenience" were similar in the different severity groups. This implies that effectiveness of treatment is the major factor affecting "global satisfaction," which is supported by previous studies on, for example, patients with psoriasis and lichen sclerosis. These studies found that patients reported treatment effectiveness as the most important factor for overall treatment satisfaction.^{2,22,23} The group using systemic treatment presented significantly higher satisfaction scores with regard to the "effectiveness," compared with the group without systemic treatment. The "global satisfaction" was significantly higher for alitretinoin, ciclosporin, and dupilumab compared with nonsystemic treatments. In patients with psoriasis data also showed lower "global satisfaction" scores for patients receiving nonsystemic treatment.^{24,25} The use of biologicals for psoriasis resulted in substantially higher global patient satisfaction scores.^{24,26} Recent observational studies showed promising results regarding the effectiveness of dupilumab in patients with hand eczema and might offer future perspectives for patients with difficult-to-treat vesicular hand eczema.^{27,28}

Treatment adherence was significantly lower in patients receiving nonsystemic treatment compared with systemic treatment. The perception of the relative ineffectiveness and inconvenience of topical treatment and sometimes corticophobia are well known in dermatology. This may hinder adherence and treatment effectiveness.²⁹⁻³¹ Concerning adherence and QOLHEQ subdomains there was a significant association for the QOLHEQ overall and "emotional" subdomain scores, indicating that high adherence comes in line with less (emotional) HRQoL impairment (Table 4). However, a longitudinal study is needed to verify if less emotional impairment leads to higher adherence or if adherence leads to less emotional problems. A higher medication adherence was also significantly associated with a higher "global satisfaction," while this effect was not seen in the TSQM subdomains "side effects" and "effectiveness."

Some clinical and etiological characteristics need to be highlighted. Of note, half of the patients had ICD during treatment phase (>3 months) and even in the group treated with systemic therapy 40% had an ICD. In our department advanced nurse practitioners provide one-to-one patient education for every patient with hand eczema. These are offered personalized glove advice to protect hands from irritant and allergic factors and improve topical treatment compliance. From the high proportion of ICD it can be deduced that despite all efforts it seems impossible for a large proportion of patients to avoid exposure to irritants.

Moreover, we found a high proportion of patients with allergic contact dermatitis (40%), compared with other studies.^{32,33} A possible explanation is the fact that our center is a tertiary reference center for hand eczema. Finally, atopic dermatitis is a well-known risk factor for more severe and chronic hand eczema.³⁴ The number of patients with an atopic hand eczema in this study was in line with previous studies (21.5%–57.5%).^{32,33}

A limitation of our study is the monocentric design in a tertiary referral center. Presumably this patient cohort included more patients with a difficult-to-treat hand eczema in all groups. Non-systemic treatment was compared with systemic treatment in terms of HRQoL and treatment satisfaction. Patients on systemic treatment are in general more difficult to treat and an effective treatment will influence their HRQoL and treatment satisfaction more strongly. Another limitation of our study is the smaller number of participants treated with systemic medication compared with nonsystemic medication and the small subgroups with individual systemic treatments. The majority of the patients reported relatively high satisfaction scores for systemic treatment. However, patients with higher levels of satisfaction were more likely to continue with treatment and therefore maybe overrepresented. Patients who discontinued treatment because of side effects or inefficacy within 3 months were not included because of our inclusion criteria of treatment longer than 3 months. This is probably one of the reasons for the favorable results for alitretinoin, which was previously demonstrated to be less successful in vesicular hand eczema.³⁵ If alitretinoin is effective, patients will continue treatment after 3 months.

In conclusion, our results indicate that disease severity affects both HRQoL and treatment satisfaction in patients with vesicular hand eczema. Patients only using topical treatment are less satisfied with their treatment and their treatment adherence is lower. Systemic treatment of severe hand eczema could improve the severity and as a result also HRQoL, treatment satisfaction, and medication adherence. New systemic treatment options for patients with severe hand eczema, for example, biologicals or small molecules, could possibly contribute to this.

Table 5. Multivariate linear regression analysis assessing factors that would affect the health-related quality of life subdomain scores as the dependent variable

Variable	Symptoms subdomain <i>R</i> ² = 0.41		Emotions subdomain <i>R</i> ² = 0.26		Functioning subdomain <i>R</i> ² = 0.33		Treatment and prevention subdomain <i>R</i> ² = 0.25		QOLHEQ overall score <i>R</i> ² = 0.37	
	Standardized β	<i>P</i> -value	Standardized β	<i>P</i> -value	Standardized β	<i>P</i> -value	Standardized β	<i>P</i> -value	Standardized β	<i>P</i> -value
Sex (female)	0.23	<001	-	-	-	-	0.23	<001	0.25	<001
High education	-	-	-0.06	.37	-	-	-	-	-0.25	.80
Current systemic treatment	-0.10	.11	-	-	-	-	-	-	0.05	.51
Severity	0.33	<001	0.16	.04	0.19	.01	0.14	.08	0.22	<001
Low adherence	0.05	.45	-0.03	.63	0.01	.88	0.05	.51	0.07	.31
Higher TSQM global satisfaction score	-0.36	<001	-0.41	<001	-0.43	<001	-0.40	<001	-0.44	<001

Note: Numbers in bold italic represent *P* < .05 and standardized β coefficients >0.2.

Note: Variables with a indent (-) had a *P* value > .2 in the univariate regression analysis and were not suitable for inclusion in the concerning subdomain.

Abbreviations: QOLHEQ, Quality of Life in Hand Eczema Questionnaire; TSQM, Treatment Satisfaction Questionnaire for Medication

References

- Menné T, Johansen JD, Sommerlund M, Veien NK. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. *Contact Dermatitis*. 2011;65(1): 3–12.
- Cazzaniga S, Ballmer-Weber BK, Gräni N, et al. Medical, psychological and socio-economic implications of chronic hand eczema: a cross-sectional study. *J Eur Acad Dermatol Venereol*. 2016;30(4): 628–637.
- Dibenedetti D, Baranowski E, Zelt S, Reynolds M, Sherrill B. Assessing United States patient and dermatologist experiences with severe chronic hand eczema. *J Clin Aesthet Dermatol*. 2015;8(11): 19–27.
- Barrett A, Hahn-Pedersen J, Kragh N, Evans E, Gnanasakthy A. Patient-reported outcome measures in atopic dermatitis and chronic hand eczema in adults. *Patient – Patient-Centered Outcomes Res*. 2019; 12(5):445–459.
- Christoffers W, Coenraads P, Svensson Å et al. Interventions for hand eczema. *Cochrane Database of Systematic Reviews*. 2019; 4: CD004055. <https://doi.org/10.1002/14651858.CD004055.pub2>.
- Agner T, Andersen KE, Brand-ao FM, et al. Hand eczema severity and quality of life: a cross-sectional, multicentre study of hand eczema patients. *Contact Dermatitis*. 2008;59(1):43–47.
- Ofenloch RF, Weisshaar E, Dumke AK, Molin S, Diepgen TL, Apfelbacher C. The quality of life in hand eczema questionnaire (QOLHEQ): validation of the German version of a new diseasespecific measure of quality of life for patients with hand eczema. *Br J Dermatol*. 2014;171(2):304–312.
- Oosterhaven JA, Ofenloch R F, Schuttelaar M-LA. Interpretability of the quality of life in hand eczema questionnaire. *J Invest Dermatol*. 2020;140(4):785–790.
- Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the treatment satisfaction questionnaire for medication (TSQM), using a national panel study of chronic disease. *Health Qual Life Outcomes*. 2004;13:1–13.
- Tan X, Patel I, Chang J. Review of the four item morisky medication adherence scale (MMAS-4) and eight item morisky medication adherence scale (MMAS-8). *Innov Pharm*. 2014;5(3):165.
- Barbosa CD, Balp MM, Kulich K, Germain N, Rofail D. A literature review to explore the link between treatment satisfaction and adherence, compliance, and persistence. *Patient Prefer Adherence*. 2012;6: 39–48.
- Oosterhaven JAF, Flach PA, Bultmann U, Schuttelaar MLA. Presenteeism in a Dutch hand eczema population—a cross-sectional survey. *Contact Dermatitis*. 2018;79(1):10–19.
- Nederlandse Vereniging voor Dermatologie en Venereologie (NVDV). Richtlijn Handeczeem 2019. <https://nvdv.nl/professionals/richtlijnen-onderzoek/richtlijnen/richtlijn-handeczeem>. Accessed December 3, 2019.
- Ariens LFM, van der Schaft J, Bakker DS, et al. Dupilumab is very effective in a large cohort of difficult-to-treat adult atopic dermatitis patients: first clinical and biomarker results from the BioDay registry. *Allergy*. 2020;75(1):116–126.
- Coenraads PJ, van der Walle H, Thestrup-Pedersen K, et al. Construction and validation of a photographic guide for assessing severity of chronic hand dermatitis. *Br J Dermatol*. 2005;152(2): 296–301.
- Oosterhaven JA, Ofenloch RF, Schuttelaar M-LA. Validation of the Dutch quality of life in hand eczema questionnaire. *Br J Dermatol*. 2019;183(1):86–95.
- Nieminen P, Lehtiniemi H, Vähäkangas K, Huusko A, Rautio A. Standardised regression coefficient as an effect size index in summarising findings in epidemiological studies. *Epidemiol Biostat Public Health*. 2013;10(4):1–15.
- Cazzaniga S, Ballmer-Weber BK, Gräni N, et al. Chronic hand eczema: a prospective analysis of the Swiss CARPE registry focusing on factors associated with clinical and quality of life improvement. *Contact Dermatitis*. 2018;79(3):136–148.
- Marron SE, Tomas-Aragones L, Navarro-Lopez J, et al. The psychosocial burden of hand eczema: data from a european dermatological multicentre study. *Contact Dermatitis*. 2018;78(6):406–412.
- Al-Jabi SW, Zyoud SH, Sweileh WM, et al. Relationship of treatment satisfaction to health-related quality of life: Findings from a crosssectional survey among hypertensive patients in Palestine. *Health Expect*.

- 2015;18(6):3336–3348.
21. Khanna PP, Shiozawa A, Walker V, et al. Health-related quality of life and treatment satisfaction in patients with gout: results from a crosssectional study in a managed care setting. *Patient Prefer Adherence*. 2015;9:971–981.
22. van Cranenburgh OD, Nijland SBW, Lindeboom R, et al. Patients with lichen sclerosus experience moderate satisfaction with treatment and impairment of quality of life: results of a cross-sectional study. *Br J Dermatol*. 2017;176(6):1508–1515.
23. van Cranenburgh OD, de Korte J, Sprangers MAG, de Rie MA, Smets EMA. Satisfaction with treatment among patients with psoriasis: a web-based survey study. *Br J Dermatol*. 2013;169(2): 398–405.
24. Callis Duffin K, Yeung H, Takeshita J, et al. Patient satisfaction with treatments for moderate-to-severe plaque psoriasis in clinical practice. *Br J Dermatol*. 2014;170(3):672–680.
25. Florek AG, Wang CJ, Armstrong AW. Treatment preferences and treatment satisfaction among psoriasis patients: a systematic review [Internet]. Vol 310. Springer Berlin Heidelberg: Archives of Dermatological Research; 2018:271–319.
26. Hjortsberg C, Bergman A, Bjarnason A, et al. Are treatment satisfaction, quality of life, and self-assessed disease severity relevant parameters for patient registries? Experiences from finnish and swedish patients with psoriasis. *Acta Derm Venereol*. 2011;91(4):409–414.
27. Zirwas MJ. Dupilumab for hand eczema. *J Am Acad Dermatol*. 2018; 79(1):167–169.
28. Oosterhaven JAF, Voorberg AN, Romeijn GLE, de Bruin-Weller MS, Schuttelaar MLA. Effect of dupilumab on hand eczema in patients with atopic dermatitis: An observational study. *J Dermatol*. 2019;46(8):680–685.
29. Chan SA, Hussain F, Lawson LG, Ormerod AD. Factors affecting adherence to treatment of psoriasis: comparing biologic therapy to other modalities. *J Dermatolog Treat*. 2013;24(1): 64–69.
30. Aubert-Wastiaux H, Moret L, Le Rhun A, et al. Topical corticosteroid phobia in atopic dermatitis: a study of its nature, origins and frequency. *Br J Dermatol*. 2011;165(4):808–814.
31. Furue M, Onozuka D, Takeuchi S, et al. Poor adherence to oral and topical medication in 3096 dermatological patients as assessed by the morisky medication adherence scale-8. *Br J Dermatol*. 2015;172(1): 272–275.
32. Brans R, John SM. Clinical patterns and associated factors in patients with hand eczema of primarily occupational origin. *J Eur Acad Dermatol Venereol*. 2016;30(5):798–805.
33. Johansen JD, Hald M, Andersen BL, et al. Classification of hand eczema: clinical and aetiological types. Based on the guideline of the Danish contact dermatitis Group. *Contact Dermatitis*. 2011;65(1):13–21.
34. Halling-Overgaard AS, Zachariae C, Thyssen JP. Management of atopic hand dermatitis. *Dermatol Clin*. 2017;35(3):365–372.
35. Politiek K, Christoffers WA, Coenraads PJ, Schuttelaar MLA. Alitretinoin and acitretin in severe chronic hand eczema; results from a retrospective daily practice study. *Dermatol Ther*. 2016;29(5): 364–371.

Klaziena Politiek^{1*}

Jart A.F. Oosterhaven^{1*}

Karin M. Vermeulen²

Marie-Louise A. Schuttelaar¹

^{*}Authors contributed equally

¹ Department of Dermatology, University Medical Center Groningen,
University of Groningen, Groningen, The Netherlands

² Department of Epidemiology, University Medical Center Groningen,
University of Groningen, Groningen, The Netherlands

Published in

Contact Dermatitis. 2016;75(2):67–76

Chapter 8

Systematic Review of Cost-of-Illness Studies
in Hand Eczema

Summary

The individual burden of disease in hand eczema patients is considerable. However, little is known about the socio-economic impact of this disease. The aims of this review were to evaluate the literature on cost-of-illness in hand eczema, and to compose a checklist for future use. The literature was retrieved from the MEDLINE and EMBASE databases up to October 2015. Quality evaluation was based on seven relevant items in cost-of-illness studies. Cost data (direct and indirect) were extracted and converted into euros (2014 price level) by use of the Dutch Consumer Price Index. Six articles were included. The mean annual total cost per patient ranged from €1311 to €9792 (direct cost per patient, €521 to €3722; and indirect cost per patient, €100 to €6846). Occupational hand eczema patients showed indirect costs up to 70% of total costs, mainly because of absenteeism. A large diversity in hand eczema severity was found between studies. The socio-economic burden of hand eczema is considerable, especially for more severe and/or occupational hand eczema. Absenteeism from paid work leads to a high total cost-of-illness, although disregard of presenteeism often leads to underestimation of indirect costs. Differences in included cost components, the occupational status of patients and hand eczema severity make international comparison difficult. A checklist was added to standardize the approach to cost-of-illness studies in hand eczema.

Introduction

Hand eczema is a common condition in the general population, with a 1-year prevalence of up to 10%.¹ It is a persistent and often relapsing disease.² Hand eczema can have far-reaching personal consequences, and may have a drastic impact on the lives of those affected. In patients with chronic hand eczema, the long-term prognosis is poor, involving low health-related quality of life and negative occupational consequences.^{3,4} Furthermore, chronic hand eczema, especially of occupational origin, frequently results in productivity loss, owing to presenteeism (i.e. 'working while sick'), absenteeism, or even job loss.^{5,6}

Cost-of-illness studies identify and measure all of the costs of a disease, and generate a monetary estimate of the total burden of a particular disease. These studies are important for identifying benefits that would be obtained with prevention of the disease or with more effective treatment. Several cost-of-illness studies have been performed for hand eczema. These studies are valuable, because they give an insight into the factors that contribute to high costs incurred by this often disabling disease. The first objective of this study is to present a systematic review of these cost-of-illness studies in hand eczema. The quality of included studies is evaluated, and differences between studies are identified. On the basis of this review, our second objective is to compose a checklist for future cost-of-illness studies in hand eczema to increase standardized reporting across countries, in order to enhance comparability.

Methods

We performed this review in accordance with relevant standards from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.⁷ A comprehensive literature search in the electronic databases MEDLINE (via PubMed) and EMBASE was conducted to identify published studies on cost-of-illness in hand eczema up to October 2015. A detailed search strategy is presented in Appendix 1 (<https://doi.org/10.1111/cod.12590>). We checked reference lists to identify additional studies. All cost studies that estimated healthcare and/or non-healthcare costs associated with hand eczema were included. Studies with a model-based cost analysis were excluded. Only studies published in English were reviewed. All results in this review are based on published data; authors were not contacted for additional information or missing data.

A data extraction sheet was developed to standardize the items to be extracted. The identified studies were independently evaluated and reviewed by three authors (K.P., J.O., and K.V.). Differences in opinion were resolved by discussion until a consensus was reached. For each selected study, information regarding study design, population (e.g. age, sex, occupational status, and hand eczema severity) and cost estimates was extracted. In cost-of-illness studies, four cost components can be distinguished:

- Direct medical costs, which are healthcare-related expenses, for example costs of visits, hospital admission, diagnostics, and treatment;
- Direct non-medical costs, which are directly associated with hand eczema but are not medical in nature, such as transport costs;
- Indirect costs, which include productivity losses related to morbidity;
- Intangible costs, which refer to psychological problems, pain, discomfort, anxiety, and suffering, usually assessed by the use of quality of life measures.

These costs are often omitted from cost-of-illness studies, because of the difficulty of quantifying them in monetary terms.⁸⁻¹⁰

The outcomes of primary interest for this review were direct (medical and non-medical), indirect and total costs of hand eczema.

The quality of the studies was evaluated on the basis of seven relevant elements in cost-of-illness studies. Reviewers in the field of rheumatology composed a concise list of elements (based on expert literature) to evaluate cost-of-illness studies, because formal international guidelines for quality analyses of such studies are lacking^{11–13}. The following elements were evaluated:

- 1) Clear perspective of the study, which includes a description of which costs are relevant according to the purpose of the study. The most commonly used approach is the societal perspective, wherein all costs are relevant, irrespective of who pays for them.
- 2) Clearly stated study population, which includes a description of the source of patient recruitment, and the sociodemographic and disease characteristics of patients.
- 3) All relevant direct costs and their data sources should be included and explained in detail.
- 4) All relevant indirect costs and their data sources should be included and explained in detail.
- 5) Incremental costs. These are most often used to refer to the difference in cost and/or effect between two or more interventions being compared in an evaluation. This is, however, often more applicable to cost-effectiveness studies and less to cost-of-illness studies, except when a comparison is made with a disease-free population.
- 6) Discounting, which should be applied to direct and indirect costs that are collected during a time period of >1 year.
- 7) A sensitivity analysis. Cost-of-illness studies rely on estimates with varying degrees of uncertainty. By creating a set of scenarios, the investigator takes uncertain (often estimated) factors into account, and thus determines a range of possible values of the real cost-of-illness.

Cost estimates were indexed to the price level of 2014 by use of the Dutch Consumer Price Index (<http://cbs.nl>). Prices were all converted into euros, according to the 2014 exchange rate (<http://www.x-rates.com>).

Results

Literature search

Our database search identified 221 studies in MEDLINE and 219 studies in EMBASE. After identification and removal of duplicates, the titles and abstracts were carefully analysed. Thirteen studies were identified for full-text analysis. From these, seven studies were excluded, which ultimately resulted in the inclusion of six studies in this review (Figure 1). The oldest identified study was published in 2006, and the most recent in 2013.

Characteristics of included studies

Methods and patient characteristics of the reviewed studies are summarized in Table 1. Five of six studies were conducted in Europe: three in Germany, one in The Netherlands, and one in Italy. One study was conducted in the United States. An important difference between studies was the variation in severity of hand eczema. Some studies included only severe hand eczema patients,¹⁴ whereas other studies included patients with different disease severities.¹⁵ Another important

difference concerned the percentage of employed patients in the studied populations and their reported days of sick leave. This ranged from an average of 7 to 76 days per year, with high average numbers of sick days (absenteeism) being reported by two German studies on occupational hand eczema.^{16,17} The methodology used to estimate cost-of-illness regarding the data collection on healthcare consumption also varied among the included studies. One study used medical claims,¹⁸ but most studies used medical charts in combination with questionnaires that focused mainly on sick leave and non-medical direct costs. For calculating indirect costs, the human capital approach was used in most studies. Only van Gils et al. used the friction cost method.¹⁹

Figure 1. Flowchart of data inclusion

Costs of hand eczema

Table 2 shows an overview of the reported annual cost-of-illness; when reported, this is broken down by cost components and hand eczema severity. Although the included cost components were reasonably similar between studies, variable costs were found. The mean annual direct cost per patient ranged from €521 to €3722. The mean annual indirect cost per patient ranged from €100 to €6846. The mean total annual cost per patient ranged from €1311 to €9792. Costs are higher with more severe hand eczema. This is mainly because of the use of more expensive

Table 1. Characteristics of included studies

	Augustin, 2011, Germany ¹⁵	Cortesi, 2013, Italy ¹⁴	Diepgen, 2013, Acta Derm Ger- many ¹⁷
Population characteristics: number, age (years), % male	<i>n</i> = 223, mean age: 45.7, 43.9% male	<i>n</i> = 104, mean age: 44.5, 39.4% male	SHI: <i>n</i> = 223, OHI: <i>n</i> = 87 mean age: 45.7, 46.5% male
Inclusion criteria	Adult patients with clinically diagnosed CHE and insured by SHI. No adequate response to at least one therapy attempt with topical steroids (II–IV) in the last 4 weeks. Initial diagnosis >12 months previous. Patient treated in relevant center on a continuous basis in last 12 months.	Severe CHE patients from tertiary referral centers. Eligible patients had to identify with criteria similar to the study of Ruzicka et al. from 2008. ²⁶	SHI patients were included as described in Augustin et al. from 24 dermatology practices and clinics across Germany. ¹⁵ OHI patients were recruited from two OHI centers. These patients had CHE that was considered to be related to work or occupational exposure and their treatment costs were reimbursed by the OHI.
Severity score hand eczema	PGA, photographic guide	PGA, photographic guide and mTLSS	PGA, photographic guide and mTLSS
Hand eczema severity at time of inclusion	Clear: <i>n</i> = 1, Almost clear: <i>n</i> = 27, Mild: <i>n</i> = 54, Moderate: <i>n</i> = 107, Severe: <i>n</i> = 31	Severe: <i>n</i> = 104	Clear/almost clear: <i>n</i> = 45, Mild: <i>n</i> = 74, Moderate: <i>n</i> = 140, Severe: <i>n</i> = 51
Mean disease duration (years)	9.3	6.7	8.2
Employed (%)	65.8	61.5	73.5 (SHI) / 100 (OHI)
Patients with at least 1 day absence from work (%), (measured period)	33.9 (12 months)	45.3 (1 month)	33.9 (SHI)/62.7 (OHI) (12 months)
Sick days per working patient (mean), (measured period)	7.2 (12 months)	4.9 (1 month)	47.2 (12 months)
Type of analysis	Cost–outcome discription	Cost–outcome discription	Cost–outcome discription
Period of data collection	2008	2009 and 2010	2008
Duration of study	1 year	8 weeks	1 year
Method of cost data collection	Questionnaire and retrospective chart reviews	Questionnaire and retrospective chart reviews	Questionnaire and retrospective chart reviews
Reported indirect costs	HCM	HCM	HCM
Valuta	Euro	Euro	Euro

CHE: Chronic Hand Eczema; FCM: Friction Cost Method; HCM: Human Capital Method; HECSI: The Hand Eczema Severity Index; NR: Not Reported; OHI: Occupational Health Insurance; OHSI: Osnabrück Hand eczema Severity Index; PGA: Physician Global Assessment; mTLSS: modified Total Lesion Symptom Score; SHI: Statutory Health Insurance; VAS: Visual Analog Scale.

Table 1 continued

Diepgen, 2013, Contact Dermatitis Germany ¹⁶	Fowler, 2006, USA ¹⁸	Gils van, 2013, Netherlands ¹⁹
<i>n</i> = 151, mean age: 44.9, 64.9% male	<i>n</i> = 507, mean age: 45.7, 40.7% male	IC: <i>n</i> = 101; UC: <i>n</i> = 95 mean age: 43.0, 50.5% male
Occupational hand eczema, diagnosed in a specialized hand eczema clinic (University Clinic Heidelberg). The OHI confirmed the diagnosis and referred the patients for tertiary individual prevention.	Adult patients (≥18 year). Diagnosed with CHE using a postal questionnaire with questions based on a clinical algorithm (see appendices of this publication).	Patients ≥16 years, moderate to severe CHE, >3 months. Patients with mild hand dermatitis on sick leave from work because of their dermatitis or patients that scored at least 4 points on a VAS for perceived burden of disease in the last 3 months before baseline, were also eligible for inclusion.
PGA and OHSI	Severity score not performed	Photographic guide and HECSI
Clear/almost clear/mild: <i>n</i> = 58, Moderate/severe: <i>n</i> = 93	Hand eczema severity not specified	Hand eczema severity not specified
NR	NR	NR
100	NR	NR
62.9 (12 months)	NR	NR
76.4 (12 months)	NR	NR
Cost-outcome discription	Cost-outcome discription	Cost-effectiveness and cost-utility
4/2006 – 4/2007	3/2001 – 11/2003	7/2008 – 11/2010
1 year	33 months	1 year
Retrospective chart reviews and patient interview	Health plan paid amount and patient copayment	Prospective questionnaires and retrospective chart reviews
HCM	HCM	FCM
Euro	Dollar	Euro

Table 2. Reported annual cost-of-illness of hand eczema (HE)

	Cost			
	Augustin, 2011 ⁵			
	Almost clear ^a , n = 9	Moderate HE ^a , n = 39	Severe HE ^a , n = 39	Very severe HE ^a , n = 14
Direct costs				
Medical				
- Visits (GP, SC, other, phone)	89	116	118	147
- Hospital admission	126 ^c	235 ^c	470 ^c	1140 ^c
- Outpatient rehabilitation	-	-	-	-
- Diagnostics	√	√	√	√
- UV irradiation	177	258	329	519
- Medication	358	362	643	827
- Emollients	√	√	√	√
- OTC medicines	-	-	-	-
- Other visits	-	-	-	-
Non-medical				
- Out-of-pocket costs	√	√	√	√
- Transport	-	-	-	-
Total direct cost (/patient/year)	1211	1383	2199	3228
Indirect costs				
- Production losses (presenteeism)	-	-	-	-
- Absenteeism from paid work	100	347	364	1054
Total indirect cost (/patient/year)	100	347	364	1054
Total cost (/patient/year)	1311	1730	2563	4282

GP, general practitioner; IC, integrated care; OHI, occupational health insurance; OTC, over-the-counter; SC, secondary care; SHI, statutory health insurance; UC, usual care; UV, ultraviolet.

All prices in mean euros/year.

A hyphen (-) means that this cost item was not included in this study as such. Cost components with checkmarks (√) are included in total costs. If they are reported by the authors as being merged with other cost components, this is specified below.

^aAugustin et al. reported four ways of depicting hand eczema severity. We chose to show prices based on the maximum hand eczema severity in the past 12 months as measured by use of the photographic guide. In our opinion, this is the best available option to retrospectively link costs to severity.

^bThis was reported as 'outpatient services'. The components of these 'services' were not specified.

^cHospital costs included both hospital admission and daycare.

^dThis was reported as 'inpatient rehabilitation'. Whether this is the same as the inpatient treatment (including daycare) of Augustin et al. is unclear.

^eOutpatient rehabilitation was reported as 'outpatient services'. It included costs of psoralen and UVA/UVB therapy, but other components of these 'services' were not specified.

^fUV irradiation was included in emollients, and this was called 'non-pharmacological therapy'.

^gEmollients were included in medication.

^hEmollients were included in OTC medicines. OTC medicines were excluded from total costs.

ⁱThese were not further specified. The authors report that there might be some overlap between out-of-pocket expenses and complementary therapies (other visits).

^jOut-of-pocket costs included at least: 'Products and instruments such as gloves or gauze bandages, vacuum cleaners and cosmetics'.

Table 2 continued

Cost					
Cortesi, 2013 ¹⁴		Diepgen, 2013 ¹⁷	Diepgen, 2013 ¹⁵	Fowler, 2006 ¹⁸	van Gils, 2013 ¹⁹
All types of HE severity n = 223	Severe HE, n = 104	All types of HE severity n = 310	All types of HE severity n = 151	All types of HE severity n = 140	All types of HE severity n = 196
119	522	√	√	2105 ^b	√
441 ^c	857	√	1253 ^d	674	–
–	–	–	773 ^e	–	–
274	250	√	294	–	√
315	√ ^f	√	√ ^e	–	–
412	232	√	167	943	√
122	238	√	√ ^g	√ ^h	√
–	–	–	–	166 ^h	–
–	–	–	225 ⁱ	–	–
256	346 ^j	√	235	–	–
–	553	–	√	–	–
1939	2997	1939 SHI 3682 OHI	2945	3722	521 UC 1039 IC
–	√	–	–	–	–
430	√	√	6846	–	–
430	2329	430 SHI 3808 OHI	6846	–	1191 UC 2883 IC
2369	5326	2369 SHI 7490 OHI	9792	3722	1712 UC 3922 IC

treatment and the higher incidence of hospitalization in this group. The latter represents the most substantial cost item in direct costs.^{14–16} Wide variation can be found in mean medication cost, ranging from €167 to €934 per patient per year, in proportion to hand eczema severity.

In studies evaluating costs of occupational hand eczema, high indirect costs are reported. In the study of Diepgen et al., all patients had occupation-related hand eczema, and only tertiary referral patients were included. These patients were all at risk of losing their job, and had high rates of absenteeism. This resulted in the highest indirect and total costs of all included studies. Although indirect costs amounted to 70% of the total costs, direct costs were also high. Cost items that contributed highly to direct costs were hospital admission, utilized by 26% of the patients in the last 12 months, and outpatient services, which also included the costs of psoralen and ultraviolet (UV) A (PUVA)/UVB therapy. Usually, the patients had 12 visits to the dermatologist a year, because this monthly frequency is typical for the special report ('Hautarztbericht') requested by the statutory work insurance provider in occupation-related cases in Germany.¹⁶

Fowler et al. did not collect direct non-medical and indirect costs at all, and this, by definition, results in a substantial underestimation of the total cost-of-illness.¹⁸ Presenteeism (leading to productivity loss during work) was only included by Cortesi et al., who measured it with a short version of the Health and Labour Questionnaire (SF-HLQ). The authors found that 65% of the included patients with severe hand eczema reported loss of productivity at work, with an average of 10.1 days per patient per month.¹⁴ All studies included assessments of health-related quality of life; however, no intangible costs were given. Augustin et al. claim to report intangible costs, although they actually only report outcome measures in their natural units (Dermatology Life Quality Index (DLQI))/skindex scores); no translation to costs was made.¹⁵

In two evaluated studies, only total direct and indirect costs were shown, and no details of cost components were reported.^{17,19} Owing to this lack of insight into the division of the total costs, split data could not be shown in Table 2. Finally, two studies reported missing data on costs, which obviously also results in an underestimation of the true costs.^{18,19}

Quality evaluation

All studies were critically evaluated on the basis of seven elements (Table 3). The first element, the perspective of the study, was well described. All studies determined costs from a societal perspective. The population (second element) was not clearly described in three studies. Cortesi et al. showed, in their clinical characteristics, a range of physician global assessment scores (from clear to severe) for included patients, scored at the moment of inclusion. However, in the inclusion criteria of the study, only severe hand eczema patients are described.¹⁴ Diepgen et al. characterized their study population according to a 'special report' ('Hautarztbericht'), which cannot be understood by the international reader without further information.¹⁶ The hand eczema population in the study of Fowler et al. was included by the use of a well-described postal self-assessment questionnaire. However, this questionnaire had an 85% sensitivity and 95% specificity score, which could lead to an inclusion bias. Moreover, hand eczema severity could not be specified on the basis of this questionnaire.¹⁸

Relevant direct and indirect medical cost components (third and fourth elements) were not described and/or explained in detail in all studies. Fowler et al. did not collect non-medical direct and indirect costs at all.¹⁸ Van Gils et al. and, particularly, Diepgen et al. included more direct cost components, but did not provide a detailed explanation or breakdown of these costs.^{17,19} All studies included absenteeism, but only Cortesi et al. measured presenteeism.¹⁴ Discounting (fifth element) was not applicable in any of the included studies, except for the study by Fowler et al.

In this study, patients were observed over a period of >1 year. Here, discounting should have been applied.¹⁸ Incremental costs (sixth element) were only calculated in the studies by van Gils et al. and Fowler et al. Additionally, van Gils et al. performed one sensitivity analysis (seventh element); they compared costs of productivity losses calculated with the friction cost method to productivity losses calculated with the human capital method.¹⁹ We scored this element as partly fulfilled, because the sensitivity analysis was conducted with only one element. For a solid conclusion, a broader variation in underlying assumptions and estimations is needed.

Table 3. Quality evaluation of the included studies

Study	Perspective	Population	Direct costs	Indirect costs	Discounting	Incremental/ attributable costs	Sensitivity analysis
Augustin, 2011 ¹⁵	+	+	+	[+]	NA	0	0
Cortesi, 2013 ¹⁴	+	[+]	+	+	NA	0	0
Diepgen, 2013 ¹⁷	+	+	[+]	[+]	NA	0	0
Diepgen, 2013 ¹⁶	+	[+]	+	[+]	NA	0	0
Fowler, 2006 ¹⁸	+	[+]	[+]	0	0	+	0
van Gils, 2013 ¹⁹	+	+	[+]	[+]	NA	+	[+]

+, present; [+], partly fulfilled; 0, absent; NA, not applicable.
Criteria 1–7 are defined in Methods.

Discussion

The purpose of our study was to give an overview of cost-of-illness studies that are performed for hand eczema. It is surprising that, despite the high socio-economic burden of hand eczema, only a few cost-of-illness studies have been carried out to date. The studies included in this review show that the mean annual total cost per patient with hand eczema ranges from €1311 to €9792. The mean annual direct cost per patient ranges from €521 to €3722, with higher costs in patients with severe hand eczema. The mean annual indirect cost per patient ranges from €100 to €6846, mainly because of absenteeism, with higher costs in studies evaluating patients with occupational hand eczema.

Several factors can explain the differences in mean annual total costs between studies. An important item is the heterogeneity in hand eczema severity across studies. Augustin et al. found that annual direct and indirect costs substantially increase for more severe hand eczema. They showed that higher direct costs for severe hand eczema arise from intensive treatment options such as UV irradiation, systemic treatment, and hospital admission.¹⁵ These more expensive treatment options are not indicated for mild hand eczema, largely explaining the variety in direct costs.

This finding seems logical; however, if we assume that higher severity increases costs, the timing and method of severity scoring needs to be reviewed critically. In one retrospective study, hand eczema severity was scored at the moment of inclusion, while questions about related costs in the past year were asked. This does not give a clear representation of the severity of the hand eczema that was present in the time-frame that was analysed for costs (the past year).¹⁶ An expensive intensive treatment period or prolonged absence from work in the past year could have

resulted in less severe hand eczema at the time of inclusion. Two other studies used the same method, although they acknowledged the problems with it by adding an 'average' and 'worst' severity in the past 12 months.^{15,17} In our opinion, the moment of severity assessment in relation to the data collection (prospective/retrospective) needs to be stated unambiguously, and the consequences need to be considered. We prefer a severity assessment at the start of prospective cost data collection.

The occupational impact of the disease plays a large role in the cost-of-illness of hand eczema. In one of the studies by Diepgen et al., a substantial difference in total cost-of-illness between patients with and without occupational hand eczema was reported. 'Work-impaired' patients (in whom work was affected by chronic hand eczema, but this had not yet been confirmed by the occupational health insurance (OHI) provider) and 'work-diseased' patients (with known work-related chronic hand eczema, for which the correlation had been confirmed by the OHI provider) had direct costs that were twice as high as those for 'non-working' or 'work-unaffected' patients. On top of this, the hand eczema of 'work-impaired' and 'work-diseased' patients resulted in considerable indirect costs. Therefore, this study showed that being employed in a job that is affected by, or related to, hand eczema predicts higher costs.¹⁷ This highlights the importance of a careful description of the number of employed patients in the study population and the occurrence of occupational hand eczema. The diagnosis of occupational hand eczema is not made according to internationally agreed criteria. We encourage authors to clearly state the criteria according to which hand eczema qualifies as occupational.

The other included study by Diepgen et al. included only 'work-diseased' hand eczema patients (confirmed by the OHI provider).¹⁶ Data for this patient group were collected before the start of an inpatient hand eczema prevention programme. Most of these patients were at risk of losing their job, explaining the highest percentage of indirect costs of all included studies. Also, direct costs in the year prior to inclusion were high, mainly because of inpatient rehabilitation costs and costs of outpatient services (including PUVA/UVB therapy). It is noteworthy that, among all included studies, the lowest annual medication costs were found in this 'work-diseased' group. None of the patients had used systemic treatments (other than oral corticosteroids) in the last 12 months; 78% of the patients used topical steroids, and 15% used oral corticosteroids. This is probably because the treatment of this group with mainly occupational hand eczema was largely focused on prevention of aggravating factors in the workplace.

Differences in the availability of treatment programmes can also have a large influence on costs-of-illness. Van Gils et al. compared 'integrated multidisciplinary care' with 'usual care'. This resulted in doubled direct costs for the integrated care group, mainly because this type of care involved a multidisciplinary procedure with a dermatologist, a specialized nurse, and, if the hand eczema was

work-related, a clinical occupational physician. Besides this, indirect costs were also substantially higher. The authors explained this as a 'side-effect' of the intervention, wherein patients were advised to call in sick with aggravated hand eczema.¹⁹ This shows that cost-of-illness is dependent on the availability of treatment options in referral hospitals (secondary/tertiary), such as these intervention programmes. This is also evident for the studies including patients from specialized OHI centres.^{16,17}

Finally, differences in treatment methods between countries should be mentioned as an explanation for differences between studies. Apart from treatment availability, these differences exist mostly in relation to habits regarding treatment and to procedures of the healthcare system. For example, indications for hospital admission or conventions regarding when to start with systemic

treatment differ considerably between countries. Even within a country, differences exist, mainly between specialized and non-specialized centres. These differences resulting from cultural aspects and differences in international healthcare systems are hard to avoid as long as international care is not more standardized. For between-country comparisons of cost-of-illness studies, the volume and prices of cost components should be reported clearly, in order to enable a better understanding of how differences between countries arise.

Regarding future perspectives, the systemic retinoid alitretinoin is bound to appear in subsequent cost studies on hand eczema. Alitretinoin has now been approved in several countries for all clinical subtypes of severe chronic hand eczema that are refractory to topical corticosteroids. It is recommended as second-line treatment in the European guidelines on hand eczema.²⁰ The medication costs of this drug are considerably higher than those of other systemic treatment options such as cyclosporine, methotrexate, and azathioprine. On the other hand, the use of alitretinoin could probably lead to a decrease in indirect costs. The majority of the data reviewed in our study were collected in the pre-alitretinoin period. It will be interesting to see what kind of influence the introduction of alitretinoin will have on direct and indirect costs in future cost studies.

Another important issue that needs improvement in the future is the structural underestimation of indirect costs in cost studies. Indirect costs are mostly measured only as absenteeism from paid work. Costs resulting from presenteeism are often overlooked. The underestimation that the latter causes is very substantial, particularly because it has been reported to account for an even higher monetary loss to employers than the loss attributable to absenteeism.²¹ In the reviewed studies, only Cortesi et al. included production losses.¹⁴ This was performed with the SF-HLQ. However, a recently published review on the measurement properties of instruments assessing presenteeism deemed the reliability and validity of this questionnaire to be unacceptable. In fact, none of the 21 reviewed instruments was deemed to be appropriate for predicting productivity loss at work.²² Recently, Bouwmans et al. published a feasibility study on a new instrument for measuring absenteeism and presenteeism, called the iMTA Production Cost Questionnaire.²³ Although this instrument shows a promising design in this study, its measurement properties are yet to be validated according to Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN) criteria.²⁴ In conclusion, we cannot currently advise the use of a specific instrument to measure presenteeism. Regarding absenteeism, two methods are commonly used: the human capital approach, and the friction cost method. The costs of productivity loss obtained with the friction cost method are lower than those obtained with the human capital approach, especially in the case of long-term absence. Both methods have advantages and disadvantages; however, to date, no consensus on the preferable method has been reached.²⁵

As a result of our review, we have composed a checklist for cost components that we consider to be appropriate for inclusion in cost-of-illness studies for hand eczema (Table 4). This checklist could help to increase homogeneous reporting, in order to enhance comparability and hopefully result in better insights into the different components of total cost-of-illness in hand eczema. It is important to include the total spectrum of costs caused by the disease. In particular, expenses for the employer for the prevention or treatment of the disease should not be overlooked. We omitted the cost item 'time costs' from direct non-medical costs, because of the difficulty of quantifying this in monetary terms. Also, time costs are already largely included in productivity loss.

In conclusion, this review shows a wide range of cost-of-illness associated with hand eczema. It confirms that the socio-economic burden of hand eczema is considerable, mainly in cases of more severe and/or occupational hand eczema. The included direct cost components were reasonably comparable between studies. However, it is important to realize that the reporting of

different study designs, different hand eczema severities and different proportions of patients with occupational hand eczema (along with different criteria for the diagnosis) makes studies hard to interpret and to compare. We included a checklist in this review in an effort to standardize the approach to cost-of-illness studies in hand eczema. Finally, we want to emphasize the importance of measuring presenteeism in future research on cost-of-illness in hand eczema.

Table 4. Checklist: essential components of cost-of-illness studies in hand eczema

- Clear perspective of the study, preferably a societal perspective
- Study population: include hand eczema severity, proportion of patients with paid work, and proportion of patients with occupational hand eczema (and describe criteria)
- The following direct and indirect costs should be clearly stated and specified; different data sources and amounts should be included:

Direct medical costs	Direct non-medical costs	Indirect costs
<p>Visits</p> <ul style="list-style-type: none"> – Secondary care^a – General practitioner – Nurse consultation – Telephone consultation – E-consultation <p>Specialized care programmes^d (including daycare)</p> <p>Hospital admission</p> <p>Diagnostics (laboratory, patch tests, prick tests, mycology, histology, biopsy, etc.)</p> <p>Ultraviolet irradiation</p> <p>Medication: topical treatment</p> <p>Medication: systemic treatment</p> <p>Emollients</p> <p>Gloves/bandages</p> <p>Over-the-counter medicines (patient-reported)^e</p> <p>Other visits (e.g. alternative medicine)</p>	<p>Out-of-pocket costs (patient-reported) (e.g. diet, home environment changes, and specific products)^b</p> <p>Transport costs^c</p>	<p>Presenteeism from paid work</p> <p>Absenteeism from paid work</p>

- Calculate incremental costs when conducting a cost-effectiveness study or when comparing with a disease-free population
- Apply discounting when costs are collected during a time period of >1 year
- Perform sensitivity analyses on major cost drivers to determine a range of possible values of the real cost-of-illness

The total spectrum of costs paid because of hand eczema should be incorporated; this includes costs paid by the patient, the insurance company, and also the employer.

^aIf applicable, separate by different caregivers (e.g. dermatologist, internist, and occupational physician).

²⁴In principle, this should include all costs that are not covered by basic insurance. However, these costs are already included in several direct medical cost components (e.g. visits and medication). Because we encourage performing cost-of-illness studies from a societal perspective, who pays is less important. Therefore, we recommend using out-of-pocket costs as a purely non-medical component (e.g. including costs for a specific diet or home environment changes). We recommend separate reporting of direct medical costs such as emollients, gloves/bandages, and other over-the-counter medicines.

⁴If available in your country, the mean distance to the care provider and the mean cost per unit distance (depending on method of transportation) can be used for this (if stated clearly).

^dIf applicable, specify the characteristics of the (individual) programme.

⁴In principle, this should include all costs of medicines that are not covered by basic insurance. However, these costs are already included in medication, gloves/bandages, and emollients. Therefore, we recommend using over-the-counter medicines as a 'rest group' for medicines without prescription that do not fit into one of the other categories (specify).

References

- Thyssen J P, Johansen J D, Linneberg A, Menné T. The epidemiology of hand eczema in the general population – prevalence and main findings. *Contact Dermatitis* 2010; 62: 75–87.
- Coenraads P J. Hand eczema. *N Engl J Med* 2012; 367: 1829–1837.
- Moberg C, Alderling M, Meding B. Hand eczema and quality of life: a population-based study. *Br J Dermatol* 2009; 161: 397–403.
- Petersen A H, Johansen J D, Hald M. Hand eczema – prognosis and consequences: a 7-year follow-up study. *Br J Dermatol* 2014; 171: 1428–1433.
- Mätkönen T, Alanko K, Jolanki R et al. Long-term follow-up study of occupational hand eczema. *Br J Dermatol* 2010; 163: 999–1006.
- Boehm D, Schmid-Ott G, Finkeldey F et al. Anxiety, depression and impaired health-related quality of life in patients with occupational hand eczema. *Contact Dermatitis* 2012; 67: 184–192.
- Liberati A, Altman D G, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009; 6: e1000100.
- Larg A, Moss J R. Cost-of-illness studies: a guide to critical evaluation. *Pharmacoeconomics* 2011; 29: 653–671.
- Hakkaart-van Roijen L, Tan S, Bouwmans CAM. Handleiding voor kostenonderzoek, methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. College voor Zorgverzekeringen Geactualiseerde versie. 2010.
- Onukwugha E, McRae J, Kravetz A et al. Cost-of-illness studies: an updated review of current methods. *Pharmacoeconomics* 2016; 34: 43–58.
- Rothfuss J, Mau W, Zeidler H, Brenner MH. Socioeconomic evaluation of rheumatoid arthritis and osteoarthritis: a literature review. *Semin Arthritis Rheum* 1997; 26: 771–779.
- Zhu T Y, Tam L S, Li E K. Cost-of-illness studies in systemic lupus erythematosus: a systematic review. *Arthritis Care Res (Hoboken)* 2011; 63: 751–760.
- Drummond M F, Sculpher M, Claxton K et al. Critical assessment of economic evaluation. In: *Methods for the Economic Evaluation of Health Care Programmes*, 4th edition: New York, Oxford University Press, 2015: pp. 41–76.
- Cortesi P A, Scalone L, Belisari A et al. Cost and quality of life in patients with severe chronic hand eczema refractory to standard therapy with topical potent corticosteroids. *Contact Dermatitis* 2013; 70: 158–168.
- Augustin M, Kuessner D, Purwins S et al. Cost-of-illness of patients with chronic hand eczema in routine care: results from a multicentre study in Germany. *Br J Dermatol* 2011; 165: 845–851.
- Diepgen T L, Scheidt R, Weisshaar E et al. Cost of illness from occupational hand eczema in Germany. *Contact Dermatitis* 2013; 69: 99–106.
- Diepgen T L, Purwins S, Posthumus J et al. Cost-of-illness analysis of patients with chronic hand eczema in routine care in Germany: focus on the impact of occupational disease. *Acta Derm Venereol* 2013; 93: 538–543.
- Fowler J F, Ghosh A, Sung J et al. Impact of chronic hand dermatitis on quality of life, work productivity, activity impairment, and medical costs. *J Am Acad Dermatol* 2006; 54: 448–457.
- van Gils R F, Bosmans J E, Boot C R et al. Economic evaluation of an integrated care programme for patients with hand dermatitis. *Contact Dermatitis* 2013; 69: 144–152.
- Diepgen T L, Andersen K E, Chosidow O et al. Guidelines for diagnosis, prevention and treatment of hand eczema. *J Dtsch Dermatol Ges* 2015; 13: e1–e22.
- Collins J J, Baase C M, Sharda C E et al. The assessment of chronic health conditions on work performance, absence, and total economic impact for employers. *J Occup Environ Med* 2005; 47: 547–557.
- Ospina M B, Dennett L, Wayne A et al. A systematic review of measurement properties of instruments assessing presenteeism. *Am J Manag Care* 2015; 21: e171–e185.
- Bouwmans C, Krol M, Severens H et al. The iMTA Productivity Cost Questionnaire: a standardized instrument for measuring and valuing health-related productivity losses. *Value Health* 2015; 18: 753–758.
- Terwee C B, Mokkink L B, Knol D L et al. Rating

the methodological quality in systematic reviews of studies on measurement properties: a scoring system for the COSMIN checklist. *Qual Life Res* 2012; 21: 651–657.

25. Krol M, BrouwerW, Rutten F. Productivity costs in economic evaluations: past, present, future. *Pharmacoeconomics* 2013; 31: 537–549.
26. Ruzicka T, Lynde CW, Jemec G B et al. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. *Br J Dermatol* 2008; 158: 808–817.

Part IV

Chapter 9

General Discussion and Future Perspectives

Introduction

The consequences of having severe hand eczema are extensive. Subjective symptoms include itching, burning, pain, and sleep and mood disturbances, resulting in considerable distress and suffering and producing negative social and economic effects.^{1,2} Although hand eczema is a very common chronic disease, and one of the most reported occupational diseases, because it is not life threatening it is often overlooked.³ This final chapter summarizes and discusses the main outcomes of this thesis about different aspects of hand eczema, and suggests perspectives for future research.

Pathogenesis

The pathogenesis of hand eczema is largely unknown and has not yet been further specified in relation to different hand eczema subtypes. In the first part of this thesis, **Chapter 2**, we describe a pilot project on the pathogenesis of hyperkeratotic hand eczema (HHE). The clinical phenotype of HHE is currently classified as a subtype of hand eczema, although previous studies have questioned whether HHE should be considered as eczema, since it is monomorphic.^{4,5} Comparing our results with the limited available data on the pathophysiology of hand eczema, the main finding in our study was that filaggrin stainings were not decreased in lesional skin biopsies, which is in contrast with the findings of two previous studies of hand eczema.^{6,7} The two previous studies showed filaggrin expression to be downregulated in lesional skin. The question is whether the difference between our study and the previous two studies, with respect to expression of filaggrin, can be explained by different morphological types of hand eczema, since previous studies did not focus specifically on HHE. It could be considered whether HHE is a subtype of hand eczema or has another etiology. We hypothesized that cytokine profiles in HHE might differ from those in other subtypes of chronic hand eczema, although further studies are needed.^{6,7}

The clinical phenotype of HHE can share similarities with palmar psoriasis, and previous studies have shown similarities in their histopathology and cytokine profiles.^{4,8} Our study confirmed, however, that histopathology alone is not decisive in distinguishing the two. An interesting finding was the strong up-regulation of K6, K16 and K17 in lesional skin. These keratins are well-known hallmarks of wound healing and psoriasis.⁹ K17 seems to play an important role in the pathogenesis of psoriasis by stimulating psoriatic T-cells (Th-17) and production of specific cytokines (IL-17).^{10,11} Possibly the inflammation in the clinical phenotype of HHE is, like psoriasis, more Th17 driven. This underlines that the results should be compared with skin samples of palmoplantar psoriasis to elucidate whether the two diseases share a common pathogenesis.

Furthermore, as described in Chapter 2, whole exome sequencing was performed to analyze a panel of 135 genes related to palmoplantar keratoderma. No monogenetic mutations related to palmar hyperkeratosis were found, but a contributing role for one of the variants of unknown significance (VOUS) cannot be completely excluded. Future analysis of additional network genes associated with eczema and psoriasis may elucidate whether patients share common genetic risk genes in developing palmoplantar skin diseases.

Treatment

The second part of this thesis focuses on effectiveness and safety in the daily practice use of systemic treatment for severe chronic hand eczema, by means of drug survival studies (**Chapters 3 to 6**).

The main findings of Chapters 3 to 6 are summarized in Table 1. Most patients were treated with alitretinoin, acitretin and cyclosporine. Alitretinoin has been widely used in the Netherlands since 2013, and is considered as second line treatment in adult hand eczema patients after unresponsive first line treatment of a (potent) topical corticosteroid.^{12,13} Acitretin and cyclosporine, on the other hand, have for decades been prescribed off-label to treat chronic hand eczema. Cyclosporine is registered for atopic dermatitis only, although it also plays an important role in treatment of severe (vesicular) hand eczema. For this drug survival rates up to 13.7 years were reported in Chapter 4. Moreover, cyclosporine has the longest median drug survival, probably because of its rapid relief of symptoms. Long-term treatment with cyclosporine should be cautious because of the risk of adverse events, including hypertension and renal dysfunction; in our study, a relatively high number of patients discontinued cyclosporine due to subjective adverse events. However, the relatively safe usage of cyclosporine in dermatology was confirmed by a long-term retrospective study in AD.¹⁴ Due to the chronicity, in daily practice long-term treatments have been reported for atopic dermatitis and hand eczema.^{12,15,16}

Methotrexate ($n=42$) and azathioprine ($n=30$) are less often prescribed, and our studies included only small groups of patients. A high number of patients discontinued treatment prematurely. Especially in the case of azathioprine, more than half of the patients discontinued treatment due to adverse events. MTX is known as a safe long-term treatment for other skin diseases, although for hand eczema it was found to have a remarkably short median drug survival (4.8 months) when compared, for example, to psoriasis (25.9 months).¹⁷ A general finding in our drug survival studies was that daily practice treatments were often discontinued, primarily due to adverse events and/or ineffectiveness. However, when patients report mild subjective adverse events or ineffectiveness using alitretinoin, MTX, and azathioprine in the first weeks, physicians should, if possible, motivate patients to continue. To give treatment effectiveness a real chance a duration of 12 weeks is preferred.

Our median drug survival durations were quite similar to results reported by a recent retrospective drug survival study on alitretinoin and cyclosporine. Jang et al. reported a mean drug survival of 0.8 year for cyclosporine ($n=65$) and 0.6 year for alitretinoin ($n=53$). However, in our study patients more often discontinued treatment of alitretinoin due to ineffectiveness, and treatment of cyclosporine due to adverse events. The reported adverse events profiles also differed. For example, hypertension (cyclosporine), elevated triglycerides (alitretinoin), and above all nausea (with both), were less often reported in the study by Jang et al.¹⁸ Possibly environmental, and among others pharmacogenetical, variants could clarify the differences between Korean and Dutch patients. At the moment there are insufficient indicators to predict an individual treatment response. Further research should investigate predictors such as genetic variations, physiological aspects (gender, age, body size, ethnicity), environment, lifestyle factors, and comorbidities to analyze their effect on the extent of adverse events and/or treatment effectiveness. A better insight into treatment predictors could lead to greater treatment success.

Direct comparison among the different treatments (Table 1, Chapters 3–6) is not feasible because of the retrospective and daily practice study designs. Baseline characteristics differ depending on

Table 1. Drug survival and reasons for discontinuation of different systemic treatments for hand eczema

Treatment	n	Median drug survival (years)	Adverse events	Reason for discontinuation of treatment (%)			
				Top 3 reported adverse events as reason for discontinuation	Ineffectiveness	Controlled hand eczema	Other
Acitretin (Chapter 3)	109	0.4	37.6	Dry mucosa (13) Headache (7) Hairloss (5)	17.4	23.9	13.8
Alitretinoin (Chapter 3)	95	0.4	25.3	Headache (15) GI complaints (10) ↑ Triglyceriden (3)	18.9	27.4	13.7
Azathioprine (Chapter 6)	30	0.3*	50.0	GI symptoms (23) ↑ Liver enzymes (17) Flu-like symptoms (7)	16.7	3.3	23.3
Ciclosporin (Chapter 4)	102	0.9	43.1	↑ Blood pressure (21) GI symptoms (8) Headache (6)*	17.6	10.8	7.8
Methotrexate (Chapter 5)	42	0.4	23.8	GI symptoms (7) Flu-like symptoms (7) Headache (5)	33.3	11.9	7.2

n, number of patients; GI, gastrointestinal; *, unpublished data

the hand eczema subtypes, severity, treatment history, age, and patient comorbidities. Moreover, treatments like cyclosporine, azathioprine and MTX may have been given to a more treatment-refractory study group, since these treatments are indicated as third line treatment. Daily practice data may be limited in that their quality depends on treatment uniformity, including dose schemes, visit schedules, reporting of side-effects, and treatment efficacy. However, in our center we used consistent treatment protocols, resulting in realistic daily-practice data.

The main advantage of daily practice data is its reflection of real-life treatment “effectiveness” under routine circumstances. Interestingly, discontinuation rates due to ineffectiveness and/or adverse events are often higher in daily practice than those reported in RCTs.^{19–21} In clinical research RCTs are considered to be the gold standard to provide information on treatment “efficacy”. However, patients included in RCTs are not always representative, since strict in- and exclusion criteria result in idealized patient populations and health-care settings. These conditions are often different from real-life settings: patients may have comorbidities, be less motivated, and in general have lower treatment adherence.^{22,23} Another disadvantage can be the limited treatment duration of RCTs. In an ideal world, it is useful to complement both daily practice and RCTs, to provide valuable information about effectiveness and safety. However, it is difficult to realize RCTs for all the various systemic treatment options in hand eczema, as recruitment of this specific population can cost more time and funding than are available. In the meantime, daily-life studies are thus the only way to get more experience regarding the different treatment options.

Burden

The last part of this thesis explores the burden of hand eczema in terms of health-related quality of life (HRQoL), treatment satisfaction, and cost of illness. **Chapter 7** presents a cross-sectional study, one of the first studies to use the Quality of Life in Hand Eczema Questionnaire (QOLHEQ). The Dutch QOLHEQ was recently validated, and single band scores were given to provide interpretation of the QOLHEQ.²⁴ The HRQoL is one of the most important patient-reported outcomes, and many studies have focused on this aspect since hand eczema has a considerable morbidity due to discomfort in normal daily activities, poor occupational functioning, and work impairment.^{2,25–28} HRQoL can be measured by generic instruments like the Dermatology Life Quality Index (DLQI), Skindex or disease specific instruments which assess the impairments caused by one specific disease. The QOLHEQ is for hand eczema the only validated disease specific instrument, and therefore preferred, since scores measure disease specific domains of impairment.²⁹ The QOLHEQ covers 4 different domains: ‘symptoms’, ‘emotions’, ‘functioning’ and ‘treatment and prevention’. For example, severe impairment in the ‘symptoms’ scale can lead the clinician to consider changing the therapy. On the other hand, strong impairment in the ‘emotion’ and ‘functioning’ scales should encourage attention to psychological and educational interventions. Attention to these subdomains is relevant in order to provide customized treatment, as well as greater insight for both patient and clinician.

Chapter 7 evaluates the burden of patients with vesicular hand eczema (VHE).⁵ In our study a multivariate regression analysis showed that female gender, severe hand eczema, and lower treatment satisfaction were associated with more impact on HRQoL. Female gender is a well known demographic factor affecting the HRQoL of patients with hand eczema.^{29–31} The same is true of severity; our study, like previous ones, has found more severe hand eczema to be associated with a greater impact on HRQoL.^{30,32} Clinicians should, especially with (female) patients with moderate/severe hand eczema, focus attention on all aspects of HRQoL to optimize treatment success. Skin examination alone is insufficient to indicate the actual impact of a skin disease.

Chapter 7 further underlines the need for new treatment options to improve treatment satisfaction in the care of vesicular hand eczema patients. Patients with severe/very severe hand eczema had significantly lower global satisfaction scores compared to other severity groups in our study. Not unexpectedly, considering that almost a quarter of the patients, after being treated for at least 3 months, still had severe or very severe hand eczema. Global satisfaction and treatment adherence were significantly higher in patients using systemic treatment compared to those using only topical treatment. Probably, merely topical treatment was not (yet) sufficient to suppress their hand eczema symptoms. However, the perception of the relative inefficacy and inconvenience of topical treatment, and sometimes corticophobia, may also have hindered adherence and treatment effectiveness.^{33–35} Previous studies of psoriasis showed significantly higher satisfaction scores for biologics compared to other (traditional) treatments.^{36,37} In our study a small group ($n=7$) of atopic hand eczema patients were treated with off-label dupilumab. Compared with the group receiving only topical treatment, this group had significantly higher satisfaction scores. This study, as well as a few other observational studies, shows very positive effects for the use of dupilumab for (vesicular) hand eczema, and confirms the importance of new treatment options for this subtype of hand eczema.^{38–41}

The last subject in Chapter 7 was treatment adherence. Our study confirmed that adherence is

higher with oral treatment than with topical treatment. This is not new for dermatology, and specifically hand eczema.⁴² The lower adherence to topical treatment can partly clarify its ineffectiveness with some patients. A well-known quote is: 'Drugs don't work in patients who don't take them' (C.E. Koop 1985).⁴³ It is expected that adherence is even lower than in our findings, as actual treatment adherence is often lower than that reported by patients.^{42,44} Therefore, in case of ineffectiveness it is important to be aware of predictors of poor treatment adherence. Major predictors are psychological problems (particularly depression), cognitive impairment, side effects, missed appointments, lack of belief in treatment benefit, and lack of insight into the illness. In contrast, treatment adherence can be improved by knowledge about the disease, and confidence in and perception of the benefit of the treatment.⁴³ In our center every hand eczema patient receives a one-on-one patient education consultation about the use of topical treatment and, among others, avoidance of irritants. Yet, despite this extra attention patients had only an overall medium treatment adherence. Probably, continuous encouragement by text messaging (for example SMS/whats app) could increase the use of topical and oral medication in future hand eczema care.⁴⁵

Chapter 7 confirmed that systemic treatments could reduce severity and, as a result, health-related quality of life, treatment satisfaction, and treatment adherence. This finding suggests that clinicians should probably intensify anti-inflammatory treatment sooner in cases of severe chronic hand eczema with its significant impact on HRQoL due, for example, to absenteeism and/or depression. Earlier intervention could help to prevent long-term severity of disease and mental consequences, and furthermore reduce costs (as due to absenteeism). The often underutilized role of systemic treatment for occupational hand eczema is illustrated by a recent study of systemic treatment among Danish occupational hand eczema patients. This study found that only 13.3% of the patients with moderate to severe hand eczema received systemic treatment during a follow-up period of 5 years.⁴⁶ It was clear that treatment of (occupational) hand eczema is largely focused on prevention of aggravating factors in the workplace. However, some patients cannot reduce their amount of irritants and cannot easily switch their occupations, and sometimes their hand eczema cannot heal because of its severity. Especially these patients need earlier systemic treatment to prevent both loss of their jobs and progression into more severe chronic hand eczema. Prevention of chronicity is possible if the disease is taken seriously at an early stage.

Besides its individual burden, the socio-economic burden of hand eczema is considerable, especially for those with more severe and/or occupational hand eczema. It can have far-reaching personal and occupational consequences like productivity loss owing to absenteeism, or even job loss. When we reviewed the literature with respect to the costs of hand eczema (**Chapter 8**), we noted a wide range of mean annual direct (€521 – €3722) and indirect costs (€100 to €6846). In more severe hand eczema costs are higher. Moreover, for occupational hand eczema patients, indirect costs amounted to up to 70% of the total costs, mainly because of absenteeism. Being employed in a job that is affected by, or related to, hand eczema predicts higher costs in general.⁴⁷ The majority of the data reviewed in our study were collected in the pre-alitretinoin period. It will be interesting to see what kind of influence the introduction of alitretinoin and other upcoming treatments can have on direct and indirect costs in future cost studies. The medication costs of these drugs are expected to be considerably higher than those of conventional systemic treatment options such as cyclosporine, methotrexate, and azathioprine. However, indirect costs could probably drop due to effective new (oral) treatment options.

Future perspectives

This thesis supports the need for optimization of both topical and systemic treatment options to improve HRQoL, treatment satisfaction, and treatment adherence. At the moment, topical treatment mainly involves the use of (potent) corticosteroids. However, some patients are unresponsive to this first-line treatment and require systemic treatment.^{48,49} Alitretinoin and cyclosporine can be efficacious treatment options (**Chapters 3-6**), although this thesis has also showed that the current available systemic treatments for hand eczema are frequently limited by adverse events and ineffectiveness. For this reason (new) topical and systemic treatment options will need to be expanded.

Recently, topical treatment with delgocitinib, a novel pan-Janus kinase (JAK) inhibitor, was presented in a randomized, double-blind, phase IIa study (2019).⁵⁰ This RCT observed patients for 8 weeks and indicated delgocitinib to be an efficacious and well-tolerated topical treatment for (unclassified) chronic hand eczema. As no plateau phase of efficacy was observed, longer treatment could probably lead to even more improvement. This new topical treatment could be promising for patients with disease inadequately controlled on topical corticosteroids. However further studies will be needed to establish the long-term potency of topical JAK inhibitors and find out which patients benefit from this new treatment option.^{50,51}

For atopic dermatitis, exciting progress has been made in treatment success since new targeted treatments have become available or are in the pipeline. Although these treatments, encompassing biologics and small molecule drugs, are not yet available for hand eczema. Dupilumab is a human monoclonal antibody inhibiting interleukin (IL) 4 and IL-13 signaling, and has been successfully approved for the treatment of moderate-to-severe atopic dermatitis.^{52,53} It has also shown promising perspectives in small observational studies in patients with difficult to treat atopic hand eczema.^{38,54,55} Moreover, case studies in non atopic individuals with isolated recurrent vesicular ($n=16$) and chronic fissured hand eczema ($n=1$) have reported substantial beneficial effects of dupilumab.^{40,41,56} Future RCTs are required to evaluate the efficacy of dupilumab for hand eczema, and observe whether it has long term effects on this often multifactorial and chronic disease.

Hand eczema can have multiple etiologies and morphological subtypes, but no correlation has been found between the etiology and the clinical morphological pattern. Furthermore, various classification systems have been described, but none has been generally accepted.^{57,58} It is expected that different hand eczema subtypes will be found to have different subsets of disease specific biomarkers, and therefore probably require different therapeutic approaches.⁵⁹ Future studies are needed to understand the pathogenesis and identify key cytokines and receptors involved in the pathogenesis of these different subtypes. A uniform classification system is needed to evaluate the effect of new treatments in future clinical trials of hand eczema. Insight into the pathogenesis of hand eczema may help in the development of such a classification system, wherein morphological subtypes (phenotypes) are combined with molecular subtypes (endotypes). This should improve disease-specific treatment approaches and is expected to further augment efficacy and safety, and offer more potential for long-term improvement of health-related quality of life.⁵³

References

1. Meding B, Wrangsjö K, Jarvholm B. Fifteen-year follow-up of hand eczema: persistence and consequences. *Br J Dermatol*. 2005;152(5):975–80.
2. Marron SE, Tomas-Aragones L, Navarro-Lopez J et al. The psychosocial burden of hand eczema: Data from a European dermatological multicentre study. *Contact Dermatitis*. 2018;78(6):406–12.
3. Carøe TK, Ebbelhøj N, Agner T. A survey of exposures related to recognized occupational contact dermatitis in Denmark in 2010. *Contact Dermatitis*. 2014 Jan;70(1):56–62.
4. Park JY, Cho EB, Park EJ, Park HR, Kim KH, Kim KJ. The histopathological differentiation between palmar psoriasis and hand eczema: A retrospective review of 96 cases. *J Am Acad Dermatol*. 2017;77(1):130–5.
5. Johansen JD, Hald M, Andersen BL et al. Classification of hand eczema: Clinical and aetiological types. Based on the guideline of the Danish Contact Dermatitis Group. *Contact Dermatitis*. 2011;65(1):13–21.
6. Molin S, Merl J, Dietrich KA et al. The hand eczema proteome: imbalance of epidermal barrier proteins. *Br J Dermatol*. 2015 Apr;172(4):994–1001.
7. Kumari V, Timm K, Kühl AA, Heine G, Worm M. Impact of systemic alitretinoin treatment on skin barrier gene and protein expression in patients with chronic hand eczema. *Br J Dermatol*. 2016;175(6):1243–50.
8. Lillis J V, Guo C-S, Lee JJ, Blauvelt A. Increased IL-23 expression in palmoplantar psoriasis and hyperkeratotic hand dermatitis. *Archives of dermatology*. United States; 2010;146:918–9.
9. Zhang X, Yin M, Zhang L. Keratin 6, 16 and 17—Critical Barrier Alarmin Molecules in Skin Wounds and Psoriasis. *Cells*. 2019;8(8):807.
10. Yang L, Zhang S, Wang G. Keratin 17 in disease pathogenesis: from cancer to dermatoses. *J Pathol*. 2019;247(2):158–65.
11. Shi X, Jin L, Dang E et al. IL-17A upregulates keratin 17 expression in keratinocytes through STAT1-and STAT3-dependent mechanisms. *J Invest Dermatol*. 2011;131(12):2401–8.
12. Nederlandse Vereniging voor Dermatologie en Venereologie (NVDV). Richtlijn Handeczeem 2019. <https://nvdv.nl/professionals/richtlijnen-en-onderzoek/richtlijnen/richtlijn-handeczeem>. Accessed December 3, 2019.
13. Christoffers W, Coenraads P, Svensson Å et al. Interv hand eczema Cochrane Database Syst Rev 2019, Issue 4 Art No CD004055 DOI 10.1002/14651858CD004055.pub2.
14. van der Schaft J, Van Zuilen AD, Deinum J, Bruijnzeel-Koomen CAFM, De Bruin-Weller MS. Serum creatinine levels during and after long-term treatment with cyclosporine a in patients with severe atopic dermatitis. *Acta Derm Venereol*. 2015;95(8):963–7.
15. Schmitt J, Schmitt N, Meurer M. Cyclosporin in the treatment of patients with atopic eczema – a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol*. 2007;21(5):606–19.
16. van der Schaft J, Politiek K, van den Reek JM et al. Drug survival for cyclosporin A in a long-term daily practice cohort of adult patients with atopic dermatitis. *Br J Dermatol*. 2015 Feb 13;
17. Shalom G, Zisman D, Harman-Boehm I et al. Factors associated with drug survival of methotrexate and acitretin in patients with psoriasis. *Acta Derm Venereol*. 2015;95(8):973–7.
18. Jang Y, Yoon J, Park E, Kim K, Kim K. Efficacy and Safety of Treatment with Oral Alitretinoin and Oral Cyclosporine for Chronic Hand Eczema: A Retrospective Review of 118 Cases. *Acta Derm Venereol*. 2019;0.
19. Martin K, Begaud B, Latry P, Miremont-Salame G, Fourrier A, Moore N. Differences between clinical trials and postmarketing use. *Br J Clin Pharmacol*. 2004 Jan;57(1):86–92.
20. Agarwal US BR. 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;79:101–3.
21. Schram ME, Roekevisch E, Leeflang MM, Bos JD, Schmitt J, Spuls PL. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. *J Allergy Clin Immunol*. 2011 Aug;128(2):353–9.
22. Van Onzenoort HAW, Menger FE, Neef C et al. Participation in a clinical trial enhances adherence and persistence to treatment: A retrospective

- cohort study. *Hypertension*. 2011;58(4):573–8.
23. Cohen AT, Goto S, Schreiber K, Torp-Pedersen C. Why do we need observational studies of everyday patients in the real-life setting? *Eur Hear Journal, Suppl*. 2015;17:D2–8.
24. Oosterhaven, Jart AF, Ofenloch Robert F, Schuttelaar M-LA. Validation of the Dutch Quality Of Life in Hand Eczema Questionnaire. *Br J Dermatol*. 2020;183(1):86–95.
25. Apfelbacher CJ, Ofenloch RF, Weisshaar E et al. Chronic hand eczema in Germany: 5-year follow-up data from the CARPE registry. *Contact Dermatitis*. 2019;80(1):45–53.
26. Boehm D, Schmid-Ott G, Finkeldey F et al. Anxiety, depression and impaired health-related quality of life in patients with occupational hand eczema. *Contact Dermatitis*. 2012;67(4):184–92.
27. Oosterhaven JAF, Flach PA, Bultmann U, Schuttelaar MLA. Presenteeism in a Dutch hand eczema population—a cross-sectional survey. *Contact Dermatitis*. 2018 Jul;79(1):10–9.
28. Maccari F, Ezzedine K, Fougerousse AC et al. Building a scale for measuring burden of hand eczema: BoHEM. *J Am Acad Dermatol*. 2019;80(6):1784–5.
29. Ofenloch RF, Weisshaar E, Dumke AK, Molin S, Diepgen TL, Apfelbacher C. The Quality of Life in Hand Eczema Questionnaire (QOLHEQ): validation of the German version of a new disease-specific measure of quality of life for patients with hand eczema. *Br J Dermatol*. 2014 Aug;171(2):304–12.
30. Agner T, Andersen KE, Brandao FM et al. Hand eczema severity and quality of life: a cross-sectional, multicentre study of hand eczema patients. *Contact Dermatitis*. 2008 Jul;59(1):43–7.
31. Cazzaniga S, Ballmer-Weber BK, Gräni N et al. Medical, psychological and socio-economic implications of chronic hand eczema: A cross-sectional study. *J Eur Acad Dermatology Venereol*. 2016;30(4):628–37.
32. Cazzaniga S, Ballmer-Weber BK, Gräni N et al. Chronic hand eczema: A prospective analysis of the Swiss CARPE registry focusing on factors associated with clinical and quality of life improvement. *Contact Dermatitis*. 2018 Sep;79(3):136–48.
33. Chan SA, Hussain F, Lawson LG, Ormerod AD. Factors affecting adherence to treatment of psoriasis: Comparing biologic therapy to other modalities. *J Dermatolog Treat*. 2013;24(1):64–9.
34. Aubert-Wastiaux H, Moret L, Le Rhun A et al. Topical corticosteroid phobia in atopic dermatitis: A study of its nature, origins and frequency. *Br J Dermatol*. 2011;165(4):808–14.
35. Furue M, Onozuka D, Takeuchi S et al. Poor adherence to oral and topical medication in 3096 dermatological patients as assessed by the Morisky Medication Adherence Scale-8. *Br J Dermatol*. 2015;172(1):272–5.
36. Hjortsberg C, Bergman A, Bjarnason A et al. Are treatment satisfaction, quality of life, and self-assessed disease severity relevant parameters for patient registries? Experiences from finnish and swedish patients with psoriasis. *Acta Derm Venereol*. 2011;91(4):409–14.
37. Callis Duffin K, Yeung H, Takeshita J et al. Patient satisfaction with treatments for moderate-to-severe plaque psoriasis in clinical practice. *Br J Dermatol*. 2014;170(3):672–80.
38. Zirwas MJ. Dupilumab for hand eczema. *J Am Acad Dermatol*. 2018;79(1):167–9.
39. Oosterhaven JAF, Voorberg AN, Romeijn GLE, de Bruin-Weller MS, Schuttelaar MLA. Effect of dupilumab on hand eczema in patients with atopic dermatitis: An observational study. *J Dermatol*. 2019;(April):1346–8138.14982.
40. Waldman RA, DeWane ME, Sloan B, Grant-Kels JM, Lu J. Dupilumab for the Treatment of Dyshidrotic Eczema in 15 Consecutive Patients. *J Am Acad Dermatol*. 2020;82(5):1251–1252.
41. Halling AS, Zachariae C, Thyssen JP. Severe treatment-resistant acute and recurrent vesicular chronic hand eczema successfully treated with dupilumab. *Contact Dermatitis*. 2020;83(1):37–38.
42. Krejci-Manwaring J, Ann McCarty M, Camacho F et al. Adherence With Topical Treatment Is Poor Compared With Adherence With Oral Agents: Implications for Effective Clinical Use of Topical Agents. *J Am Acad Dermatol*. 2006;54(5 SUPPL. 1):235–6.
43. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353(5):487–97.

44. Lee J, Tay TR, Radhakrishna N et al. asthma biologics and thermoplasty. 2018; Available from: <http://dx.doi.org/10.1183/13993003.01836-2017>
45. Erdil D, Koku Aksu AE, Falay Gür T, Gürel MS. Hand eczema treatment: Change behaviour with text messaging, a randomized trial. *Contact Dermatitis*. 2020;82(3):153–160
46. Sedeh, B.F. Ebbehøj N.E., Agner TCTK. Systemic therapy and the use of complementary and alternative medicine in patients with recognised occupational hand eczema in Denmark: a cross-sectional questionnaire-based study. *Contact Dermatitis*. 2020;82(5):272–278
47. Diepgen TL, Purwins S, Posthumus J, Kuessner D, John SM, Augustin M. Cost-of-illness analysis of patients with chronic hand eczema in routine care in Germany: focus on the impact of occupational disease. *Acta Derm Venereol*. 2013;93(5):538–43.
48. Diepgen TL, Agner T, Aberer W, Berth-Jones J, Cambazard F, Elsner P, et al. Management of chronic hand eczema. *Contact Dermatitis*. 2007;57(4):203–10.
49. Diepgen TL, Andersen KE, Chosidow O et al. Guidelines for diagnosis, prevention and treatment of hand eczema—short version. *J Dtsch Dermatol Ges*. 2015;13(1):77–85.
50. Worm M, Bauer A, Elsner P, Mahler V, Molin S, Nielsen TSS. Efficacy and safety of topical delgocitinib in patients with chronic hand eczema: data from a randomized, double-blind, vehicle-controlled phase IIa study. *Br J Dermatol*. 2020;182(5):1103–1110.
51. He H, Guttman-Yassky E. JAK Inhibitors for Atopic Dermatitis: An Update. *Am J Clin Dermatol*. 2019;20(2):181–192.
52. Han Y, Chen Y, Liu X et al. Efficacy and safety of dupilumab for the treatment of adult atopic dermatitis: A meta-analysis of randomized clinical trials. *J Allergy Clin Immunol*. 2017;140(3):888–891.e6.
53. Deleuran M, Thaçi D, Beck LA, de Bruin-Weller M, Blauvelt A, Forman S, et al. Dupilumab shows long-term safety and efficacy in moderate-to-severe atopic dermatitis patients enrolled in a phase 3 open-label extension study. *J Am Acad Dermatol*. 2020;82(2):377–388.
54. Oosterhaven JAF, Voorberg AN, Romeijn GLE, de Bruin-Weller MS, Schuttelaar MLA. Effect of dupilumab on hand eczema in patients with atopic dermatitis: An observational study. *J Dermatol*. 2019; 46(8):680–685.
55. Lee N, Chipalkatti N, Zancanaro P, Kachuk C, Dumont N, Rosmarin D. A Retrospective Review of Dupilumab for Hand Dermatitis. *Dermatology*. 2019;235(3):187–8.
56. Zhu GA, Honari G, Ko JM, Chiou AS, Chen JK. Dupilumab for occupational irritant hand dermatitis in a nonatopic individual: A case report. *JAAD Case Reports*. 2020;6(4):296–8.
57. Agner T, Aalto-Korte K, Andersen KE et al. Classification of hand eczema. *J Eur Acad Dermatology Venereol*. 2015;29(12):2417–22.
58. Menné T, Johansen JD, Sommerlund M, Veien NK. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. *Contact Dermatitis*. 2011 Jul;65(1):3–12.
59. Garzorz-Stark N, Eyerich K. Molecular diagnostics of hand eczema. *Hautarzt*. 2019;70(10):760–5.

Chapter 10

Summary

Hand eczema is a common condition in the general population. Previous studies showed a life-time prevalence of about 15%. Most patients develop hand eczema as young adults, although patients can develop hand eczema at all ages. Hand eczema is associated with itching, pain, and social stigma, and often has far-reaching personal consequences. This thesis is divided into three parts, discussing different aspects of hand eczema: pathogenesis, treatment and burden of disease.

Part I – Pathogenesis

The pathogenesis of hand eczema is largely unknown and has not yet been further specified in relation to different hand eczema subtypes. In the first part of this thesis, **Chapter 2**, we describe a pilot project on the pathogenesis of hyperkeratotic hand eczema (HHE). The clinical phenotype of HHE is currently classified as a subtype of hand eczema, although previous studies have questioned whether HHE should be considered as eczema, since it is monomorphic and shares similarities with palmar psoriasis and palmoplantar keratoderma.

The aim of this study was to gain more insight into the pathophysiology by investigating histopathology, expression of keratins (K), epidermal barrier proteins, and adhesion molecules in HHE. Palmar skin biopsies (lesional and perilesional) were obtained from seven HHE patients and two healthy controls for histopathology and immunofluorescence (IF) stainings. IF stainings were performed to analyze the expression of K1, K2e, K5, K6, K9, K10, K14, K15, K16, K17, desmoglein-1, desmoglein-3, plakophilin-1, plakoglobin, desmoplakin, filaggrin, loricrin, involucrin and corneodesmosin in lesional, perilesional, and healthy control skin. Moreover, 135 candidate genes associated with palmoplantar keratoderma were screened.

In all lesional skin samples histopathology showed uniform histological features: confluent parakeratosis, plasma in the parakeratotic foci, presence of the stratum granulosum, epidermal hyperplasia, spongiosis and exocytosis of lymphocytes. These features are not different from those of palmar psoriasis, and it is questionable if differentiation based on histopathology is possible. Furthermore, substantial changes were found in the keratin, epidermal barrier proteins, and adhesion molecules. IF staining showed a significant reduction of K9 and K14 in lesional skin. Upregulation was found for K5, K6, K16, and K17 in lesional skin compared to perilesional and healthy palmar skin. Further, upregulation of involucrin and alternating loricrin staining, both in an extracellular staining pattern, was found. Filaggrin expression was similar in lesional, perilesional and healthy control skin. Finally, no monogenetic mutations were found.

Currently, the phenotype of HHE is included in the hand eczema classification system; however, it is not certain whether this is justified. The evident expression of filaggrin and involucrin in lesional skin does not support a pathogenesis of atopic eczema. The upregulation of K6, K16 and K17 and reduction of K9 and K14 may contribute to the underlying pathogenesis. Unfortunately, comparison with hand eczema studies is not yet possible because similar protein expression studies are lacking.

Part II – Treatment

The second part of this thesis focuses on effectiveness and safety in the daily practice use of systemic treatment for severe chronic hand eczema, by means of drug survival studies (**Chapters 3 to 6**). Alitretinoin is the only registered systemic treatment for CHE, and has been well studied in randomized controlled trials. Data on other systemic treatments such as acitretin, cyclosporine,

methotrexate (MTX) and azathioprine is less extensive. In four retrospective studies we analyzed the drug survival of the above systemic treatments in a cohort of severe CHE patients. Drug survival is an outcome measure to evaluate drugs extensively regarding effectiveness, safety, and patients' and doctors' preference. We also studied adverse events and reasons for discontinuation. Direct comparison among the different treatments was not feasible because of the retrospective and daily practice study designs.

Patients treated with alitretinoin (**Chapter 3**) had a median drug survival of 4.6 months (20 weeks), and more than half of the patients had a good effect of treatment. Alitretinoin is registered for a treatment duration of 24 weeks, and treatment was often discontinued because a cleared hand eczema in this period affected the drug survival. Another retinoid, acitretin, has been used off-label for years to treat chronic hand eczema, but is less often prescribed since the approval of alitretinoin. (Chapter 3). The drug survival of acitretin was 4.5 months; however, more patients discontinued treatment due to adverse events. Both treatments showed the highest efficacy in patients with HHE. Alitretinoin is approved in several countries; nevertheless acitretin can be considered as an adequate treatment option in countries where alitretinoin is not yet available. Cyclosporine (**Chapter 4**) had a longer median drug survival (10.3 months). Most patients included had a vesicular hand eczema (65%), which seems to have a positive effect on the drug survival. However patients treated with cyclosporine also often discontinued treatment due to adverse events, mainly early in treatment.

Finally, we studied drug survival on MTX (**Chapter 5**) and azathioprine (**Chapter 6**). MTX and azathioprine are less often prescribed, and our studies included only small groups of patients. These studies showed drug survival durations of respectively 5.2 and 3.6 months. A high number of patients discontinued treatment prematurely. Especially in the case of azathioprine, more than half of the patients discontinued treatment due to adverse events.

These drug survival studies showed that systemic treatments have an important role in (severe) CHE. However, daily practice treatments were often discontinued primarily due to adverse events and/or ineffectiveness, thereby hindering evaluation of effectiveness. If patients report mild subjective adverse events or ineffectiveness using alitretinoin, MTX, and azathioprine in the first weeks, physicians should, if possible, motivate patients to continue. To give treatment effectiveness a real chance a duration of 12 weeks is preferred. Furthermore, these studies underline the need for new treatment options in severe hand eczema, especially if alitretinoin and cyclosporine are ineffective.

Part III – Burden

The last part of this thesis explores the burden of hand eczema in terms of health-related quality of life (HRQoL), treatment satisfaction, and cost of illness. **Chapter 7** evaluates the burden of patients with vesicular hand eczema (VHE). This cross-sectional study included 168 VHE patients treated for at least 3 months. Questionnaires were collected containing the: 'Quality of Life in Hand Eczema Questionnaire' (QOLHEQ) for HRQoL, 'Treatment Satisfaction Questionnaire for Medication' for treatment satisfaction and the '4-item Morisky Medication Adherence Scale' for treatment adherence.

Using a multivariate regression analysis, this study showed that female gender, severe hand eczema, and lower treatment satisfaction were associated with more impact on HRQoL. Patients with severe/very severe hand eczema had significantly lower global satisfaction scores compared to other severity groups. The "global satisfaction" and treatment adherence in patients using systemic

systemic treatment were significantly higher compared with those using only topical treatment. Furthermore, a higher adherence was associated with more HRQoL and treatment satisfaction. In conclusion, disease severity affects both HRQoL and treatment satisfaction. Systemic treatment of severe hand eczema could reduce the severity and, as a result, also HRQoL, treatment satisfaction, and medication adherence. This again underlines the need for new (systemic) treatment options to improve care of vesicular hand eczema patients.

Chapter 8 as final chapter is a review of the socio-economic impact of hand eczema. The aims of this review were to evaluate the literature on cost-of-illness in hand eczema, and to compose a checklist for future use. The literature was retrieved from MEDLINE and EMBASE databases up to October 2015. Quality evaluation was based on seven relevant items in cost-of-illness studies. Cost data (direct and indirect) were extracted and converted into euros (2014 price level) using the Dutch Consumer Price Index. Six articles were included, with a heterogeneous study design. The mean annual total cost per patient ranged from €1311 to €9792 (direct cost per patient, €521 to €3722; and indirect cost per patient, €100 to €6846). In more severe hand eczema cases costs are higher. Moreover, for occupational hand eczema patients, indirect costs amounted to up to 70% of the total costs, mainly because of absenteeism. The socio-economic burden of hand eczema is considerable, especially for more severe and/or occupational hand eczema. Absenteeism from paid work leads to a high total cost-of-illness, although disregard of presenteeism often leads to underestimation of indirect costs. Differences in included cost components, the occupational status of patients, and hand eczema severity make international comparison difficult. A checklist was added to standardize the approach to cost-of-illness studies in hand eczema. It will be interesting to see what kind of influence the introduction of new upcoming treatments can have on future cost studies. The costs of these drugs are expected to be considerably higher than those of conventional systemic treatment options, although indirect costs could probably drop due to effective new (oral) treatment options.

In conclusion, this thesis supports the need for optimization of treatment options in hand eczema. If we better understand the pathogenesis and better identify key cytokines and receptors involved in the pathogenesis, further disease-specific treatment approaches are expected to augment efficacy and safety, and offer more potential for long-term improvement of health-related quality of life, treatment satisfaction and treatment adherence.

Chapter 11

Samenvatting

Handeczeem is een veel voorkomende aandoening in de algemene bevolking. De prevalentie om gedurende de levensloop (mild) handeczeem te ontwikkelen ligt rond de 15%. Hoewel de aandoening regelmatig jonge mensen treft, kan handeczeem op alle leeftijden voorkomen. Klachten als jeuk, pijn en schaamte hebben een behoorlijke impact op het functioneren en de kwaliteit van leven van patiënten. Handeczeem wordt gezien als een multifactoriële aandoening, waarbij aanleg, blootstelling aan irriterende stoffen en contactallergenen de belangrijkste bijdragende oorzaken zijn. Daarnaast kent handeczeem verschillende klinische subtypes. De klinische subtypes die het meest voorkomen zijn chronisch gefissureerd, vesiculeus en hyperkeratotisch handeczeem. De onderliggende pathogenese van deze verschillende subtypes is nog grotendeels onbekend. De behandeling van handeczeem kan moeizaam zijn. Circa 2-4% van alle handeczeem patiënten heeft een moeilijk te behandelen, (ernstig) chronisch handeczeem. Deze groep heeft onvoldoende baat bij de eerstelijnsbehandeling met corticosteroïd zalven en komt in aanmerking voor behandeling middels systemische behandelingen (tabletten/injecties). Dit proefschrift heeft als doel om meer inzicht te krijgen in de pathogenese, de effectiviteit en veiligheid van systemische behandelingen en de ziektelast van (ernstig) handeczeem.

Deel I – Pathogenese

De pilotstudie uit **hoofdstuk 2** richt zich op de pathogenese van hyperkeratotisch handeczeem. Dit is een subtype van handeczeem met een typische presentatie. Patiënten hebben forse, scherp begrensde hyperkeratose (eelt) op de handpalmen. De onderliggende oorzaak is onbekend en het kan klinisch lijken op palmaire psoriasis en palmoplantaire keratoderma. Het doel van dit onderzoek was inzicht in de pathogenese te vergroten middels genetisch onderzoek, histopathologie en immunofluorescentie onderzoek.

We includeerden 7 patiënten en 2 gezonde controles, allen waren man met een gemiddelde leeftijd van 59 jaar. Bij elke patiënt werden vier huidbipten afgenomen: één bipt voor histopathologie (PA) en één bipt voor immunofluorescentie (IF) onderzoek van aangedane en niet-aangedane huid. Van de controles werden twee gezonde bipten afgenomen voor PA en IF-onderzoek. Daarnaast werd een genpanel van 135 genen onderzocht die betrokken zijn bij palmoplantaire keratoderma. Bij geen van de patiënten werd een onderliggende monogenetische oorzaak voor de hyperkeratose gevonden. Histopathologisch onderzoek toonde in alle aangedane huidbipten vergelijkbare kenmerken zoals een aanwezig stratum granulosum, een verbrede epidermis en spongiose. Dit kan goed passen bij eczeem, echter is niet onderscheidend van bijvoorbeeld palmaire psoriasis.

IF-kleuringen van verschillende keratines, celbruggen en huidbarrière eiwitten lieten duidelijke verschillen zien tussen aangedane versus niet aangedane huid en gezonde controle huidbipten. Keratine 9 bijvoorbeeld, een belangrijk eiwit dat normaal gesproken alleen op handpalmen en voetzolen voorkomt, was in 5 van de 7 aangedane huidbipten grotendeels afwezig. Daarnaast waren keratine 5, 6, 16 en 17, betrokken bij onder andere wondgenezing en psoriasis, sterk verhoogd aanwezig in lesionale huid. Een andere verrassende bevinding was de normale aanwezigheid van filaggrine in de lesionale huidbipten. Dit barrière eiwit is bij aangedane huid van andere subtypes van (hand)eczeem verminderd aanwezig. Hetzelfde geldt voor het barrière eiwit involucrine. Involucrine lijkt juist toegenomen in hyperkeratotisch handeczeem en heeft een ander, extracellulair, expressiepatroon. Deze uitkomsten leiden tot de vraag in hoeverre hyperkeratotisch handeczeem een subtype van handeczeem is, danwel een opzichzelfstaande entiteit. Toekomstig onderzoek zal hyperkeratotisch handeczeem moeten vergelijken met andere subtypes van hand-

eczeem en andere palmaire huidziekten zoals palmaire psoriasis.

Deel II – Behandeling

Het tweede deel (**hoofdstuk 3-6**) van dit proefschrift focust zich op de effectiviteit en veiligheid van systemische (orale) behandelingen van handeczeem in de dagelijkse praktijk. Deze data zijn waardevol omdat het in tegenstelling tot klinische trials informatie biedt over de lange termijn behandeling van ongeselecteerde patiëntengroepen. Op dit moment is alitretinoïne de enige geregistreerde behandeling voor chronisch handeczeem. De effectiviteit en veiligheid van deze van vitamine A afgeleide stof (retinoïd) is goed onderzocht in gerandomiseerde klinische trials. Data over de effectiviteit en veiligheid van alternatieve (off-label) behandelingen voor handeczeem zoals acitretine, ciclosporine, methotrexaat en azathioprine zijn beperkter.

We hebben in een viertal retrospectieve studies de verschillende behandelingen geëvalueerd middels drug survival analyse. Drug survival geeft de behandelduur weer middels een Kaplan-Meier survival analyse. De duur wordt hierbij beïnvloed door het gedrag van patiënt en arts en weerspiegelt de potentie van het geneesmiddel voor de lange termijn. De behandelingen werden niet onderling vergeleken gezien de patiëntkarakteristieken per behandeling te veel kunnen verschillen. Patiënten die werden behandeld met alitretinoïne (**hoofdstuk 3**) hadden een mediane drug survival van 4.6 maanden (20 weken). Voor ruim de helft van de patiënten, in het bijzonder patiënten met hyperkeratotisch en chronisch gefissureerd handeczeem, had het middel een gunstig effect. Alitretinoïne is geregistreerd voor een behandelduur van 24 weken en behandeling zal bij goed effect veelal rond deze periode gestaakt worden, hetgeen de drug survival beïnvloed. Een ander retinoïd dat al jarenlang wordt voorgeschreven is acitretine (**hoofdstuk 3**). Acitretine liet een vergelijkbare effectiviteit zien, eveneens ten gunste van hyperkeratotisch en chronisch gefissureerd handeczeem. Echter, meer patiënten stopten de behandeling omwille van bijwerkingen. Dit resulteerde in een vergelijkbare mediane drug survival (4.5 maanden). Ciclosporine (**hoofdstuk 4**) had een langere mediane drug survival (10.3 maanden). Van de behandelde patiënten had 65% een vesiculeus handeczeem, dit subtype leek een gunstig effect te hebben op de drug survival. Echter, ook bij ciclosporine behandeling waren bijwerkingen de hoofdreden dat patiënten de therapie stakten. Tot slot hebben we de drug survival van methotrexaat (**hoofdstuk 5**) en azathioprine (**hoofdstuk 6**) bestudeerd. Deze minder frequent voorgeschreven alternatieven lieten in kleine patiëntengroepen een beperkte effectiviteit zien, een drug survival van respectievelijk, 5.2 en 3.6 maanden. Patiënten stopten veelal met de behandeling vanwege bijwerkingen en ineffectiviteit. De belangrijkste conclusies uit de drug survival studies zijn dat systemische behandelingen een belangrijke bijdrage leveren aan de behandeling van (ernstig) chronisch handeczeem in de dagelijkse praktijk. Echter regelmatig worden behandelingen vroegtijdig gestaakt, met name omwille van bijwerkingen maar ook ineffectiviteit, waardoor de effectiviteit niet optimaal beoordeeld kan worden. Het optimaliseren van de dosering, behandelduur en de verwachtingen van de patiënt zou mogelijk kunnen bijdragen aan een langere drug survival. Daarnaast is er, zeker indien behandeling met alitretinoïne en ciclosporine onvoldoende effectief zijn, vraag naar nieuwe behandel mogelijkheden voor patiënten met ernstig handeczeem.

Deel III – Ziektelast

De behandeling van chronisch (vesiculeus) handeczeem is regelmatig een uitdaging en kan een grote impact op de kwaliteit van leven hebben. Het doel van het laatste onderdeel van dit proef-

schrift was de ziektelast van vesicleus handeczeem in kaart brengen aan de hand van patiënt gerapporteerde uitkomsten (**hoofdstuk 7**). Daarnaast werd de financiële impact van handeczeem onderzocht middels een kostenreview (**hoofdstuk 8**).

In hoofdstuk 7 werd bij 168 patiënten met chronisch vesicleus handeczeem, welke minimaal 3 maanden behandeld werden, een vragenlijst afgenomen. De vragenlijst bestond uit de 'Quality of Hand Eczema Questionnaire' voor ziekte gerelateerde kwaliteit van leven, 'Treatment Satisfaction Questionnaire for Medication' voor behandeltevredenheid en '4-item Morisky Medication Adherence Scale' voor therapietrouw.

We vonden in deze studie dat de ziekte gerelateerde kwaliteit van leven lager was voor vrouwen, patiënten met een ernstiger handeczeem en minder tevreden patiënten. Patiënten met een ernstiger handeczeem waren daarnaast minder tevreden over de behandeling dan patiënten met een minder ernstig handeczeem. De patiënten die behandeld werden met dupilumab, alitretinoïne en ciclosporine waren significant tevredener dan patiënten met alleen lokale behandeling. Dit laatste ondersteunt dat de huidige systemische behandelingen met alitretinoïne en ciclosporine waardevol kunnen zijn voor patiënten met (ernstig) vesicleus handeczeem. Daarnaast onderschrijft de hoge tevredenheid bij dupilumab, een behandeling die op dit moment alleen voor constitutioneel eczeem geregistreerd is, de vraag naar nieuwe effectieve behandelopties voor handeczeem. Tot slot werd therapietrouw onderzocht. Patiënten met systemische behandeling hadden een hogere therapietrouw dan patiënten met alleen lokale behandeling. Daarbij was een hogere therapietrouw geassocieerd met een hogere ziekte gerelateerde kwaliteit van leven en hogere tevredenheid.

De conclusies uit deze studie zijn dat ernst van het handeczeem de ziekte gerelateerde kwaliteit van leven en de tevredenheid beïnvloed. Waarbij de verwachting is dat toekomstige effectieve (systemische) behandelingen de ernst van het handeczeem verminderen en daarmee ziekte gerelateerde kwaliteit van leven, tevredenheid en therapietrouw verbeteren.

Hoofdstuk 8 geeft tot slot een overzicht van de financiële impact van handeczeem op de patiënt zelf en de maatschappij. Zes studies voldeden aan de inclusiecriteria en lieten een brede range aan totale jaarlijkse kosten van handeczeem zien, onder andere wegens een grote heterogeniteit in studieopzet. De kosten varieerden per patiënt van €1311 tot €9742 per jaar. Bij ernstiger handeczeem werden hogere kosten gevonden, met name door meer kosten van verschillende behandelingen, poliklinische zorg en eventuele opname. Daarbij brengt arbeid gerelateerd handeczeem hoge (indirecte) kosten met zich mee, voornamelijk door ziekteverzuim en in sommige gevallen ontslag. Voor verder onderzoek zou het interessant zijn om de invloed van nieuwe behandelingen op de totale kosten te evalueren. Nieuwe behandelopties zullen waarschijnlijk gepaard gaan met hogere directe kosten, maar indirecte kosten zullen daarentegen mogelijk dalen door een hogere effectiviteit.

Samengevat ondersteunt dit proefschrift de noodzaak voor het verbeteren van de behandelopties in handeczeem. Als we de pathogenese van handeczeem beter begrijpen, kunnen we gericht behandeling inzetten om de effectiviteit van de behandelingen te vergroten. Gerichte, ziekte specifieke aanpak heeft daarbij potentie voor betere lange termijn effecten om zo ziekte gerelateerde kwaliteit van leven, tevredenheid en ook therapietrouw te verbeteren.

Appendices

List of publications

Thesis

- **Politiek K**, Loman L, Pas HH, Diercks GFH, Lemmink HH, Commandeur-Jan SZ, van den Akker P, Bolling MC, Schuttelaar MLA. Hyperkeratotic hand eczema – eczema or not. *Contact Dermatitis*. 2020. Online ahead of print.
- **Politiek K**, Ofenloch RF, Angelino M, van den Hoed E, Schuttelaar MLA. Quality of life, treatment satisfaction and treatment adherence in chronic vesicular hand eczema. *Contact Dermatitis*. 2020;82(4):201-210
- Oosterhaven JAF, **Politiek K**, Schuttelaar MLA. Azathioprine treatment and drug survival in patients with chronic hand eczema – results from daily practice. *Contact Dermatitis*. 2017;76(5):304-307.
- **Politiek K**, Christoffers WA, Coenraads PJ, Schuttelaar MLA. Alitretinoin and acitretin in severe chronic hand eczema; result from a retrospective daily practice study. *Dermatologic therapy*. 2016;29(5):364-371
- **Politiek K**, Oosterhaven JA, Vermeulen KM, Schuttelaar ML. Systematic review of cost-of-illness studies in hand eczema. *Contact Dermatitis*. 2016;75(2):67-76.
- **Politiek K**, Van der Schaft J, Christoffers WA, Coenraads PJ, Van den Reek JMPA, De Jong EMGJ, De Bruin-Weller MS, Schuttelaar MLA. Drug survival of methotrexate treatment in hand eczema patients: results from a retrospective daily practice study. *J Eur Acad Dermatol Venereol*. 2016;30(8):1405-7.
- Christoffers WA, **Politiek K**, Coenraads PJ, Van der Schaft, De Bruin-Weller MS, Schuttelaar MLA. Drug survival of cyclosporine in the treatment of hand eczema: a multicentre, daily use study. *J Eur Acad Dermatol Venereol*. 2016;30(1):63-6.

Other

- Prens LM, Rondags A, Volkering RJ, Janse IC, **Politiek K**, Zuidema YS, Turcan I, van Hasselt J, van der Zee HH, Horváth B. The refined Hurley classification: the interrater and intrarater reliability and face validity. *Br J Dermatol*. 2019;181(6):1335-1337.
- Garritsen FM, van der Schaft J, van den Reek JM, **Politiek K**, van Os-Medendorp H, van Dijk M, Hijnen DJ, de Graaf M, Bruijnzeel-Koomen CA, de Jong EM, Schuttelaar MA, Bruin-Weller MS. Risk of Non-melanoma Skin Cancer in Patients with Atopic Dermatitis Treated with Oral Immunosuppressive Drugs. *Acta Derm Venereol*. 2017;97(6):724-730.
- Dittmar, D, **Politiek K**, Coenraads, P. J, Flach, P. A, Schuttelaar, M.L. Allergic contact dermatitis in two employees of an ethylene amine-producing factory. *Contact Dermatitis* 2017;76(5):310-312.
- Bosker HM, **Politiek K**, Urgert MC, Flach PA, Coenraads PJ, Schuttelaar ML. Occupational allergic contact dermatitis caused by 1-propanol in a hand disinfectant. *Contact Dermatitis*. 2017;76(4):241-243.
- Van der Schaft J, **Politiek K**, van den Reek JM, Kievit W, de Jong EM, Bruijnzeel-Koomen CA, Schuttelaar ML, de Bruin-Weller MS. Drug survival for azathioprine and enteric-coated mycophenolate sodium in a long-term daily practice cohort of adult patients with atopic dermatitis. *Br J Dermatol*. 2016;175(1):199-202.
- **Politiek K**, van der Schaft J, Coenraads PJ, de Bruin-Weller MS, Schuttelaar ML. Drug survival for methotrexate in a daily practice cohort of adult patients with severe atopic dermatitis. *Br J Dermatol*. 2016;174(1):201-3.
- Van der Schaft J, **Politiek K**, Van den Reek JMPA et al. Drug survival for ciclosporin A in a long-term daily practice cohort of adult patients with atopic dermatitis. *Br J Dermatol*. 2015; 172(6):1621-1627.

List of co-authors and affiliations*

Peter C. van den Akker

University of Groningen, University Medical Centre Groningen, Department of Genetics, Groningen, the Netherlands

Marius J. Angelino

University of Groningen, University Medical Center Groningen, Medical student, Groningen, the Netherlands

Maria C. Bolling

University of Groningen, University Medical Center Groningen, Department of Dermatology, Groningen, the Netherlands

Marjolein S. de Bruin-Weller

Utrecht University, University Medical Center Utrecht, Department of Dermatology & Allergology, Utrecht, the Netherlands

Wietske A. Christoffers

University of Groningen, University Medical Center Groningen, Department of Dermatology, Groningen, the Netherlands

Pieter-Jan Coenraads

University of Groningen, University Medical Center Groningen, Department of Dermatology, Groningen, the Netherlands

Sabrina Z. Commandeur-Jan

University of Groningen, University Medical Centre Groningen, Department of Genetics, Groningen, the Netherlands

Gilles F.H. Diercks

University of Groningen, University Medical Centre Groningen, Department of Pathology, Groningen, the Netherlands

Ewoud van den Hoed

University of Groningen, University Medical Center Groningen, Medical student, Groningen, the Netherlands

Elke M.G.J. de Jong

Radboud University, Radboud University Medical Centre, Department of Dermatology, Nijmegen, The Netherlands

Henny H. Lemmink

University of Groningen, University Medical Centre Groningen, Department of Genetics, Groningen, the Netherlands

Laura Loman

University of Groningen, University Medical Center Groningen, Department of Dermatology, Groningen, the Netherlands

Robert F. Ofenloch

Department of Occupational and Environmental Dermatology, University Hospital Heidelberg, Heidelberg, Germany

Jart A.F. Oosterhaven

University of Groningen, University Medical Center Groningen, Department of Dermatology, Groningen, the Netherlands

Henri H. Pas

University of Groningen, University Medical Center Groningen, Department of Dermatology, Groningen, the Netherlands

Juul M.P.A. van den Reek

Radboud University, Radboud University Medical Centre, Department of Dermatology, Nijmegen, The Netherlands

Jorien van der Schaft

Utrecht University,, University Medical Center Utrecht, Department of Dermatology & Allergology, Utrecht, the Netherlands

Marie L.A Schuttelaar

University of Groningen, University Medical Center Groningen, Department of Dermatology, Groningen, the Netherlands

Karin M. Vermeulen

University of Groningen, University Medical Center Groningen, Department of Epidemiology, Groningen, the Netherlands

Promoveren doe je nooit alleen!

Een high five voor een ieder die hieraan heeft bijgedragen!

Alle fijne mensen die me de afgelopen jaren gemotiveerd, gestimuleerd en vergezeld hebben!

DANK

Voor de medewerking en investering van patiënten aan deze projecten

Voor de goede input en feedback van promotores en mede auteurs,

De altijd geïnteresseerde en behulpzame mede onderzoekers,

TOPPERS van collega's zowel binnen als buiten de werkuren,

Geweldige vrienden waarmee ik geniet van toppen, maar die er ook zijn bij dalen,

Evenals als mijn ontzettend lieve, warme familie & vooral m'n lief Jacob!

Jullie energie en vertrouwen zijn onmisbaar!

"Samen bergen verzetten"

Curriculum vitae

Klaziena Politiek werd geboren op 18 januari 1989 in Sneek. Ze groeide op in Wons en in 2007 behaalde ze haar middelbare school examen op het Bogerman college in Sneek. Aansluitend begon ze met haar studie Geneeskunde aan de Rijks Universiteit Groningen, waar ze in 2013 haar artsexamen behaalde. Haar interesse in dermatologie werd gewekt tijdens haar co-schap in het Antonius Ziekenhuis in Sneek. Dat dermatologie een prachtig vak is werd bevestigd tijdens haar stage wetenschap en semi arts-stage in het Universitar Medisch Centrum Groningen (UMCG). Haar stage wetenschap was een leerzame en succesvolle periode wat leidde tot een vervolg als onderzoeksarts bij dr. M.L.A. Schuttelaar. In eerste instantie met de focus op systemische behandelingen bij constitutioneel eczeem en vervolgens handeczeem.

In juli 2014 startte zij met de opleiding Dermatologie, gecombineerd met onderzoek naar pathogenese, behandeling en impact van handeczeem. Het promotieonderzoek deed zij onder begeleiding van haar promotor dr. M.L.A. Schuttelaar (afdeling Dermatologie UMCG) en Prof dr. P.J. Coenraads (afdeling Dermatologie UMCG). Haar opleiding rondde zij af in december 2019. Per 1 januari 2020 werkt zij als dermatoloog in het Medisch Centrum Leeuwarden.

Zij woont samen met Jacob Visser in Groningen.

Research Institute SHARE

This thesis is published within the **Research Institute SHARE** (Science in Healthy Ageing and healthcaRE) of the University Medical Center Groningen / University of Groningen.

Further information regarding the institute and its research can be obtained from our internet site: <http://www.share.umcg.nl/>

More recent theses can be found in the list below.
(supervisors are between brackets)

2020

Renting N

Clinical workplace learning today; how competency frameworks inform clinical workplace learning (and how they do not)

(prof ROB Gans, prof ADC Jaarsma, prof JCC Borlefs)

Kramer T

How to develop a Grand Slam winner...; physical and psychological skills in Dutch junior tennis players

(dr MT Elferink-Gemser, prof C Visscher, dr BCH Huijgen)

Raven D

Where's the need? The use of specialist mental health services in adolescence and young adulthood

(prof AJ Oldehinkel, prof RA Schoevers, dr F Jörg)

Stoter IK

Staying on track; the road to elite performance in 1500 m speed skating

(dr MT Elferink-Gemser, prof C Visscher, prof FJ Hettinga)

Silva Lagos LA

Gestational diabetes mellitus and fetoplacental vasculature alterations; exploring the role of adenosine kinase in endothelial (dys)function

(dr MM Faas, prof T Plösch, prof P de Vos, prof L Sobrevia)

Reints R

On the design and evaluation of adjustable footwear for the prevention of diabetic foot ulcers

(prof ir GJ Verkerke, prof K Postema, dr JM Hijmans)

Bekhuis E

A body-mind map; epidemiological and clinical aspects of the relation between somatic, depressive and anxiety symptomatology

(prof JGM Rosmalen, prof RA Schroevers, dr L Boschloo)

Havinga PJ

Breaking the cycle? Intergenerational transmission of depression/anxiety and opportunities for intervention

(prof RA Schoevers, prof CA Hartman, dr L Boschloo)

Geer SJ van der

Trismus in head and neck cancer patients

(prof PU Dijkstra, prof JLN Rodenburg, dr H Reintsema)

Salavati N

Preconception environmental factors and placental morphometry in relation to pregnancy outcome

(prof JJHM Erwich, prof RM van der Beek, dr MK Bakker, dr SJ Gordijn)

Fels IMJ van der

Movement, cognition and underlying brain functioning in children

(dr E Hartman, prof C Visscher, prof RJ Bosker, dr J Smith)

Braaksma P

Moving matters for children with developmental coordination

(prof R Dekker, prof CK van der Sluis, dr MM Schoemaker, dr I Stuive)

Akkerman M

Functioning beyond pediatric burns

(prof LHV van der Woude, dr LJ Mouton, dr MK Nieuwenhuis)

Buurke TJW

Adaptive control of dynamic balance in human walking

(dr CJC Lamoth, prof LHV van der Woude, dr AR den Otter)

Bos GJFJ

Physical activity and physical fitness in children with chronic conditions

(prof PU Dijkstra, prof JHB Geertzen)

Heugten P van

Talent in international business defined: implications and applications for honours education

(prof ADC Jaarsma, dr MVC Wolfensberger, dr M Heijne-Pennninga)

Kranenburg HA

Adverse effects following cervical manual physical therapy techniques

(prof CP van der Schans, dr MA Schmidt, dr GJR Luijckx)

Lameijer CM

Perspectives on outcome following hand and wrist injury in non-osteoporotic patients

(prof CK van der Sluis, prof HJ ten Duis, dr M El Moumni)

2019

Nijholt W

Gaining insight in factors associated with successful ageing: body composition, nutrition, and cognition

(prof CP van der Schans, dr JSM Hobbelen, dr H Jager-Wittenaar)

Schaap FD

Dementia Care Mapping in the care for elderly people with an intellectual disability and dementia

(prof SA Reijneveld, dr EJ Finnema, dr GJ Dijkstra)

For earlier theses visit our website