BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020192
Article Type:	Protocol
Date Submitted by the Author:	24-Oct-2017
Complete List of Authors:	Oosterhaven, Jart; University Medical Center Groningen, Dermatology Schuttelaar, Marie-Louise; University of Groningen/ University Medical Center Groningen, Dermatology
Keywords:	hand eczema, alitretinoin, cyclosporine, Clinical trials < THERAPEUTICS, vesicular

Study protocol: efficacy of oral alitretinoin versus oral cyclosporine A in patients with severe recurrent vesicular hand eczema (ALICsA). A randomized prospective open-label trial with blinded outcome assessment.

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Conflicts of interest: Both authors have received honoraria for services rendered to GlaxoSmithKline, wholly unrelated to this study.

Author contributions: JO and MLS contributed equally to this work. JO and MLS conceived this trial. JO drafted and MLS revised the study protocol and this manuscript. JO and MLS read and approved the final version of the study protocol and this manuscript. MLS is principal investigator of this trial.

Starting date of study (inclusion of first patient): May 29, 2017

Ethical approval: This protocol was reviewed and approved by the Medical Ethical Review Board of the University Medical Center Groningen (reference METc 2015/375).

Funding statement: This research is supported by a grant provided by the Netherlands Organisation for Health Research and Development (ZonMw, project number 848015010).

Key words: hand eczema, vesicular, alitretinoin, cyclosporine, clinical trial

Word count (plain text): 5821

Figure count: 1

Table count: 1

Supplement count: 1

Abstract

Introduction: systemic treatment with alitretinoin is registered for all clinical types of severe chronic hand eczema. However, it is especially effective in the hyperkeratotic subtype, and less effective in non-hyperkeratotic forms. Cyclosporine A (cyclosporine) is prescribed for hand eczema in daily practice as well. It has shown to be especially effective in patients with vesicular hand eczema. The primary objective of this study is to compare efficacy of alitretinoin and cyclosporine in the treatment of severe recurrent vesicular hand eczema.

Methods and analysis: this is an investigator-initiated randomized prospective open-label trial with blinded outcome assessment. Severity assessments and laboratory measurements will be conducted corresponding to daily practice. The study population will consist of 72 adult patients (age 18-75 years) with severe recurrent vesicular hand eczema. Patients are treated with either (group I) alitretinoin 30mg once daily, or (group II) cyclosporine with a starting dose of 5 mg/kg/day and a decrease in dosage after 8 weeks to 3 – 3.5 mg/kg/day. The treatment period is 24 weeks for both drugs. Primary endpoint for efficacy is response to treatment, defined as an improvement of ≥ 2 steps on a Physician Global Assessment, using a validated Photoguide, after 24 weeks of treatment. Secondary endpoints are improvement of: Hand Eczema Severity Index, Quality Of Life in Hand Eczema Questionnaire, and a Patient Global Assessment. Adverse events and time to response will be registered. Furthermore cost-utility, Quality Adjusted Life Years and cost-effectiveness will be assessed with the EQ-5D-5L questionnaire while monitoring costs.

Ethics and dissemination: this study will be conducted according to the principles of the Declaration of Helsinki, in accordance with the Dutch Medical Research Involving Human Subjects Act. The results will be offered for publication in a peer reviewed journal. In a publication all data will be handled anonymously.

Registration details: this study was registered on ClinicalTrials.gov. Identifier: NCT03026946. European Union Clinical Trials Registry (EudraCT) No 2015-003488-12

Protocol version: Clinical Study Protocol Version 3, May 2, 2016.

Strengths and limitations of this study

- This study compares two systemic drugs for severe recurrent vesicular hand eczema head-to-head and aims to answer both a relevant clinical and economical question.
- A strength of the study is that blinded assessment of severity will be performed in order to obtain an objective result for efficacy, despite the open-label design.
- The study is limited by the fact that there will be no follow up after the end of treatment at 24 weeks, meaning that this study will not address the long-term efficacy of both drugs.

INTRODUCTION

Hand eczema is a common condition. It can have far-reaching personal, psychological and occupational consequences that may have a drastic impact on the life of those affected. A point prevalence of 4% and a 1-year-period prevalence up to 10% in the general population in Sweden have been reported.[1] A Danish study in young adults showed an incidence of 8.8 per 1000 person-years, a point prevalence of 7.1% and a 1-year-period prevalence of 14.3%. Women are significantly more often affected than men.[2]

The clinical presentation of severe hand eczema varies widely, ranging from chronic fissured skin to a vesicular eruption or palmar hyperkeratosis. The disease could also be approached etiologically, considering exogenous factors causing allergic contact dermatitis (e.g. nickel, perfumes) and irritant contact dermatitis (e.g. water, soap) in addition to endogenous factors like atopic dermatitis.[3]

There is general consensus concerning the first line treatment of hand eczema in various guidelines. Emollients and topical corticosteroids are considered to be the mainstay of treatment in mild and moderate forms. If these fail, secondary options like phototherapy and systemic treatment are available. However, to date an evidence-based recommendation regarding the treatment of more severe hand eczema cannot be made. Particularly, more head-to-head trials are needed. [4]

Alitretinoin is the only registered systemic treatment option for all clinical types of severe chronic hand eczema. It is currently the most investigated drug in terms of patient numbers in the second line treatment of severe chronic hand eczema. In well-designed, pharmaceutical sponsored trials, 30 mg alitretinoin a day resulted in a clear or almost clear response in 48% of the participants, compared to 17% in placebo. In the hyperkeratotic subtype 54% responded, compared to 12% in the placebo group. In two non-hyperkeratotic subgroups (defined as pompholyx (vesicular) and fingertip in the study) only 33% and 44% of participants reached clearance or almost clearance, compared to 12-30% in the placebo group.[5, 6]

In our clinical experience, supported by a retrospective drug survival study of cyclosporine, cyclosporine has beneficial effects on hand eczema in daily practice. This concerns mainly the vesicular forms in which a response of 68% is estimated.[7] Also other small studies have shown that cyclosporine may have a beneficial effect on hand eczema. In a case study, Reitamo et al reported that 87.5% of the patients with a chronic dermatitis on the hands responded to cyclosporine treatment within a few weeks.[8] In a study by Granlund et al, 41 patients were treated with cyclosporine for chronic hand eczema; 50% of the patients reported a beneficial effect of the

treatment.[9] In a second, open label study, 27 patients treated for 6 weeks with oral cyclosporine 3 mg/kg/day, showed a one-year success rate of 74% for chronic hand eczema.[10] A previous trial comparing alitretinoin to cyclosporine in atopic hand eczema ended prematurely due to the inability to include the total number of participants.[11]

In several European countries cyclosporine is registered for use in patients with atopic dermatitis. Schmitt et al. performed a meta-analysis of controlled and uncontrolled trials of cyclosporine treatment in patients with atopic dermatitis. Fifteen studies including 602 patients were analyzed. All studies reported a decrease in the mean severity of atopic dermatitis with a relative effectiveness of 55% (95% confidence interval 48-62%) after 6 to 8 weeks of cyclosporine treatment.[12]

Although alitretinoin is the only registered systemic treatment for severe chronic hand eczema, this treatment has never been compared to immunomodulating/immunosuppressive systemic drugs that are currently considered to be a third line alternative treatment for this condition.[4] This trial aims to compare alitretinoin to cyclosporine in the treatment of severe chronic recurrent vesicular hand eczema. The study assesses the efficacy of both treatments and will show head-to-head results, which should contribute to uncovering the best treatment strategy for hand eczema.

OBJECTIVES

Primary objective: to compare the efficacy of alitretinoin and cyclosporine in patients with severe recurrent vesicular hand eczema.

Secondary objectives:

- to compare time to response
- to compare health related quality of life
- to compare improvement in severity of hand eczema, as assessed by the patient
- to compare safety
- to compare cost-utility and cost-effectiveness

METHODS AND ANALYSIS

Study design

This study is designed as a randomized prospective open label study. Assessment of disease severity, laboratory measurements and quality of life in this study will be conducted comparable to daily practice assessments. The duration of the study for an individual patient is 24 weeks. Planned inclusion period is two years.

Study population

The study population will exist of adult patients with severe recurrent vesicular hand eczema. Vesicular hand eczema will be diagnosed following the criteria of the Danish Contact Dermatitis Group.[13] The severity of the hand eczema at screening will be graded by means of a Physician Global Assessment using a validated Photoguide.[14] Woman in the fertile age will be required to use proper contraception methods. Men and women of all ethnicities of 18 years and older will be recruited. Patients meeting all inclusion criteria, while not meeting any of the exclusion criteria, will be asked to participate. See Figure 1 for a study flow chart.

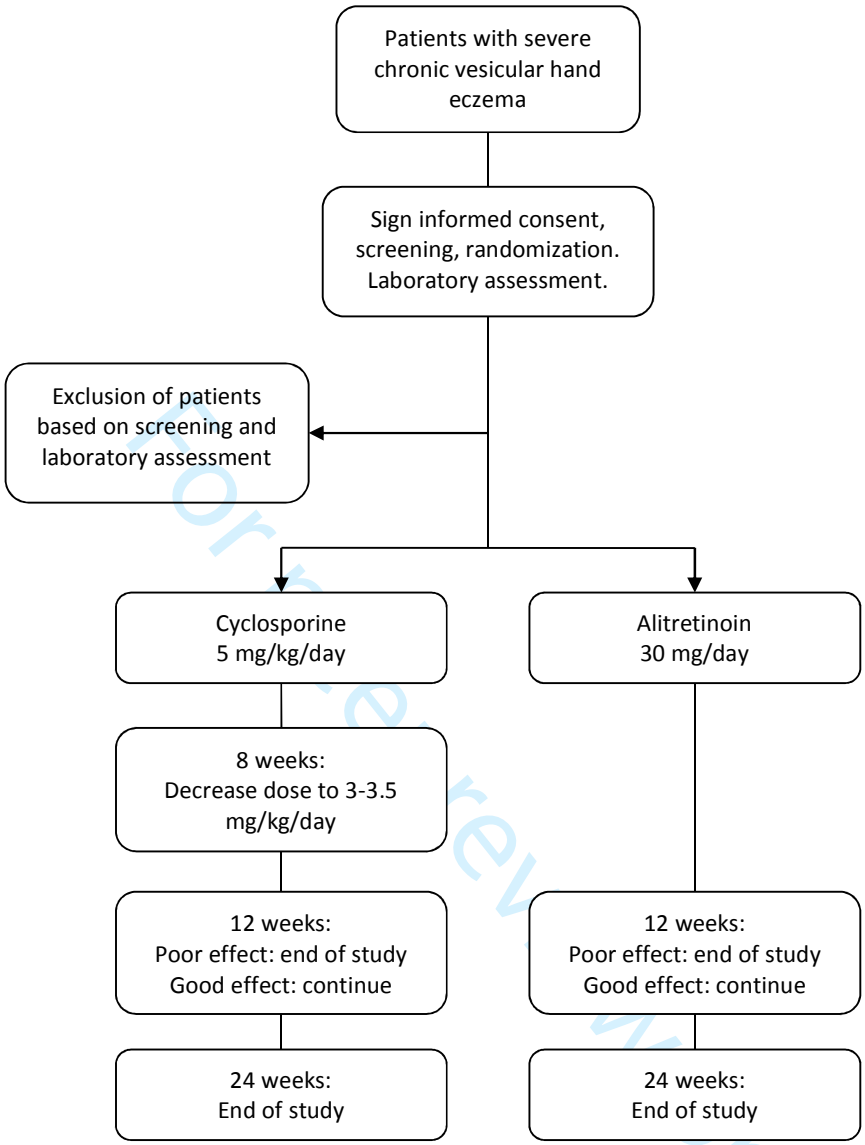

Figure 1 Study flow chart

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age ≥ 18 years and ≤ 75 years
- Severe or very severe recurrent vesicular hand eczema for a minimum duration of 3 months as defined by a Physician Global Assessment (PGA) using a validated Photoguide [14]
- Refractory to standard therapy, defined as:

- Patients received treatment with topical corticosteroids of class II or higher for at least 8 weeks within 3 months before enrolment, with either no response or a transient response
- Patients has also received standard skin care, including emollients and barrier protection as appropriate, without significant improvement
- Patients has avoided irritants and contact allergens, if identified, without significant improvement

- Women of childbearing potential are required to use at least two forms of contraception for at least 1 month before starting treatment, during treatment, and for at least 1 month after finishing treatment; these women are required to take monthly pregnancy tests
- Able to provide written Informed Consent
- Able to speak and read the Dutch language

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

General criteria prior to randomization

- Treated with alitretinoin or cyclosporine in the previous 3 months
- Other morphologic types of hand eczema as defined by the Danish Contact Dermatitis Group[13]
- Patients with predominantly atopic dermatitis, in which the hands are also involved. (Patients with controlled atopic dermatitis, in which the hands are mainly affected, are eligible for inclusion.)
- Psoriasis of the hands
- Active bacterial, fungal, or viral infection of the hands
- Pregnant/lactating or planning to become pregnant during the study period
- Treatment with systemic medication or UV radiation within the previous 4 weeks
- Mentally incompetent
- Immunocompromised status
- Uncontrolled arterial hypertension (minimally 3 measurements). Systolic pressure > 160 mmHg or diastolic pressure > 95 mmHg, despite starting anti-hypertensive medication [15]
- Known or suspected allergy to ingredients in the study medications
- Inclusion in a study of an investigational drug within 60 days prior to start of treatment

- Current malignancy (other than successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and⁄or localized carcinoma in situ of the cervix)
- Current active pancreatitis
- Evidence of alcohol abuse or drug addiction
- Malabsorption
- Currently active gout
- Recurring convulsions / epilepsy
- Living vaccine (including bacillus Calmette-Guérin (BCG), varicella, measles, mumps, rubella, yellow fever, oral polio and oral typhoid) in the last 2 weeks or the planned application of such a vaccine during the study period
- Chronic or recurrent infectious diseases
- Contact sensitizations with clinical relevance to the hands, in which exposure to allergens is not avoided.
- Hypervitaminosis A due to the use of vitamin A supplements containing >2000 IU
- Use of drugs with potential to change the effective dose of study drugs within the previous 2 weeks

Laboratory exclusion criteria post randomization

- Alanine aminotransferase (ALAT) and⁄or aspartate aminotransferase (ASAT) values > 200% of the upper limit of normal
- Impaired renal function as indicated by a clinically relevant abnormal creatinine value (to be determined by investigator or treating physician)
- Anemia as indicated by a clinically relevant lowered hemoglobin value (to be determined by investigator or treating physician)

Alitretinoin specific

- Triglycerides > 200% of the upper limit of normal,
- Cholesterol or low density lipoprotein (LDL) cholesterol values > 200% of the upper limit of normal
- Uncontrolled hypothyroidism (to be determined by investigator or treating physician)

Cyclosporine specific:

- Impaired renal function as indicated by a clinically relevant abnormal creatinine value (to be determined by investigator or treating physician)
- Uremia

- Hyperkalemia
- Hyperuricemia in patients with a medical history of gout

Recruitment and consent

Recruitment takes place at a university center Dermatology department, during specialized eczema consulting hours every week. Several Dermatology departments in general hospitals are provided with the study protocol and asked to refer eligible patients. All referred patients (by general practitioner or dermatologist) will visit the department several times for diagnostics (patch testing) and initial therapy. Only when these patients prove refractory to standard therapy and avoidance of irritants and allergens does not give significant improvement, they will be approached at the outpatient clinic to participate in the study. Patients will be extensively informed about the trial.

It is the responsibility of the investigator, or a person designated by the investigator, to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives and potential hazards of the study. It will also be explained to patients that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason. Patients will be given a period of one week to consider participation before they are asked to sign the informed consent form.

Treatment of subjects

Interventions

Group I will receive an oral *alitretinoin* capsule of 30mg once daily for a total of 24 weeks. In a dose-finding study, the effectiveness and tolerability of this dose was established and it is recommended to use this as the standard dose for the prescription of alitretinoin in hand eczema.[5, 6, 16]

Group II will receive oral *cyclosporine* tablets twice daily in a dose of 5mg/kg/day (split in 2 doses) and decrease this dose after 8 weeks to 3 - 3.5 mg/kg/day (split in 2 doses).[17]

Dosage reduction is allowed in both groups in case of abnormal findings on physical examination, laboratory markers, and/or adverse events. For alitretinoin, dose can be reduced from 30 mg/day to 10 mg/day, in accordance with the Summary of Product Characteristics (SPC) text.[16] For cyclosporine, in case of increased creatinine levels > 30% of baseline, laboratory measurement should be repeated after two weeks. If creatinine levels are still increased at least > 30%, dosage will

be reduced with the recommended 30-50%.[15] Developing hypertension should be re-evaluated with at least 3 measurements (if necessary by the general practitioner). If repeated values of a systolic pressure > 160 mmHg or diastolic pressure > 105 mmHg are found, the general practitioner will be requested to start an antihypertensive drug (preferably calcium channel blockers). [15, 18]

Preparation and labelling of the study drugs will be carried out according to usual practice by the community pharmacy, honouring Good Manufacturing Practice guidelines. Medication will be dispensed and used in the same way as in routine clinical practice, according to (among other regulations) their marketing authorisations.

Use of concomitant medication

All patients will be given an emollient cream with instructions to apply it frequently (advice: minimum 2 times a day). One week before the first intake of study drugs, concomitant treatment with a topical class II corticosteroid at maximum is permitted when needed, with a maximum application of one finger-tip-unit (FTU) for each hand daily.[19] This also applies for concomitant topical corticosteroid therapy during the study period. Higher class topical corticosteroids are not allowed as maintenance therapy.

Generally prohibited concomitant treatments during therapy comprise: systemic corticosteroids, other retinoids, any other systemic or topical anti-eczema therapy, phototherapy, immunosuppressive or cytostatic drugs.

Alitretinoin specific prohibited concomitant treatment: vitamin A supplements, tetracyclines and azole antimycotics. St John's wort should not be taken because of a possible interaction with hormonal anti-conceptive drugs. This could possibly result in a pregnancy, which is absolutely contraindicated because of the teratogenic nature of alitretinoin.[16]

Cyclosporine specific prohibited concomitant treatment: medicines that are substrates for the multidrug efflux transporter P-glycoprotein or the organic anion transporter proteins (OATP). This could result in elevated plasma concentrations which are associated with serious and/or life-threatening events, e.g. bosentan, dabigatranetexilate and aliskiren.

Inductors of CYP3A4 and/or P-glycoprotein will probably lead to a decrease of cyclosporine plasma concentrations. Examples of these are: barbiturates, carbamazepine, oxcarbazepine, fenytoine, nafcilline, intravenous sulfadimine, probucol, orlistat, St John's wort (Hypericum perforatum),

ticlopidine, sulfinpyrazon, terbinafine, bosentan. Rifampicine induces metabolism of cyclosporine in the intestines and liver. Octreotide decreases oral absorption of cyclosporine.

Inhibitors of CYP3A4 and/or P-glycoprotein can increase cyclosporine plasma concentrations. Examples of these are: nicardipine, metoclopramide, methylprednisolon (high doses), allopurinol, cholic acid and derivatives, proteaseinhibitors, imatinib, colchicine, nefazodon.

Other drugs that increase cyclosporin plasma concentration are: macrolide antibiotics, azole antimycotics, verapamil, telaprevir, amiodarone, danazol, diltiazem, and lercanidipine. Furthermore, grapefruit and grapefruit juice can have an increasing effect on cyclosporine plasma concentration.

Also prohibited are drugs which result in an increased risk for nephrotoxicity when combined with cyclosporine, such as: aminoglycosides (including gentamycin, tobramycin), amphotericin B, ciprofloxacin, vancomycin, trimethoprim (+ sulfamethoxazole); fibric acid derivatives (e.g. bezafibrate, fenofibrate); NSAIDs (including diclofenac, naproxen, sulindac); melphalan, histamine H2-receptor antagonists (e.g. cimetidine, ranitidine), methotrexate.

The dosage of statins needs to be decreased when treatment with cyclosporine is started, because of a possible increase in plasma concentration of statins.[17]

Escape medication

In case of an exacerbation or postponed treatment effect, patients are allowed to receive a maximum of 3 courses of rescue medication: mometasone furoate once daily for 1 week, with a maximum application of one FTU for each hand daily.[19]

Outcome measures

Primary outcome measure

Severity of hand eczema

The PGA, based on a validated Photoguide developed by Coenraads et al, covers 5 degrees of severity (clear, almost clear, moderate, severe, very severe) and takes into account the intensity of clinical signs and percentage of hand surface involved.[14] Response to treatment is defined as an improvement of ≥ 2 steps on the PGA. Very severe hand eczema is defined as responding to

treatment if a status of at least 'moderate' is achieved. Severe hand eczema is defined as responding to treatment if a status of at least 'almost clear' is achieved.

In this study the main endpoint is the between-group difference in response to treatment between baseline and 24 weeks of treatment.

Secondary outcome measures

Severity of hand eczema

- Between-group difference in response to treatment between baseline and 12 weeks of treatment.
- Between-group difference in mean change between baseline and week 4, 8, 12 and 24, assessed by the Hand Eczema Severity Index (HECSI) score.[20] The HECSI is an objective severity assessment based on clinical symptoms only. It includes erythema, fissures, vesicles, scaling, oedema, papules and measurement of the affected area. The score ranges from 0-360, with a score > 28 indicating severe hand eczema.
- Between-group difference in time to response (time to first PGA improvement of ≥ 2 steps). This is only measured at control visits so possible outcome is limited to 4, 8, 12 and 24 weeks. This will be corrected using statistical methods (see statistical paragraph).

Patient reported outcome measures (PROMs):

Quality of life

- Between-group mean change in quality of life between baseline and 12 and 24 weeks, assessed by the Quality Of Life in Hand Eczema Questionnaire (QOLHEQ). The QOLHEQ is a multi-domain disease specific instrument for hand eczema assessing impairments in quality of life. The score ranges from 0-120, with 120 indicating worst quality of life.[21, 22]

Patient reported improvement

- Between-group difference in patients reporting improvement as 'clear or almost clear' compared to baseline at week 12 and 24, assessed by Patient Global Assessment (PaGA). The PaGA takes signs and symptoms into account. It covers 6 degrees of improvement: 'clear or almost clear' (at least 90% clearing of disease signs and symptoms compared to baseline), 'marked improvement' (at least 75% clearing), 'moderate improvement' (at least 50% clearing), 'mild improvement' (at least 25% clearing), 'no change', or 'worsening'.[6]

Safety and tolerability

- Adverse events in both groups will be registered.

Cost-utility and cost-effectiveness

- Between-group difference in mean Quality Adjusted Life Years (QALYs) will be measured by the EQ-5D-5L score at baseline, week 12 and week 24. The EQ-5D-5L is a measure for Health Related Quality of Life (HRQoL) and utility values. The EQ-5D-5L questionnaire includes a descriptive system, which comprises 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Moreover, it includes a visual analog scale (VAS), which records the respondent's self-rated health status on a graduated (0–100) scale.[23]
- Direct medical costs will be determined using standardized prices for consultation, treatment (medication; alitretinoin or cyclosporine, topical treatment with corticosteroids and emollients, if necessary oral or topical treatment with antibiotics), diagnostic tests, laboratory measurements, visits to the general practitioner for hand eczema and hospital admissions (inpatient and/or daycare). Included patients will be asked to keep track of how much they spend on over-the-counter medication and other products for their hand eczema (out-of-pocket costs). Direct non-medical costs, consisting of travel costs, will be determined using average travel costs to the hospital as determined by relevant Dutch guidelines on cost-studies in healthcare.[24, 25]
- Indirect costs, consisting mainly of productivity loss, will be also be calculated using tables from the guidelines with average income of Dutch workers stratified by age and gender, corrected for shift working / irregular working hours.[24]

Other study parameters

These comprise the following parameters: age, sex, body-mass-index, current and/or previous atopic dermatitis (both defined by U.K. Working Party criteria)[26], age of onset of atopic dermatitis, age of onset of hand eczema, work/activities (based on risk professions as named in the European Guideline on hand eczema)[4], current use of statins, current use of thyromimetics, currently smoking and amount of pack-years will be registered. Pack years are calculated by multiplying the total years smoked with the average packs per day smoked over these years.[27] For this, the online Smoking Pack Years Calculator, created by dr NJ Masters and C Tutt, will be used.[28]

Study procedures and overview

Procedures part of standard medical treatment

According to daily practice, a detailed patient history is obtained of all newly referred patients with hand eczema and they are planned for patch testing to exclude contact allergy. During this first period, patients are treated with topical corticosteroids and emollients. A structured education program by a nurse on provoking factors and treatment is provided. If a relevant contact allergy is ruled out and the hand eczema proves to be refractory to topical therapy and/or UV therapy, the next step is systemic therapy. These patients are a candidate for the current study.

Laboratory analysis is performed to verify contra-indications for alitretinoin or cyclosporine. During therapy, standard monitoring of blood values is carried out, according to SPC texts and current guidelines. At every visit, the PGA for severity is determined and the hand eczema is scored using the HECSI, corresponding to daily practice. Furthermore, health related quality of life is scored with a Dutch version of the QOLHEQ at the start of therapy, at week 12 and week 24.

Standard laboratory tests to be performed include:
Alitretinoin: at week 0, 4, 8, 12 and 24, laboratory tests are carried out, including: full blood count, ASAT, ALAT, ALP, γ-GT, serum creatinine, cholesterol, triglycerides, HDL, TSH, T4, glucose and TARC. Also, a urine pregnancy test will be carried out.
Cyclosporine: at week 0, 4, and 12 laboratory tests are carried out, including: full blood count, potassium, magnesium, ASAT, ALAT, ALP, γ-GT, bilirubin, LDH, albumin, serum creatinine, uric acid, cholesterol, triglycerides and TARC.
At week 4 and 12, cyclosporine trough levels will be determined.
At week 8 and 24, serum creatinine and TARC will be determined.

Procedures extra for this study

Patients will be given one week to consider participation. Due to this, a maximum of one extra visit is needed to randomize the patient and obtain baseline data. The PaGA one-item questionnaire will be obtained at week 12 and 24. This procedure is only extra in terms of obtaining a quantitative assessment of the qualitative report that a patient provides in daily practice.

Patients will be asked to keep track of out-of-pocket costs on products for their hand eczema. During each visit, patients will be asked for direct and indirect medical and non-medical costs. Furthermore, the EQ-5D-5L questionnaire is obtained at week 0, 12 and 24, which is extra compared to daily practice.

No diagnostic procedures or other treatments will be postponed for patients participating in this study.

In Table 1, a systematic overview of the study is presented.

Table 1. Study schedule

Visit	V-1 Screening	V0 Baseline	V1	V2	V3	V4
Week	**-1**	**0**	**4**	**8**	**12**	**24**
Screening/baseline						
Check for clinical eligibility (inclusion/exclusion)	x					
Sign informed consent	x					
Randomization		x				
Baseline data / demographics / medical history / baseline costs		x				
Laboratory exclusion criteria post randomization		x				
Start medication		x				
Treatment						
Escape medication assessment			x	x	x	x
If applicable: dosage alteration assessment			x	x	x	x
Efficacy						
Severity scoring PGA / HECSI		x	x	x	x	x
Quality of life questionnaire QOLHEQ		x			x	x
PaGA of improvement					x	x
Costs						
Cost assessment		x	x	x	x	x
Cost-utility questionnaire EQ-5D-5L		x			x	x
Safety						
Lab control		x	x	x	x	x
Concomitant medication		x	x	x	x	x
Adverse events			x	x	x	x
Blood pressure measurement (cyclosporine only)		x	x	x	x	x
If applicable: premature withdrawal assessment		x	x	x	x	x

HECSI, Hand Eczema Severity Index; PaGA, Patient Global Assessment; PGA, Physician Global Assessment; QOLHEQ, Quality Of Life in Hand Eczema Questionnaire

Patients are permitted to deviate from the schedule with a maximum of 7 days during week 0-8. From week 9 a maximum deviation of 14 days is permitted.

Safety

Alitretinoin

Main risks in the alitretinoin group are[16]:

- Teratogenicity of the study drugs
- Occurrence of allergic / anaphylactic reactions
- Depression with anxiety, mood changes and suicidal tendencies
- Sunburn
- Xerostomia, xerosis cutis
- Keratoconjunctivitis sicca, keratitis, blurred (night) vision, cataract. Care must be taken when driving a vehicle or when operating machines.
- Myalgia, arthralgia, increase of CK values
- Exostosis, ankylosing spondylitis
- Headache
- Blushing
- Increase of cholesterol and triglycerides, with ultimately pancreatitis
- Decrease of TSH and T4
- Increased liver transaminases
- Decrease in effective dose of simvastatin
- Change at scarring or dermatitis during therapy and 6 months after in case of aggressive dermabrasion or epilation
- Anemia
- Epistaxis
- Alopecia
- Benign intracranial hypertension (rare and most seen in combination with tetracyclines)
- Inflammatory bowel disease (rare)
- Vasculitis (rare)

Alitretinoin is a derivative of vitamin A. Alitretinoin has been administered in oncological clinical studies at dosages of more than 10-times of the therapeutic dosage given for chronic hand eczema. The adverse effects observed were consistent with retinoid toxicity, and included severe headache, diarrhea, facial flushing, hypertriglyceridemia. These effects were reversible.

It can be concluded that the (reversible) effects can be properly managed.

Cyclosporine

Main risks in the cyclosporine group are[17]:

- Renal toxicity
- Hepatotoxicity
- Hypertension, flushing
- Nausea/vomiting, abdominal discomfort
- Headache
- Diarrhea
- Anemia, thrombocytopenia
- Leucopenia
- Hyperlipidemia
- Hyperkalemia, hypomagnesemia, hyperuricemia, hyperglycemia
- Tremor, convulsions, paresthesia
- Hirsutism/hypertrichosis
- Acne
- Myalgia
- Muscle cramps
- Tiredness
- Gynecomastia
- Occurrence of allergic / anaphylactic reactions
- Pre-existing infections may also be aggravated and reactivation of polyomavirus infections may lead to polyomavirus-associated nephropathy or to JC virus associated progressive multifocal leukopathy. Serious and/or fatal outcomes have been reported.
- Increase risk of lymphomas and other malignancies (mainly when combining multiple immunosuppressive drugs)
- Increase risk of infections
- Decreased effect of live vaccinations

Experience with acute overdosage of cyclosporine is limited. Oral doses of cyclosporine of up to 10 g (about 150 mg/kg) have been tolerated with relatively minor clinical consequences, such as vomiting, drowsiness, headache, tachycardia and in a few patients moderately severe, reversible impairment

of renal function. However, serious symptoms of intoxication have been reported following accidental parenteral overdosage with cyclosporine in premature neonates.

In all cases of overdosage, general supportive measures should be followed and symptomatic treatment applied. Forced emesis and gastric lavage may be of value within the first few hours after oral intake. Cyclosporine is not dialysable to any great extent, nor is it well cleared by charcoal hemoperfusion.

It can be concluded that the (reversible) effects can be properly managed.

Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for medical reasons. Specific criteria for withdrawal are:

- Evidence of pregnancy
- Occurrence of serious adverse events
- Lack of efficacy at 12 weeks, defined as no improvement assessed by the PGA (at least 1 step improvement is necessary to continue treatment after 12 weeks)
- Use of prohibited concomitant therapy, or a need for their use
- The need for more than 3 courses of rescue medication
- Anaphylactic reaction or other severe systemic reaction to study drug intake
- Diagnosis of malignancy during study, excluding non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix
- Any infection that is opportunistic and other infections whose nature or course may suggest an immunocompromised status
- Administration of a living vaccine
- Developing hypertension (minimally 3 measurements). Systolic pressure > 160 mmHg or diastolic pressure > 95 mmHg, despite starting anti-hypertensive medication.[15]
- Severe laboratory abnormalities including:
    - ALAT and/or ASAT values > 300% of the upper limit of normal
    - Triglycerides > 9 mmol/l
    - Creatinine increase of > 30%, despite dose reduction
- Intercurrent severe illness or major surgery
- Protocol violations or if the requirements of the protocol are not respected

- Patient lost to follow up

Serious adverse events and suspected unexpected serious adverse reactions

A serious adverse event (SAE) is any untoward medical occurrence or effect at any dose that:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;

Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

Unexpected adverse reactions are suspected unexpected serious adverse reactions (SUSARs) if the following three conditions are met:

1. the event must be serious (see SAE);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in the SPC texts.

Randomization, blinding and treatment allocation

Randomization is carried out by a computer program. This is a study with blinded efficacy assessors, which are unaware of treatment allocation. The participants and treating physician will be aware of treatment allocation. Efficacy assessment will be carried out by physicians or specialized eczema nurses who are experienced in assessing hand eczema by PGA and HECSI in daily practice. Blinding will be broken after analyzing the data.

Statistical analyses

Hypothesis and sample size calculation

This trial is designed to demonstrate a superior response to cyclosporine compared to alitretinoin in the treatment of severe recurrent vesicular hand eczema. Response to treatment is defined as an improvement of ≥ 2 steps on the PGA, based on a validated Photoguide developed by Coenraads et al [14] at 24 weeks of treatment. A sample size of 31 in each group will have 80% power to be able to reject the null hypothesis of no difference between alitretinoin and cyclosporine, using a χ^2 test with a two-sided 0.05 significance level. In this calculation we use the following assumptions: randomization ratio is 1:1, and we expect the percentage of responders in the alitretinoin group to be 33%.[6] From a retrospective study and other case studies we estimate 68% responders in the cyclosporine group.[7] We anticipate a drop-out of maximally 15% of randomized patients; a small percentage prior to first application of study drugs due to excluding laboratory measurements and a larger percentage during follow up, mainly due to subjective side effects. We therefore plan to include 72 patients in total, 36 in the alitretinoin group and 36 in the cyclosporine group.

Calculated with the sample size calculator of the Department of Statistics, University of British Columbia, Canada, available at http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html.

Primary analysis

Severity of hand eczema

Between-group difference in response to treatment between baseline and 24 weeks of treatment. For comparison of proportions in the alitretinoin and cyclosporine group a χ^2 test, or Fisher's exact test if appropriate, will be used.

Secondary analyses

Severity of hand eczema

- Between-group difference in response to treatment between baseline and 12 weeks of treatment. For comparison of proportions in the alitretinoin and cyclosporine group a χ^2 test will be used.

- Between-group difference in mean change between baseline and week 4, 8, 12 and 24, assessed by the HECSI score. This will be reported graphically. For comparison of mean change between the alitretinoin and cyclosporine group at week 12 and 24, the Student's t-test or Mann-Whitney U-test will be used, depending on distribution of data.

- Between-group difference in time to response (time to first PGA improvement of ≥ 2 steps compared to baseline). Because this outcome measure is interval-censored, the cumulative incidence of 'response' will be analyzed using of actuarial life table analysis and weighted log-rank tests for interval censored data; in particular the group proportional hazards model[29] and a generalized Wilcoxon-Mann-Whitney test[30], which emphasizes early events. The exact permutation value for the scores of the group proportional hazards model will be calculated, along with Wilcoxon-Mann-Whitney tests and the non-parametric maximum likelihood estimate of the survival distribution function.[31]

Patient reported outcome measures (PROMs):

Quality of life

- Between-group mean change in quality of life between baseline and 12 and 24 weeks, assessed by the QOLHEQ. Clinically relevant improvement is defined as an absolute improvement of 15 points (theoretically corresponding to an improvement of ≥ 1 point on 50% of the questions) compared to baseline. For comparison of proportions of patients rated as having clinically relevant improvement in the alitretinoin and cyclosporine group, a χ^2 test will be used.

Patient reported improvement

- Between-group difference in patients reporting improvement as 'clear or almost clear' at week 12 and 24, assessed PaGA. For comparison of proportions of patients rated as 'clear or almost clear' in the alitretinoin and cyclosporine group, a χ^2 test will be used.

Safety and tolerability

- Adverse events in both groups will be registered.

Cost-utility and cost-effectiveness

- For both groups (alitretinoin and cyclosporine), the mean EQ-5D scores overall and of each dimension will be reported. Results from the descriptive system of the EQ-5D-5L will be converted to a utility index value, a population based (social) value specific for the

Netherlands. With this value, Dutch utility values will be calculated in order to determine the QALYs over the study period. Mean values of the EQ-VAS will be reported with a 95% confidence interval. For comparison of means, the Student's t-test or Mann-Whitney U-test will be used, depending on distribution of data.

- The incremental cost-effectiveness ratio (ICER) will be calculated and reported as €/QALY.
- A regression model will be used to estimate the association between QALYs and the PGA.

Handling of missing data

All analyses will be based on the intention-to-treat principle to guard against attrition bias. Subjects might not only want to withdraw because the study drug works insufficient, they might also want to withdraw when their hand eczema is cured.

Missing values will be handled in a way that is dependent on assumptions about the missing data. If the extent and pattern of missing data is known (e.g. missing at random (MAR), missing completely at random (MCAR), missing not at random (MNAR)), an analysis will be chosen that is valid under a plausible assumption about the missing data (probably mixed models). This is according to a strategy proposed by White et al.[32]

Data handling

Data will be handled confidentially. Data derived from the questionnaires and other paper source documents will be coded using sequential administration numbers. A subject identification code list is used to link the data to the subjects. The code is not based on the patient initials and birth-date. The code will be safeguarded by the principal investigator, dr. M.L.A. Schuttelaar. The documents will be stored in a locked room. The digital source data will be saved in subsections of the subjects medical file. These data will be accessible to the principal investigator and the investigator, and also to other treating physicians. Data will not be accessed by the blinded efficacy assessors. All data will be recorded in electronic Case Report Forms (eCRFs) in Utopia (software for Electronic Data Capture) developed by the Trial Coordination Center, linked to the University Medical Center Groningen. The eCRFs will only be accessible with the username and password of the responsible investigator.

Data will be saved for 15 years after completion of this study.

All the data will be saved in accordance with the Dutch Personal Data Protection Act.

Monitoring

A certified monitor will carry out monitoring of this study. The monitor will get read-only access to the digital and paper documents of participants. Goal of this monitoring is to review if:

- the rights and wellbeing of subjects are being protected
- the reported data is right and fully reproducible
- the execution of the study is in accordance with this protocol and relevant legal requirements.

Data Safety Monitoring Board

No Data Safety Monitoring Board (DSMB) is established, since this study will be conducted corresponding to daily practice. In case of life-threatening diseases usually the implementation of a DSMB is indicated from an ethical point of view. But hand eczema is a non-critical indication. Frequent laboratory assessments will reduce the possibility of serious adverse events to a minimum. The patient population in this clinical trial exists of legal competent adults and the study drugs alitretinoin and cyclosporine are well-investigated, well-characterized drugs.

ETHICS AND DISSEMINATION

Ethics

This study will be conducted according to the principles of the Declaration of Helsinki (Seventh revision, Fortaleza, Brazil, October 2013), in accordance with the Medical Research Involving Human Subjects Act (WMO), and also in accordance with the International Conference on Harmonisation Good Clinical Practice Guidelines (ICH-GCP).

In this trial both groups are treated with a drug, known to be beneficial to hand eczema in a considerable amount of patients. So the intended benefit of both study drugs is to reduce the severity of hand eczema.

We hypothesize that cyclosporine has a superior efficacy compared to alitretinoin in severe chronic recurrent vesicular hand eczema. If this hypothesis is confirmed, there could be a practical, as well as a financial implication. Practically, more responding patients to cyclosporine leads to a greater beneficial effect on hand eczema in this patient group. Financially, cyclosporine is a lot less expensive than alitretinoin. If cyclosporine shows superior efficacy in severe recurrent hand eczema, this could lead to an official registration. This, in turn, could mean a decrease in financial burden for the treatment of severe recurrent vesicular hand eczema patients in the population.

We deem the overall risks for patients participating in this study to be acceptable because of the tight inclusion and exclusion criteria (ensuring a relatively healthy study population), combined with regular laboratory assessments to enhance safety monitoring. Furthermore, prior experience with both study drugs in daily practice has improved our capability to manage risks. The remaining risk is therefore small and does not differ from regular daily practice.

Dissemination

The study is designed honouring the Centrale Commissie Mensgebonden Onderzoek (CCMO) statement on publication policy. The results will be made public unreservedly; they will be offered for publication in a peer reviewed journal. In a publication all data will be handled anonymously.

Acknowledgements

The authors would like to thank K.M. Vermeulen for her valuable contributions to the health economics component of this protocol.

References

1 Thyssen JP, Johansen JD, Linneberg A, et al. The epidemiology of hand eczema in the general population--prevalence and main findings, *Contact Dermatitis* 2010;62:75-87.

2 Mortz CG, Bindslev-Jensen C, Andersen KE. Hand eczema in The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS): prevalence, incidence and risk factors from adolescence to adulthood, *Br J Dermatol* 2014;171:313-23.

3 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.

4 Diepgen TL, Andersen KE, Chosidow O, et al. Guidelines for diagnosis, prevention and treatment of hand eczema, *J Dtsch Dermatol Ges* 2015;13:e1-22.

5 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;140:1453-9.

6 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, *Br J Dermatol* 2008;158:808-17.

7 Christoffers WA, Politiek K, Coenraads PJ, et al. Drug survival of cyclosporine in the treatment of hand eczema: a multicentre, daily use study, *J Eur Acad Dermatol Venereol* 2016;30:63-6.

8 Reitamo S, Granlund H. Cyclosporin A in the treatment of chronic dermatitis of the hands, *Br J Dermatol* 1994;130:75-8.

9 Granlund H, Erkko P, Eriksson E, et al. Comparison of cyclosporine and topical betamethasone-17,21-dipropionate in the treatment of severe chronic hand eczema, *Acta Derm Venereol* 1996;76:371-6.

10 Granlund H, Erkko P, Reitamo S. Long-term follow-up of eczema patients treated with cyclosporine, *Acta Derm Venereol* 1998;78:40-3.

11 Schmitt J. Ciclosporin versus alitretinoin for severe atopic hand dermatitis (TocyDD). Last updated 2014; Available at: clinicaltrials.gov/show/NCT01231854. Last accessed 2017.

12 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;21:606-19.

13 Menné T, Johansen JD, Sommerlund M, et al. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema, *Contact Dermatitis* 2011;65:3-12.

14 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;152:296-301.

15 Nederlandse Vereniging voor Dermatologie en Venereologie. Richtlijn Constitutioneel eczeem 2006, Updated 2007.

16 Anonymous. SPC text alitretinoin. Last updated 2015; Available at: http://db.cbg-meb.nl/IB-teksten/h100957.pdf. Last accessed 2017.

17 Anonymous. SPC text cyclosporine. Last updated 2015; Available at: http://www.medicines.org.uk/emc/medicine/1307. Last accessed 2017.

18 Cai J, Huang Z, Yang G, et al. Comparing antihypertensive effect and plasma ciclosporin concentration between amlodipine and valsartan regimens in hypertensive renal transplant patients receiving ciclosporin therapy, *Am J Cardiovasc Drugs* 2011;11:401-9.

19 Long CC, Finlay AY. The finger-tip unit--a new practical measure, *Clin Exp Dermatol* 1991;16:444-7.

20 Held E, Skoet R, Johansen JD, et al. The hand eczema severity index (HECSI): a scoring system for clinical assessment of hand eczema. A study of inter- and intraobserver reliability, *Br J Dermatol* 2005;152:302-7.

21 Ofenloch RF, Weisshaar E, Dumke AK, et al. 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;171:304-12.

22 Ofenloch RF, Oosterhaven JAF, Susitaival P, et al. Cross-Cultural Validation of the Quality of Life in Hand Eczema Questionnaire (QOLHEQ), *J Invest Dermatol* 2017;137:1454-60.

23 Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L), *Qual Life Res* 2011;20:1727-36.

24 Hakkaart-van Roijen L, Tan S, Bouwmans C. Handleiding voor kostenonderzoek, methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. College voor zorgverzekeringen. Geactualiseerde versie 2010.

25 Politiek K, Oosterhaven JA, Vermeulen KM, et al. Systematic review of cost-of-illness studies in hand eczema, *Contact Dermatitis* 2016;75:67-76.

26 Williams HC, Burney PG, Pembroke AC, et al. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation, *Br J Dermatol* 1994;131:406-16.

27 Weintraub WS, Klein LW, Seelaus PA, et al. Importance of total life consumption of cigarettes as a risk factor for coronary artery disease, *Am J Cardiol* 1985;55:669-72.

28 Masters N, Tutt C. Smoking Pack Years Calculator. 2017; Available at: http://www.smokingpackyears.com. Last accessed 2017.

29 Finkelstein DM. A proportional hazards model for interval-censored failure time data, *Biometrics* 1986;42:845-54.

30 Fay MP. Rank invariant tests for interval censored data under the grouped continuous model, *Biometrics* 1996;52:811-22.

31 Fay MP. Interval: weighted logrank tests and NPMLE for interval censored data. R package version 0.1–1.1. 2014; Available at: https://cran.r-project.org/web/packages/interval/index.html. Last accessed 2017.

32 White IR, Horton NJ, Carpenter J, et al. Strategy for intention to treat analysis in randomised trials with missing outcome data, *BMJ* 2011;342:d40.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	Detailed within full protocol
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Not applicable
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not applicable

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5, 22
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	20-21
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Detailed within full protocol
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12-13
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	15-17 and Fig. 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	22
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	21
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	21, further detailed in protocol
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	21, further detailed in protocol
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	21, further detailed in protocol
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	21, further detailed in protocol
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Detailed within full protocol

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	24-25
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	22-24
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	22-24
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	24
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	25
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Detailed within full protocol
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Detailed within full protocol
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	1
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Detailed within full protocol

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	24-25, further detailed in protocol
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Detailed within full protocol
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Detailed within full protocol
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	26
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not detailed
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Detailed within full protocol
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	With Ethical Board application
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Study protocol: efficacy of oral alitretinoin versus oral cyclosporine A in patients with severe recurrent vesicular hand eczema (ALICsA). A randomized prospective open-label trial with blinded outcome assessment.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020192.R1
Article Type:	Protocol
Date Submitted by the Author:	01-Feb-2018
Complete List of Authors:	Oosterhaven, Jart; University Medical Center Groningen, Dermatology Schuttelaar, Marie-Louise; University of Groningen/ University Medical Center Groningen, Dermatology
Primary Subject Heading:	Dermatology
Secondary Subject Heading:	Health economics, Occupational and environmental medicine, Pharmacology and therapeutics, Public health
Keywords:	hand eczema, alitretinoin, cyclosporine, Clinical trials < THERAPEUTICS, vesicular

Study protocol: efficacy of oral alitretinoin versus oral cyclosporine A in patients with severe recurrent vesicular hand eczema (ALICsA). A randomized prospective open-label trial with blinded outcome assessment.

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Conflicts of interest: Both authors have received honoraria for services rendered to GlaxoSmithKline, wholly unrelated to this study.

Author contributions: JO and MLS contributed equally to this work. JO and MLS conceived this trial. JO drafted and MLS revised the study protocol and this manuscript. JO and MLS read and approved the final version of the study protocol and this manuscript. MLS is principal investigator of this trial.

Starting date of study (inclusion of first patient): May 29, 2017

Ethical approval: This protocol was reviewed and approved by the Medical Ethical Review Board of the University Medical Center Groningen (reference METc 2015/375).

Funding statement: This research is supported by a grant provided by the Netherlands Organisation for Health Research and Development (ZonMw, project number 848015010).

Key words: hand eczema, vesicular, alitretinoin, cyclosporine, clinical trial

Word count (plain text): 6101

Figure count: 1

Table count: 1

Supplement count: 2 (1 SPIRIT checklist, 1 editors only supplement)

Abstract

Introduction: systemic treatment with alitretinoin is registered for all clinical types of severe chronic hand eczema. However, it is especially effective in the hyperkeratotic subtype, and less effective in non-hyperkeratotic forms. Cyclosporine A (cyclosporine) is prescribed for hand eczema in daily practice as well. It has shown to be especially effective in patients with vesicular hand eczema. The primary objective of this study is to compare efficacy of alitretinoin and cyclosporine in the treatment of severe recurrent vesicular hand eczema.

Methods and analysis: this is an investigator-initiated randomized prospective open-label trial with blinded outcome assessment. Severity assessments and laboratory measurements will be conducted corresponding to daily practice. The study population will consist of 72 adult patients (age 18-75 years) with severe recurrent vesicular hand eczema. Patients are treated with either (group I) alitretinoin 30mg once daily, or (group II) cyclosporine with a starting dose of 5 mg/kg/day and a decrease in dosage after 8 weeks to 3 – 3.5 mg/kg/day. The treatment period is 24 weeks for both drugs. Primary endpoint for efficacy is response to treatment, defined as an improvement of ≥ 2 steps on a Physician Global Assessment, using a validated Photoguide, after 24 weeks of treatment. Secondary endpoints are improvement of: Hand Eczema Severity Index, Quality Of Life in Hand Eczema Questionnaire, and a Patient Global Assessment. Adverse events and time to response will be registered. Furthermore cost-utility, Quality Adjusted Life Years and cost-effectiveness will be assessed with the EQ-5D-5L questionnaire while monitoring costs.

Ethics and dissemination: this protocol was reviewed and approved by the Medical Ethical Review Board of the University Medical Center Groningen (reference METc 2015/375). The study will be conducted according to the principles of the Declaration of Helsinki, in accordance with the Dutch Medical Research Involving Human Subjects Act. The results will be offered for publication in a peer reviewed journal. In a publication all data will be handled anonymously.

Registration details: this study was registered on ClinicalTrials.gov. Identifier: NCT03026946. European Union Clinical Trials Registry (EudraCT) No 2015-003488-12

Protocol version: Clinical Study Protocol Version 3, May 2, 2016.

Strengths and limitations of this study

- This study compares two systemic drugs for severe recurrent vesicular hand eczema head-to-head and aims to answer both a relevant clinical and economical question.
- A strength of the study is that blinded assessment of severity will be performed in order to obtain an objective result for efficacy, despite the open-label design.
- The study is limited by the fact that there will be no follow up after the end of treatment at 24 weeks, meaning that this study will not address the long-term efficacy of both drugs.

INTRODUCTION

Hand eczema is a common condition. It can have far-reaching personal, psychological and occupational consequences that may have a drastic impact on the life of those affected. A point prevalence of 4% and a 1-year-period prevalence up to 10% in the general population in Sweden have been reported.[1] A Danish study in young adults showed an incidence of 8.8 per 1000 person-years, a point prevalence of 7.1% and a 1-year-period prevalence of 14.3%. Women are significantly more often affected than men.[2]

The clinical presentation of severe hand eczema varies widely, ranging from chronic fissured skin to a vesicular eruption or palmar hyperkeratosis. The disease could also be approached etiologically, considering exogenous factors causing allergic contact dermatitis (e.g. nickel, perfumes) and irritant contact dermatitis (e.g. water, soap) in addition to endogenous factors like atopic dermatitis.[3]

There is general consensus concerning the first line treatment of hand eczema in various guidelines. Emollients and topical corticosteroids are considered to be the mainstay of treatment in mild and moderate forms. If these fail, secondary options like phototherapy and systemic treatment are available. However, to date an evidence-based recommendation regarding the treatment of more severe hand eczema cannot be made. Particularly, more head-to-head trials are needed. [4]

Alitretinoin is the only registered systemic treatment option for all clinical types of severe chronic hand eczema. It is currently the most investigated drug in terms of patient numbers in the second line treatment of severe chronic hand eczema. In well-designed, pharmaceutical sponsored trials, 30 mg alitretinoin a day resulted in a clear or almost clear response in 48% of the participants, compared to 17% in placebo. In the hyperkeratotic subtype 54% responded, compared to 12% in the placebo group. In two non-hyperkeratotic subgroups (defined as pompholyx (vesicular) and fingertip in the study) only 33% and 44% of participants reached clearance or almost clearance, compared to 12-30% in the placebo group.[5, 6]

In our clinical experience cyclosporine has beneficial effects on hand eczema in daily practice. This concerns mainly the vesicular subtype in which a response of 68% was estimated in a retrospective drug survival study.[7] Other small studies have also shown that cyclosporine may have a beneficial effect on hand eczema. In a case study, Reitamo et al reported that 87.5% of the patients with a chronic dermatitis on the hands responded to cyclosporine treatment within a few weeks.[8] In a study by Granlund et al, 41 patients were treated with cyclosporine for chronic hand eczema; 50% of the patients reported a beneficial effect of the treatment.[9] In a second, open label study, 27

patients treated for 6 weeks with oral cyclosporine 3 mg/kg/day, showed a one-year success rate of 74% for chronic hand eczema.[10] A previous trial comparing alitretinoin to cyclosporine in atopic hand eczema ended prematurely due to the inability to include the total number of participants.[11]

In several European countries cyclosporine is registered for use in patients with atopic dermatitis. Schmitt et al. performed a meta-analysis of controlled and uncontrolled trials of cyclosporine treatment in patients with atopic dermatitis. Fifteen studies including 602 patients were analyzed. All studies reported a decrease in the mean severity of atopic dermatitis with a relative effectiveness of 55% (95% confidence interval 48-62%) after 6 to 8 weeks of cyclosporine treatment.[12]

Although alitretinoin is the only registered systemic treatment for severe chronic hand eczema, this treatment has never been compared to immunomodulating/immunosuppressive systemic drugs that are currently considered to be a third line alternative treatment for this condition.[4] Since alitretinoin showed a good response in hyperkeratotic subtypes, the drug should be used as first systemic choice in this subtype. In the vesicular subtype however, its action was less convincing. Cyclosporine on the other hand showed good response in vesicular hand eczema. This trial aims to compare alitretinoin to cyclosporine in the treatment of severe chronic recurrent vesicular hand eczema. The study assesses the efficacy of both treatments and will show head-to-head results, which should contribute to uncovering the best treatment strategy for hand eczema.

OBJECTIVES

Primary objective: to compare the efficacy of alitretinoin and cyclosporine in patients with severe recurrent vesicular hand eczema.

Secondary objectives:

- to compare time to response
- to compare health related quality of life
- to compare improvement in severity of hand eczema, as assessed by the patient
- to compare safety
- to compare cost-utility and cost-effectiveness

METHODS AND ANALYSIS

Study design

This study is designed as a randomized prospective open label study. Assessment of disease severity, laboratory measurements and quality of life in this study will be conducted comparable to daily practice assessments. The duration of the study for an individual patient is 24 weeks. Planned inclusion period is two years.

Study population

The study population will consist of adult patients with severe recurrent vesicular hand eczema. Recurrent vesicular hand eczema will be diagnosed following the criteria of the Danish Contact Dermatitis Group.[13] The definition of recurrent vesicular hand eczema is: recurrent eruptions of vesicles on the palms and/or on the sides of the fingers and possibly also on the palmar aspects of the fingers and around the fingernails. Eruptions may occur at intervals of weeks or months. The severity of the hand eczema at screening will be graded by means of a Physician Global Assessment using a validated Photoguide.[14] Woman in the fertile age will be required to use proper contraception methods. Men and women of all ethnicities of 18 years and older will be recruited. Patients meeting all inclusion criteria, while not meeting any of the exclusion criteria, will be asked to participate. See Figure 1 for a study flow chart.

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age ≥ 18 years and ≤ 75 years
- Severe or very severe recurrent vesicular hand eczema for a minimum duration of 3 months as defined by a Physician Global Assessment (PGA) using a validated Photoguide [14]
- Refractory to standard therapy, defined as:
    - Patients received treatment with topical corticosteroids of class II or higher for at least 8 weeks within 3 months before enrolment, with either no response or a transient response
    - Patients has also received standard skin care, including emollients and barrier protection as appropriate, without significant improvement
    - Patients has avoided irritants and contact allergens, if identified, without significant improvement
- Women of childbearing potential are required to use at least two forms of contraception for at least 1 month before starting treatment, during treatment, and for at least 1 month after finishing treatment; these women are required to take monthly pregnancy tests

- Able to provide written Informed Consent
- Able to speak and read the Dutch language

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

General criteria prior to randomization

- Treated with alitretinoin or cyclosporine in the previous 3 months
- Other morphologic types of hand eczema as defined by the Danish Contact Dermatitis Group[13]
- Patients with predominantly atopic dermatitis, in whom the hands are also involved, but no main concern. (Patients with controlled atopic dermatitis, in which the hands are mainly affected, are eligible for inclusion.)
- Psoriasis of the hands
- Active bacterial, fungal, or viral infection of the hands
- Pregnant/lactating or planning to become pregnant during the study period
- Treatment with systemic immunosuppressive medication or UV radiation within the previous 4 weeks
- Mentally incompetent
- Immunocompromised status (to be determined by investigator or treating physician)
- Uncontrolled arterial hypertension (minimally 3 measurements). Systolic pressure > 160 mmHg or diastolic pressure > 95 mmHg, despite starting anti-hypertensive medication [15]
- Known or suspected allergy to ingredients in the study medications
- Inclusion in a study of an investigational drug within 60 days prior to start of treatment
- Current malignancy (other than successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix)
- Current active pancreatitis
- Evidence of alcohol abuse or drug addiction
- Malabsorption
- Currently active gout
- Recurring convulsions / epilepsy
- Living vaccine (including bacillus Calmette-Guérin (BCG), varicella, measles, mumps, rubella, yellow fever, oral polio and oral typhoid) in the last 2 weeks or the planned application of such a vaccine during the study period

- Chronic or recurrent infectious diseases
- Contact sensitizations with clinical relevance to the hands, in which exposure to allergens is not avoided.
- Hypervitaminosis A due to the use of vitamin A supplements containing >2000 IU
- Use of drugs with potential to change the effective dose of study drugs within the previous 2 weeks

Laboratory exclusion criteria post randomization

- Alanine aminotransferase (ALAT) and /or aspartate aminotransferase (ASAT) values > 200% of the upper limit of normal
- Impaired renal function as indicated by a clinically relevant abnormal creatinine value (to be determined by investigator or treating physician)
- Anemia as indicated by a clinically relevant lowered hemoglobin value (to be determined by investigator or treating physician)

Alitretinoin specific

- Triglycerides > 200% of the upper limit of normal,
- Cholesterol or low density lipoprotein (LDL) cholesterol values > 200% of the upper limit of normal
- Uncontrolled hypothyroidism (to be determined by investigator or treating physician)

Cyclosporine specific:

- Impaired renal function as indicated by a clinically relevant abnormal creatinine value (to be determined by investigator or treating physician)
- Uremia
- Hyperkalemia
- Hyperuricemia in patients with a medical history of gout

Recruitment and consent

Recruitment takes place at a university center Dermatology department, during specialized eczema consulting sessions every week. Several Dermatology departments in general hospitals are provided with the study protocol and asked to refer eligible patients. All referred hand eczema patients (by general practitioner or dermatologist) will visit the department several times for diagnostics (patch testing) and initial therapy. Only when these patients have a diagnosis of severe or very severe

recurrent vesicular hand eczema, prove refractory to standard therapy, and avoidance of irritants and allergens does not give significant improvement (i.e. meet the key inclusion criteria), they will be approached at the outpatient clinic to participate in the study. Patients will be extensively informed about the trial.

It is the responsibility of the investigator, or a person designated by the investigator, to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives and potential hazards of the study. It will also be explained to patients that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason. Patients will be given a period of one week to consider participation before they are asked to sign the informed consent form.

Treatment of subjects

Interventions

Group I will receive an oral *alitretinoin* capsule of 30mg once daily for a total of 24 weeks. In a dose-finding study, the effectiveness and tolerability of this dose was established and it is recommended to use this as the standard dose for the prescription of alitretinoin in hand eczema.[5, 6, 16]

Group II will receive oral *cyclosporine* tablets twice daily in a dose of 5mg/kg/day (split in 2 doses) and decrease this dose after 8 weeks to 3 - 3.5 mg/kg/day (split in 2 doses).[17]

Dosage reduction is allowed in both groups in case of abnormal findings on physical examination, laboratory markers, and/or adverse events. For alitretinoin, dose can be reduced from 30 mg/day to 10 mg/day, in accordance with the Summary of Product Characteristics (SPC) text.[16] For cyclosporine, in case of increased creatinine levels > 30% of baseline, laboratory measurement should be repeated after two weeks. If creatinine levels are still increased at least > 30%, dosage will be reduced with the recommended 30-50%.[15] Developing hypertension should be re-evaluated with at least 3 measurements (if necessary by the general practitioner). If repeated values of a systolic pressure > 160 mmHg or diastolic pressure > 105 mmHg are found, the general practitioner will be requested to start an antihypertensive drug (preferably calcium channel blockers). [15, 18]

Preparation and labelling of the study drugs will be carried out according to usual practice by the community pharmacy, honouring Good Manufacturing Practice guidelines. Medication will be dispensed and used in the same way as in routine clinical practice, according to (among other regulations) their marketing authorisations.

Use of concomitant medication

All patients will be given an emollient cream with instructions to apply it frequently (advice: minimum 2 times a day). One week before the first intake of study drugs, concomitant treatment with a topical class II corticosteroid (e.g. triamcinolone acetonide ointment 0.1%) at maximum is permitted when needed, with a maximum application of one finger-tip-unit (FTU) for each hand daily.[19] This also applies for concomitant topical corticosteroid therapy during the study period. High potency topical corticosteroids are not allowed as maintenance therapy.

Generally prohibited concomitant treatments during therapy comprise: systemic corticosteroids, other retinoids, any other systemic or topical anti-eczema therapy, phototherapy, immunosuppressive or cytostatic drugs.

Alitretinoin specific prohibited concomitant treatment: vitamin A supplements, tetracyclines and azole antimycotics. St John's wort should not be taken because of a possible interaction with hormonal contraceptive drugs. This could possibly result in a pregnancy, which is absolutely contraindicated because of the teratogenic nature of alitretinoin.[16]

Cyclosporine specific prohibited concomitant treatment: medicines that are substrates for the multidrug efflux transporter P-glycoprotein or the organic anion transporter proteins (OATP). This could result in elevated plasma concentrations which are associated with serious and/or life-threatening events, e.g. bosentan, dabigatranetexilate and aliskiren.

Inductors of CYP3A4 and/or P-glycoprotein will probably lead to a decrease of cyclosporine plasma concentrations. Examples of these are: barbiturates, carbamazepine, oxcarbazepine, phenytoin, nafcilline, intravenous sulfadimine, probucol, orlistat, St John's wort (Hypericum perforatum), ticlopidine, sulfinpyrazon, terbinafine, bosentan. Rifampicine induces metabolism of cyclosporine in the intestines and liver. Octreotide decreases oral absorption of cyclosporine.

Inhibitors of CYP3A4 and/or P-glycoprotein can increase cyclosporine plasma concentrations. Examples of these are: nicardipine, metoclopramide, methylprednisolon (high doses), allopurinol, cholic acid and derivatives, proteaseinhibitors, imatinib, colchicine, nefazodon.

Other drugs that increase cyclosporin plasma concentration are: macrolide antibiotics, azole antimycotics, verapamil, telaprevir, amiodarone, danazol, diltiazem, and lercanidipine. Furthermore, grapefruit and grapefruit juice can have an increasing effect on cyclosporine plasma concentration.

Also prohibited are drugs which result in an increased risk for nephrotoxicity when combined with cyclosporine, such as: aminoglycosides (including gentamycin, tobramycin), amphotericin B, ciprofloxacin, vancomycin, trimethoprim (+ sulfamethoxazole); fibric acid derivatives (e.g. bezafibrate, fenofibrate); NSAIDs (including diclofenac, naproxen, sulindac); melphalan, histamine H2-receptor antagonists (e.g. cimetidine, ranitidine), methotrexate.

The dosage of statins needs to be decreased when treatment with cyclosporine is started, because of a possible increase in plasma concentration of statins.[17]

Escape medication

In case of an exacerbation or postponed treatment effect, patients are allowed to receive a maximum of 3 courses of rescue medication: mometasone furoate once daily for 1 week, with a maximum application of one FTU for each hand daily.[19]

Outcome measures

Primary outcome measure

Severity of hand eczema

The PGA, based on a validated Photoguide developed by Coenraads et al, covers 5 degrees of severity (clear, almost clear, moderate, severe, very severe) and takes into account the intensity of clinical signs and percentage of hand surface involved.[14] Response to treatment is defined as an improvement of ≥ 2 steps on the PGA. Very severe hand eczema is defined as responding to treatment if a status of at least 'moderate' is achieved. Severe hand eczema is defined as responding to treatment if a status of at least 'almost clear' is achieved.

In this study the main endpoint is the between-group difference in response to treatment between baseline and 24 weeks of treatment.

Secondary outcome measures

Severity of hand eczema

- Between-group difference in response to treatment between baseline and 12 weeks of treatment.
- Between-group difference in mean change between baseline and week 4, 8, 12 and 24, assessed by the Hand Eczema Severity Index (HECSI) score.[20] The HECSI is an objective severity assessment based on clinical symptoms only. It includes erythema, fissures, vesicles, scaling, oedema, papules and measurement of the affected area. The score ranges from 0-360, with a score > 28 indicating severe hand eczema.
- Between-group difference in time to response (time to first PGA improvement of ≥ 2 steps). This is only measured at control visits so possible outcome is limited to 4, 8, 12 and 24 weeks. This will be corrected using statistical methods (see statistical paragraph).

Patient reported outcome measures (PROMs):

Quality of life

- Between-group mean change in quality of life between baseline and 12 and 24 weeks, assessed by the Quality Of Life in Hand Eczema Questionnaire (QOLHEQ). The QOLHEQ is a multi-domain disease specific instrument for hand eczema assessing impairments in quality of life. The score ranges from 0-120, with 120 indicating worst quality of life.[21, 22]

Patient reported improvement

- Between-group difference in patients reporting improvement as 'clear or almost clear' compared to baseline at week 12 and 24, assessed by Patient Global Assessment (PaGA). The PaGA takes signs and symptoms into account. It covers 6 degrees of improvement: 'clear or almost clear' (at least 90% clearing of disease signs and symptoms compared to baseline), 'marked improvement' (at least 75% clearing), 'moderate improvement' (at least 50% clearing), 'mild improvement' (at least 25% clearing), 'no change', or 'worsening'.[6]

Safety and tolerability

- Adverse events in both groups will be registered.

Cost-utility and cost-effectiveness

- Between-group difference in mean Quality Adjusted Life Years (QALYs) will be measured by the EQ-5D-5L score at baseline, week 12 and week 24. The EQ-5D-5L is a measure for Health Related Quality of Life (HRQoL) and utility values. The EQ-5D-5L questionnaire includes a descriptive system, which comprises 5 dimensions of health: mobility, self-care, usual

activities, pain/discomfort, and anxiety/depression. Moreover, it includes a visual analog scale (VAS), which records the respondent's self-rated health status on a graduated (0–100) scale.[23]

- Direct medical costs will be determined using standardized prices for consultation, treatment (medication; alitretinoin or cyclosporine, topical treatment with corticosteroids and emollients, if necessary oral or topical treatment with antibiotics), diagnostic tests, laboratory measurements, visits to the general practitioner for hand eczema and hospital admissions (inpatient and/or daycare). Included patients will be asked to keep track of how much they spend on over-the-counter medication and other products for their hand eczema (out-of-pocket costs). Direct non-medical costs, consisting of travel costs, will be determined using average travel costs to the hospital as determined by relevant Dutch guidelines on cost-studies in healthcare.[24, 25]
- Indirect costs, consisting mainly of productivity loss, will be also be calculated using tables from the guidelines with average income of Dutch workers stratified by age and gender, corrected for shift working / irregular working hours.[24]

Other study parameters

These comprise the following parameters: age, sex, body-mass-index, current and/or previous atopic dermatitis (both defined by U.K. Working Party criteria)[26], age of onset of atopic dermatitis, age of onset of hand eczema, work/activities (based on risk professions as named in the European Guideline on hand eczema)[4], current use of statins, current use of thyromimetics, currently smoking and amount of pack-years will be registered. Pack years are calculated by multiplying the total years smoked with the average packs per day smoked over these years.[27] For this, the online Smoking Pack Years Calculator, created by dr NJ Masters and C Tutt, will be used.[28]

Study procedures and overview

Procedures part of standard medical treatment

According to daily practice, a detailed patient history is obtained of all newly referred patients with hand eczema and they are planned for patch testing to exclude contact allergy. During this first period, patients are treated with topical corticosteroids and emollients. A structured education program by a nurse on provoking factors and treatment is provided. If a relevant contact allergy is

ruled out and the hand eczema proves to be refractory to topical therapy and/or UV therapy, the next step is systemic therapy. These patients are a candidate for the current study if they are diagnosed with severe or very severe recurrent vesicular hand eczema.

Laboratory analysis is performed to verify contra-indications for alitretinoin or cyclosporine. During therapy, standard monitoring of blood values is carried out, according to SPC texts and current guidelines. At every visit, the PGA for severity is determined and the hand eczema is scored using the HECSI, corresponding to daily practice. Furthermore, health related quality of life is scored with a Dutch version of the QOLHEQ at the start of therapy, at week 12 and week 24.

Standard laboratory tests to be performed include:
Alitretinoin: at week 0, 4, 8, 12 and 24, laboratory tests are carried out, including: full blood count, ASAT, ALAT, ALP, γ-GT, serum creatinine, cholesterol, triglycerides, HDL, TSH, T4 and glucose. Also, a urine pregnancy test will be carried out.
Cyclosporine: at week 0, 4, and 12 laboratory tests are carried out, including: full blood count, potassium, magnesium, ASAT, ALAT, ALP, γ-GT, bilirubin, LDH, albumin, serum creatinine, uric acid, cholesterol and triglycerides.
At week 4 and 12, cyclosporine trough levels will be determined.
At week 8 and 24, serum creatinine will be determined.

Procedures extra for this study

Patients will be given one week to consider participation. Due to this, a maximum of one extra visit is needed to randomize the patient and obtain baseline data. The PaGA one-item questionnaire will be obtained at week 12 and 24. This procedure is only extra in terms of obtaining a quantitative assessment of the qualitative report that a patient provides in daily practice.

Patients will be asked to keep track of out-of-pocket costs on products for their hand eczema. During each visit, patients will be asked for direct and indirect medical and non-medical costs. Furthermore, the EQ-5D-5L questionnaire is obtained at week 0, 12 and 24, which is extra compared to daily practice.

Serum Thymus and Activation-Regulated Chemokine (TARC / CCL17) will be determined at all visits to study whether this chemokine is a suitable biomarker for hand eczema severity and/or disease activity over time.

No diagnostic procedures or other treatments will be postponed for patients participating in this study.

In Table 1, a systematic overview of the study is presented.

Table 1. Study schedule

Visit	V-1 Screening	V0 Baseline	V1	V2	V3	V4
Week	**-1**	**0**	**4**	**8**	**12**	**24**
Screening/baseline						
Check for clinical eligibility (inclusion/exclusion)	x					
Sign informed consent	x					
Randomization		x				
Baseline data / demographics / medical history / baseline costs		x				
Laboratory exclusion criteria post randomization		x				
Start medication		x				
Treatment						
Escape medication assessment			x	x	x	x
If applicable: dosage alteration assessment			x	x	x	x
Efficacy						
Severity scoring PGA / HECSI		x	x	x	x	x
Quality of life questionnaire QOLHEQ		x			x	x
PaGA of improvement					x	x
Costs						
Cost assessment		x	x	x	x	x
Cost-utility questionnaire EQ-5D-5L		x			x	x
Safety						
Lab control		x	x	x	x	x
Concomitant medication		x	x	x	x	x
Adverse events			x	x	x	x
Blood pressure measurement (cyclosporine only)		x	x	x	x	x
If applicable: premature withdrawal assessment		x	x	x	x	x

HECSI, Hand Eczema Severity Index; PaGA, Patient Global Assessment; PGA, Physician Global Assessment; QOLHEQ, Quality Of Life in Hand Eczema Questionnaire

Patients are permitted to deviate from the schedule with a maximum of 7 days during week 0-8. From week 9 a maximum deviation of 14 days is permitted.

Safety

Alitretinoin

Main risks in the alitretinoin group are[16]:

- Teratogenicity of the study drugs
- Occurrence of allergic / anaphylactic reactions
- Depression with anxiety, mood changes and suicidal tendencies
- Sunburn
- Xerostomia, xerosis cutis
- Keratoconjunctivitis sicca, keratitis, blurred (night) vision, cataract. Care must be taken when driving a vehicle or when operating machines.
- Myalgia, arthralgia, increase of CK values
- Exostosis, ankylosing spondylitis
- Headache
- Blushing
- Increase of cholesterol and triglycerides, with ultimately pancreatitis
- Decrease of TSH and T4
- Increased liver transaminases
- Decrease in effective dose of simvastatin
- Change at scarring or dermatitis during therapy and 6 months after in case of aggressive dermabrasion or epilation
- Anemia
- Epistaxis
- Alopecia
- Benign intracranial hypertension (rare and most seen in combination with tetracyclines)
- Inflammatory bowel disease (rare)
- Vasculitis (rare)

Alitretinoin is a derivative of vitamin A. Alitretinoin has been administered in oncological clinical studies at dosages of more than 10-times of the therapeutic dosage given for chronic hand eczema. The adverse effects observed were consistent with retinoid toxicity, and included severe headache, diarrhea, facial flushing, hypertriglyceridemia. These effects were reversible.

It can be concluded that the (reversible) effects can be properly managed.

Cyclosporine

Main risks in the cyclosporine group are[17]:

- Renal toxicity
- Hepatotoxicity
- Hypertension, flushing
- Nausea/vomiting, abdominal discomfort
- Headache
- Diarrhea
- Anemia, thrombocytopenia
- Leucopenia
- Hyperlipidemia
- Hyperkalemia, hypomagnesemia, hyperuricemia, hyperglycemia
- Tremor, convulsions, paresthesia
- Hirsutism/hypertrichosis
- Acne
- Myalgia
- Muscle cramps
- Tiredness
- Gynecomastia
- Occurrence of allergic / anaphylactic reactions
- Pre-existing infections may also be aggravated and reactivation of polyomavirus infections may lead to polyomavirus-associated nephropathy or to JC virus associated progressive multifocal leukopathy. Serious and/or fatal outcomes have been reported.
- Increase risk of lymphomas and other malignancies (mainly when combining multiple immunosuppressive drugs)
- Increase risk of infections
- Decreased effect of live vaccinations

Experience with acute overdosage of cyclosporine is limited. Oral doses of cyclosporine of up to 10 g (about 150 mg/kg) have been tolerated with relatively minor clinical consequences, such as vomiting, drowsiness, headache, tachycardia and in a few patients moderately severe, reversible impairment

of renal function. However, serious symptoms of intoxication have been reported following accidental parenteral overdosage with cyclosporine in premature neonates.

In all cases of overdosage, general supportive measures should be followed and symptomatic treatment applied. Forced emesis and gastric lavage may be of value within the first few hours after oral intake. Cyclosporine is not dialysable to any great extent, nor is it well cleared by charcoal hemoperfusion.

It can be concluded that the (reversible) effects can be properly managed.

Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for medical reasons. Specific criteria for withdrawal are:

- Evidence of pregnancy
- Occurrence of serious adverse events
- Lack of efficacy at 12 weeks, defined as no improvement assessed by the PGA (at least 1 step improvement is necessary to continue treatment after 12 weeks)
- Use of prohibited concomitant therapy, or a need for their use
- The need for more than 3 courses of rescue medication
- Anaphylactic reaction or other severe systemic reaction to study drug intake
- Diagnosis of malignancy during study, excluding non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix
- Any infection that is opportunistic and other infections whose nature or course may suggest an immunocompromised status
- Administration of a living vaccine
- Developing hypertension (minimally 3 measurements). Systolic pressure > 160 mmHg or diastolic pressure > 95 mmHg, despite starting anti-hypertensive medication.[15]
- Severe laboratory abnormalities including:
    - ALAT and/or ASAT values > 300% of the upper limit of normal
    - Triglycerides > 9 mmol/l
    - Creatinine increase of > 30%, despite dose reduction
- Intercurrent severe illness or major surgery
- Protocol violations or if the requirements of the protocol are not respected

- Patient lost to follow up

Serious adverse events and suspected unexpected serious adverse reactions

A serious adverse event (SAE) is any untoward medical occurrence or effect at any dose that:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;

Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

Unexpected adverse reactions are suspected unexpected serious adverse reactions (SUSARs) if the following three conditions are met:

1. the event must be serious (see SAE);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in the SPC texts.

Randomization, blinding and treatment allocation

Randomization is carried out by a computer program (ALEA, http://www.aleaclinical.eu). Patients will be randomly assigned in a 1:1 ratio to the two treatment arms. We will use block randomization with a random block size of 4 or 6 (random generated blocks). No stratification will be done. This is a study with blinded efficacy assessors, who are unaware of treatment allocation. The participants and treating physician will be aware of treatment allocation. Efficacy assessment will be carried out by one main blinded assessor and a second assessor in case the first assessor is unable to be present. These assessors are trained by the primary investigator and are experienced in assessing hand

eczema by PGA and HECSI in daily practice. The first assessor is expected to perform around 95% of all assessments. Blinding will be broken after analyzing the data.

Statistical analyses

Hypothesis and sample size calculation

This trial is designed to demonstrate a superior response to cyclosporine compared to alitretinoin in the treatment of severe recurrent vesicular hand eczema. Response to treatment is defined as an improvement of ≥ 2 steps on the PGA, based on a validated Photoguide developed by Coenraads et al [14] at 24 weeks of treatment. A sample size of 31 in each group will have 80% power to be able to reject the null hypothesis of no difference between alitretinoin and cyclosporine, using a χ^2 test with a two-sided 0.05 significance level. In this calculation we use the following assumptions: randomization ratio is 1:1, and we expect the percentage of responders in the alitretinoin group to be 33%.[6] From a retrospective study and other case studies we estimate 68% responders in the cyclosporine group.[7] We anticipate a drop-out of maximally 15% of randomized patients; a small percentage prior to first application of study drugs due to excluding laboratory measurements and a larger percentage during follow up, mainly due to subjective side effects. We therefore plan to include 72 patients in total, 36 in the alitretinoin group and 36 in the cyclosporine group.

Calculated with the sample size calculator of the Department of Statistics, University of British Columbia, Canada, available at http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html.

Primary analysis

Severity of hand eczema

Between-group difference in response to treatment between baseline and 24 weeks of treatment. For comparison of proportions in the alitretinoin and cyclosporine group a χ^2 test, or Fisher's exact test if appropriate, will be used.

Secondary analyses

Severity of hand eczema

- Between-group difference in response to treatment between baseline and 12 weeks of treatment. For comparison of proportions in the alitretinoin and cyclosporine group a χ^2 test will be used.

- Between-group difference in mean change between baseline and week 4, 8, 12 and 24, assessed by the HECSI score. This will be reported graphically. For comparison of mean change between the alitretinoin and cyclosporine group at week 12 and 24, the Student's t-test or Mann-Whitney U-test will be used, depending on distribution of data.

- Between-group difference in time to response (time to first PGA improvement of ≥ 2 steps compared to baseline). Because this outcome measure is interval-censored, the cumulative incidence of 'response' will be analyzed using of actuarial life table analysis and weighted log-rank tests for interval censored data; in particular the group proportional hazards model[29] and a generalized Wilcoxon-Mann-Whitney test[30], which emphasizes early events. The exact permutation value for the scores of the group proportional hazards model will be calculated, along with Wilcoxon-Mann-Whitney tests and the non-parametric maximum likelihood estimate of the survival distribution function.[31]

Patient reported outcome measures (PROMs):

Quality of life

- Between-group mean change in quality of life between baseline and 12 and 24 weeks, assessed by the QOLHEQ. Clinically relevant improvement is defined as an absolute improvement of 15 points (theoretically corresponding to an improvement of ≥ 1 point on 50% of the questions) compared to baseline. For comparison of proportions of patients rated as having clinically relevant improvement in the alitretinoin and cyclosporine group, a χ^2 test will be used.

Patient reported improvement

- Between-group difference in patients reporting improvement as 'clear or almost clear' at week 12 and 24, assessed PaGA. For comparison of proportions of patients rated as 'clear or almost clear' in the alitretinoin and cyclosporine group, a χ^2 test will be used.

Safety and tolerability

- Descriptive statistics will be used to present adverse events.

Cost-utility and cost-effectiveness

- For both groups (alitretinoin and cyclosporine), the mean EQ-5D scores overall and of each dimension will be reported. Results from the descriptive system of the EQ-5D-5L will be converted to a utility index value, a population based (social) value specific for the Netherlands. With this value, Dutch utility values will be calculated in order to determine the QALYs over the study period. Mean values of the EQ-VAS will be reported with a 95% confidence interval. For comparison of means, the Student's t-test or Mann-Whitney U-test will be used, depending on distribution of data.
- The incremental cost-effectiveness ratio (ICER) will be calculated and reported as €/QALY.
- A regression model will be used to estimate the association between QALYs and the PGA.

Handling of missing data

All analyses will be based on the intention-to-treat principle to guard against attrition bias. Subjects might not only want to withdraw because the study drug works insufficient, they might also want to withdraw when their hand eczema is cured.

Missing values will be handled in a way that is dependent on assumptions about the missing data. If the extent and pattern of missing data is known (e.g. missing at random (MAR), missing completely at random (MCAR), missing not at random (MNAR)), an analysis will be chosen that is valid under a plausible assumption about the missing data (probably mixed models). This is according to a strategy proposed by White et al.[32]

Data handling

Data will be handled confidentially. Data derived from the questionnaires and other paper source documents will be coded using sequential administration numbers. A subject identification code list is used to link the data to the subjects. The code is not based on the patient initials and birth-date. The code will be safeguarded by the principal investigator, dr. M.L.A. Schuttelaar. The documents will be stored in a locked room. The digital source data will be saved in subsections of the subjects medical file. These data will be accessible to the principal investigator and the investigator, and also to other treating physicians. Data will not be accessed by the blinded efficacy assessors. All data will be recorded in electronic Case Report Forms (eCRFs) in Utopia (software for Electronic Data Capture)

developed by the Trial Coordination Center, linked to the University Medical Center Groningen. The eCRFs will only be accessible with the username and password of the responsible investigator.

Data will be saved for 15 years after completion of this study.

All the data will be saved in accordance with the Dutch Personal Data Protection Act.

Monitoring

A certified monitor will carry out monitoring of this study. The monitor will get read-only access to the digital and paper documents of participants. Goal of this monitoring is to review if:

- the rights and wellbeing of subjects are being protected
- the reported data is right and fully reproducible
- the execution of the study is in accordance with this protocol and relevant legal requirements.

Data Safety Monitoring Board

No Data Safety Monitoring Board (DSMB) is established, since this study will be conducted corresponding to daily practice. In case of life-threatening diseases usually the implementation of a DSMB is indicated from an ethical point of view. But hand eczema is a non-critical indication. Frequent laboratory assessments will reduce the possibility of serious adverse events to a minimum. The patient population in this clinical trial exists of legal competent adults and the study drugs alitretinoin and cyclosporine are well-investigated, well-characterized drugs.

ETHICS AND DISSEMINATION

Ethics

This protocol was reviewed and approved by the Medical Ethical Review Board of the University Medical Center Groningen (reference METc 2015/375). The study will be conducted according to the principles of the Declaration of Helsinki (Seventh revision, Fortaleza, Brazil, October 2013), in accordance with the Medical Research Involving Human Subjects Act (WMO), and also in accordance with the International Conference on Harmonisation Good Clinical Practice Guidelines (ICH-GCP).

In this trial both groups are treated with a drug, known to be beneficial to hand eczema in a considerable amount of patients. So the intended benefit of both study drugs is to reduce the severity of hand eczema.

We hypothesize that cyclosporine has a superior efficacy compared to alitretinoin in severe chronic recurrent vesicular hand eczema. If this hypothesis is confirmed, there could be a practical, as well as a financial implication. Practically, more responding patients to cyclosporine leads to a greater beneficial effect on hand eczema in this patient group. Financially, cyclosporine is a lot less expensive than alitretinoin. If cyclosporine shows superior efficacy in severe recurrent hand eczema, this could lead to an official registration. This, in turn, could mean a decrease in financial burden for the treatment of severe recurrent vesicular hand eczema patients in the population.

We deem the overall risks for patients participating in this study to be acceptable because of the tight inclusion and exclusion criteria (ensuring a relatively healthy study population), combined with regular laboratory assessments to enhance safety monitoring. Furthermore, prior experience with both study drugs in daily practice has improved our capability to manage risks. The remaining risk is therefore small and does not differ from regular daily practice.

Dissemination

The study is designed honouring the Centrale Commissie Mensgebonden Onderzoek (CCMO) statement on publication policy. The results will be made public unreservedly; they will be offered for publication in a peer reviewed journal. In a publication all data will be handled anonymously.

Acknowledgements

The authors would like to thank K.M. Vermeulen for her valuable contributions to the health economics component of this protocol.

References

1 Thyssen JP, Johansen JD, Linneberg A, et al. The epidemiology of hand eczema in the general population--prevalence and main findings, *Contact Dermatitis* 2010;62:75-87.

2 Mortz CG, Bindslev-Jensen C, Andersen KE. Hand eczema in The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS): prevalence, incidence and risk factors from adolescence to adulthood, *Br J Dermatol* 2014;171:313-23.

3 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.

4 Diepgen TL, Andersen KE, Chosidow O, et al. Guidelines for diagnosis, prevention and treatment of hand eczema, *J Dtsch Dermatol Ges* 2015;13:e1-22.

5 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;140:1453-9.

6 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, *Br J Dermatol* 2008;158:808-17.

7 Christoffers WA, Politiek K, Coenraads PJ, et al. Drug survival of cyclosporine in the treatment of hand eczema: a multicentre, daily use study, *J Eur Acad Dermatol Venereol* 2016;30:63-6.

8 Reitamo S, Granlund H. Cyclosporin A in the treatment of chronic dermatitis of the hands, *Br J Dermatol* 1994;130:75-8.

9 Granlund H, Erkko P, Eriksson E, et al. Comparison of cyclosporine and topical betamethasone-17,21-dipropionate in the treatment of severe chronic hand eczema, *Acta Derm Venereol* 1996;76:371-6.

10 Granlund H, Erkko P, Reitamo S. Long-term follow-up of eczema patients treated with cyclosporine, *Acta Derm Venereol* 1998;78:40-3.

11 Schmitt J. Ciclosporin versus alitretinoin for severe atopic hand dermatitis (TocyDD). Last updated 2014; Available at: clinicaltrials.gov/show/NCT01231854. Last accessed 2017.

12 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;21:606-19.

13 Menné T, Johansen JD, Sommerlund M, et al. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema, *Contact Dermatitis* 2011;65:3-12.

14 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;152:296-301.

15 Nederlandse Vereniging voor Dermatologie en Venereologie. Richtlijn Constitutioneel eczeem 2006, Updated 2007.

16 Anonymous. SPC text alitretinoin. Last updated 2015; Available at: http://db.cbg-meb.nl/IB-teksten/h100957.pdf. Last accessed 2017.

17 Anonymous. SPC text cyclosporine. Last updated 2015; Available at: http://www.medicines.org.uk/emc/medicine/1307. Last accessed 2017.

18 Cai J, Huang Z, Yang G, et al. Comparing antihypertensive effect and plasma ciclosporin concentration between amlodipine and valsartan regimens in hypertensive renal transplant patients receiving ciclosporin therapy, *Am J Cardiovasc Drugs* 2011;11:401-9.

19 Long CC, Finlay AY. The finger-tip unit--a new practical measure, *Clin Exp Dermatol* 1991;16:444-7.

20 Held E, Skoet R, Johansen JD, et al. The hand eczema severity index (HECSI): a scoring system for clinical assessment of hand eczema. A study of inter- and intraobserver reliability, *Br J Dermatol* 2005;152:302-7.

21 Ofenloch RF, Weisshaar E, Dumke AK, et al. 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;171:304-12.

22 Ofenloch RF, Oosterhaven JAF, Susitaival P, et al. Cross-Cultural Validation of the Quality of Life in Hand Eczema Questionnaire (QOLHEQ), *J Invest Dermatol* 2017;137:1454-60.

23 Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L), *Qual Life Res* 2011;20:1727-36.

24 Hakkaart-van Roijen L, Tan S, Bouwmans C. Handleiding voor kostenonderzoek, methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. College voor zorgverzekeringen. Geactualiseerde versie 2010.

25 Politiek K, Oosterhaven JA, Vermeulen KM, et al. Systematic review of cost-of-illness studies in hand eczema, *Contact Dermatitis* 2016;75:67-76.

26 Williams HC, Burney PG, Pembroke AC, et al. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation, *Br J Dermatol* 1994;131:406-16.

27 Weintraub WS, Klein LW, Seelaus PA, et al. Importance of total life consumption of cigarettes as a risk factor for coronary artery disease, *Am J Cardiol* 1985;55:669-72.

28 Masters N, Tutt C. Smoking Pack Years Calculator. 2017; Available at: http://www.smokingpackyears.com. Last accessed 2017.

29 Finkelstein DM. A proportional hazards model for interval-censored failure time data, *Biometrics* 1986;42:845-54.

30 Fay MP. Rank invariant tests for interval censored data under the grouped continuous model, *Biometrics* 1996;52:811-22.

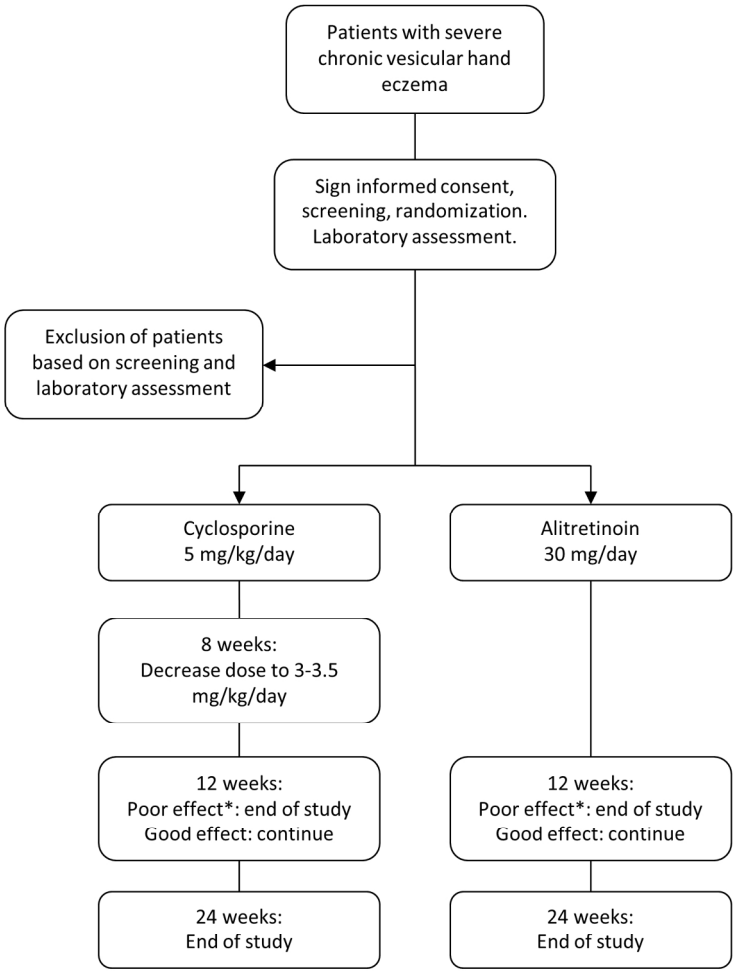
31 Fay MP. Interval: weighted logrank tests and NPMLE for interval censored data. R package version 0.1–1.1. 2014; Available at: https://cran.r-project.org/web/packages/interval/index.html. Last accessed 2017.

32 White IR, Horton NJ, Carpenter J, et al. Strategy for intention to treat analysis in randomised trials with missing outcome data, *BMJ* 2011;342:d40.

Figure legend

Figure 1. Study flow chart.

* Lack of efficacy defined as no improvement assessed by the Physician Global Assessment (Photoguide) (at least 1 step improvement is necessary to continue treatment after 12 weeks)



Study flow chart

165x174mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	Detailed within full protocol
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Not applicable
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not applicable

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5, 22
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	20-21
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Detailed within full protocol
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12-13
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	15-17 and Fig. 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	22
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	21
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	21, further detailed in protocol
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	21, further detailed in protocol
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	21, further detailed in protocol
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	21, further detailed in protocol
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Detailed within full protocol

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	24-25
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	22-24
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	22-24
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	24
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	25
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Detailed within full protocol
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Detailed within full protocol
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	1
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Detailed within full protocol

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	24-25, further detailed in protocol
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Detailed within full protocol
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Detailed within full protocol
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	26
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not detailed
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Detailed within full protocol
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	With Ethical Board application
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Study protocol: efficacy of oral alitretinoin versus oral cyclosporine A in patients with severe recurrent vesicular hand eczema (ALICsA). A randomized prospective open-label trial with blinded outcome assessment.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020192.R2
Article Type:	Protocol
Date Submitted by the Author:	12-Mar-2018
Complete List of Authors:	Oosterhaven, Jart; University Medical Center Groningen, Dermatology Schuttelaar, Marie-Louise; University of Groningen/ University Medical Center Groningen, Dermatology
Primary Subject Heading:	Dermatology
Secondary Subject Heading:	Health economics, Occupational and environmental medicine, Pharmacology and therapeutics, Public health
Keywords:	hand eczema, vesicular, alitretinoin, cyclosporine, Clinical trials < THERAPEUTICS

Study protocol: efficacy of oral alitretinoin versus oral cyclosporine A in patients with severe recurrent vesicular hand eczema (ALICsA). A randomized prospective open-label trial with blinded outcome assessment.

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Conflicts of interest: Both authors have received honoraria for services rendered to GlaxoSmithKline, wholly unrelated to this study.

Author contributions: JO and MLS contributed equally to this work. JO and MLS conceived this trial. JO drafted and MLS revised the study protocol and this manuscript. JO and MLS read and approved the final version of the study protocol and this manuscript. MLS is principal investigator of this trial.

Starting date of study (inclusion of first patient): May 29, 2017

Ethical approval: This protocol was reviewed and approved by the Medical Ethical Review Board of the University Medical Center Groningen (reference METc 2015/375).

Funding statement: This research is supported by a grant provided by the Netherlands Organisation for Health Research and Development (ZonMw, project number 848015010).

Key words: hand eczema, vesicular, alitretinoin, cyclosporine, clinical trial

Word count (plain text): 6284

Figure count: 1

Table count: 1

Supplement count: 2 (1 SPIRIT checklist, 1 editors only supplement)

Abstract

Introduction: systemic treatment with alitretinoin is registered for all clinical types of severe chronic hand eczema. However, it is especially effective in the hyperkeratotic subtype, and less effective in non-hyperkeratotic forms. Cyclosporine A (cyclosporine) is prescribed for hand eczema in daily practice as well. It has shown to be especially effective in patients with vesicular hand eczema. The primary objective of this study is to compare efficacy of alitretinoin and cyclosporine in the treatment of severe recurrent vesicular hand eczema.

Methods and analysis: this is an investigator-initiated randomized prospective open-label trial with blinded outcome assessment. Severity assessments and laboratory measurements will be conducted corresponding to daily practice. The study population will consist of 72 adult patients (age 18-75 years) with severe recurrent vesicular hand eczema. Patients are treated with either (group I) alitretinoin 30mg once daily, or (group II) cyclosporine with a starting dose of 5 mg/kg/day and a decrease in dosage after 8 weeks to 3 – 3.5 mg/kg/day. The treatment period is 24 weeks for both drugs. Primary endpoint for efficacy is response to treatment, defined as an improvement of ≥ 2 steps on a Physician Global Assessment, using a validated Photoguide, after 24 weeks of treatment. Secondary endpoints are improvement of: Hand Eczema Severity Index, Quality Of Life in Hand Eczema Questionnaire, and a Patient Global Assessment. Adverse events and time to response will be registered. Furthermore cost-utility, Quality Adjusted Life Years and cost-effectiveness will be assessed with the EQ-5D-5L questionnaire while monitoring costs.

Ethics and dissemination: this protocol was reviewed and approved by the Medical Ethical Review Board of the University Medical Center Groningen (reference METc 2015/375). The study will be conducted according to the principles of the Declaration of Helsinki, in accordance with the Dutch Medical Research Involving Human Subjects Act. The results will be offered for publication in a peer reviewed journal. In a publication all data will be handled anonymously.

Registration details: this study was registered on ClinicalTrials.gov. Identifier: NCT03026946. European Union Clinical Trials Registry (EudraCT) No 2015-003488-12

Protocol version: Clinical Study Protocol Version 3, May 2, 2016.

Strengths and limitations of this study

- This study compares two systemic drugs for severe recurrent vesicular hand eczema head-to-head and aims to answer both a relevant clinical and economical question.
- A strength of the study is that blinded assessment of severity will be performed in order to obtain an objective result for efficacy, despite the open-label design.
- The study is limited by the fact that there will be no follow up after the end of treatment at 24 weeks, meaning that this study will not address the long-term efficacy of both drugs.

INTRODUCTION

Hand eczema is a common condition. It can have far-reaching personal, psychological and occupational consequences that may have a drastic impact on the life of those affected. A point prevalence of 4% and a 1-year-period prevalence up to 10% in the general population in Sweden have been reported.[1] A Danish study in young adults showed an incidence of 8.8 per 1000 person-years, a point prevalence of 7.1% and a 1-year-period prevalence of 14.3%. Women are significantly more often affected than men.[2]

The clinical presentation of severe hand eczema varies widely, ranging from chronic fissured skin to a vesicular eruption or palmar hyperkeratosis. The disease could also be approached etiologically, considering exogenous factors causing allergic contact dermatitis (e.g. nickel, perfumes) and irritant contact dermatitis (e.g. water, soap) in addition to endogenous factors like atopic dermatitis.[3]

There is general consensus concerning the first line treatment of hand eczema in various guidelines. Emollients and topical corticosteroids are considered to be the mainstay of treatment in mild and moderate forms. If these fail, secondary options like phototherapy and systemic treatment are available. However, to date an evidence-based recommendation regarding the treatment of more severe hand eczema cannot be made. Particularly, more head-to-head trials are needed. [4]

Alitretinoin is the only registered systemic treatment option for all clinical types of severe chronic hand eczema. It is currently the most investigated drug in terms of patient numbers in the second line treatment of severe chronic hand eczema. In well-designed, pharmaceutical sponsored trials, 30 mg alitretinoin a day resulted in a clear or almost clear response in 48% of the participants, compared to 17% in placebo. In the hyperkeratotic subtype 54% responded, compared to 12% in the placebo group. In two non-hyperkeratotic subgroups (defined as pompholyx (vesicular) and fingertip in the study) only 33% and 44% of participants reached clearance or almost clearance, compared to 12-30% in the placebo group.[5, 6]

In our clinical experience cyclosporine has beneficial effects on hand eczema in daily practice. This concerns mainly the vesicular subtype in which a response of 68% was estimated in a retrospective drug survival study.[7] Other small studies have also shown that cyclosporine may have a beneficial effect on hand eczema. In a case study, Reitamo et al reported that 87.5% of the patients with a chronic dermatitis on the hands responded to cyclosporine treatment within a few weeks.[8] In a study by Granlund et al, 41 patients were treated with cyclosporine for chronic hand eczema; 50% of the patients reported a beneficial effect of the treatment.[9] In a second, open label study, 27

patients treated for 6 weeks with oral cyclosporine 3 mg/kg/day, showed a one-year success rate of 74% for chronic hand eczema.[10] A previous trial comparing alitretinoin to cyclosporine in atopic hand eczema ended prematurely due to the inability to include the total number of participants.[11]

In several European countries cyclosporine is registered for use in patients with atopic dermatitis. Schmitt et al. performed a meta-analysis of controlled and uncontrolled trials of cyclosporine treatment in patients with atopic dermatitis. Fifteen studies including 602 patients were analyzed. All studies reported a decrease in the mean severity of atopic dermatitis with a relative effectiveness of 55% (95% confidence interval 48-62%) after 6 to 8 weeks of cyclosporine treatment.[12]

Although alitretinoin is the only registered systemic treatment for severe chronic hand eczema, this treatment has never been compared to immunomodulating/immunosuppressive systemic drugs that are currently considered to be a third line alternative treatment for this condition.[4] Since alitretinoin showed a good response in hyperkeratotic subtypes, the drug should be used as first systemic choice in this subtype. In the vesicular subtype however, its action was less convincing. Cyclosporine on the other hand showed good response in vesicular hand eczema. This trial aims to compare alitretinoin to cyclosporine in the treatment of severe chronic recurrent vesicular hand eczema. The study assesses the efficacy of both treatments and will show head-to-head results, which should contribute to uncovering the best treatment strategy for hand eczema.

OBJECTIVES

Primary objective: to compare the efficacy of alitretinoin and cyclosporine in patients with severe recurrent vesicular hand eczema.

Secondary objectives:

- to compare time to response
- to compare health related quality of life
- to compare improvement in severity of hand eczema, as assessed by the patient
- to compare safety
- to compare cost-utility and cost-effectiveness

METHODS AND ANALYSIS

Study design

This study is designed as a randomized prospective open label study. Assessment of disease severity, laboratory measurements and quality of life in this study will be conducted comparable to daily practice assessments. The duration of the study for an individual patient is 24 weeks. Planned inclusion period is two years.

Study population

The study population will consist of adult patients with severe recurrent vesicular hand eczema. Recurrent vesicular hand eczema will be diagnosed following the criteria of the Danish Contact Dermatitis Group.[13] The definition of recurrent vesicular hand eczema is: recurrent eruptions of vesicles on the palms and/or on the sides of the fingers and possibly also on the palmar aspects of the fingers and around the fingernails. Eruptions may occur at intervals of weeks or months. The severity of the hand eczema at screening will be graded by means of a Physician Global Assessment using a validated Photoguide.[14] Woman in the fertile age will be required to use proper contraception methods. Men and women of all ethnicities of 18 years and older will be recruited. Patients meeting all inclusion criteria, while not meeting any of the exclusion criteria, will be asked to participate. See Figure 1 for a study flow chart.

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age ≥ 18 years and ≤ 75 years
- Severe or very severe recurrent vesicular hand eczema for a minimum duration of 3 months as defined by a Physician Global Assessment (PGA) using a validated Photoguide [14]
- Refractory to standard therapy, defined as:
    - Patients received treatment with topical corticosteroids of class II or higher for at least 8 weeks within 3 months before enrolment, with either no response or a transient response
    - Patients has also received standard skin care, including emollients and barrier protection as appropriate, without significant improvement
    - Patients has avoided irritants and contact allergens, if identified, without significant improvement
- Women of childbearing potential are required to use at least two forms of contraception for at least 1 month before starting treatment, during treatment, and for at least 1 month after finishing treatment; these women are required to take monthly pregnancy tests

- Able to provide written Informed Consent
- Able to speak and read the Dutch language

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

General criteria prior to randomization

- Treated with alitretinoin or cyclosporine in the previous 3 months
- Other morphologic types of hand eczema as defined by the Danish Contact Dermatitis Group[13]
- Patients with predominantly atopic dermatitis, in whom the hands are also involved, but no main concern. (Patients with controlled atopic dermatitis, in which the hands are mainly affected, are eligible for inclusion.)
- Psoriasis of the hands
- Active bacterial, fungal, or viral infection of the hands
- Pregnant/lactating or planning to become pregnant during the study period
- Treatment with systemic immunosuppressive medication or UV radiation within the previous 4 weeks
- Mentally incompetent
- Immunocompromised status (to be determined by investigator or treating physician)
- Uncontrolled arterial hypertension (minimally 3 measurements). Systolic pressure > 160 mmHg or diastolic pressure > 95 mmHg, despite starting anti-hypertensive medication [15]
- Known or suspected allergy to ingredients in the study medications
- Inclusion in a study of an investigational drug within 60 days prior to start of treatment
- Current malignancy (other than successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix)
- Current active pancreatitis
- Evidence of alcohol abuse or drug addiction
- Malabsorption
- Currently active gout
- Recurring convulsions / epilepsy
- Living vaccine (including bacillus Calmette-Guérin (BCG), varicella, measles, mumps, rubella, yellow fever, oral polio and oral typhoid) in the last 2 weeks or the planned application of such a vaccine during the study period

- Chronic or recurrent infectious diseases
- Contact sensitizations with clinical relevance to the hands, in which exposure to allergens is not avoided.
- Hypervitaminosis A due to the use of vitamin A supplements containing >2000 IU
- Use of drugs with potential to change the effective dose of study drugs within the previous 2 weeks

Laboratory exclusion criteria post randomization

- Alanine aminotransferase (ALAT) and /or aspartate aminotransferase (ASAT) values > 200% of the upper limit of normal
- Impaired renal function as indicated by a clinically relevant abnormal creatinine value (to be determined by investigator or treating physician)
- Anemia as indicated by a clinically relevant lowered hemoglobin value (to be determined by investigator or treating physician)

Alitretinoin specific

- Triglycerides > 200% of the upper limit of normal,
- Cholesterol or low density lipoprotein (LDL) cholesterol values > 200% of the upper limit of normal
- Uncontrolled hypothyroidism (to be determined by investigator or treating physician)

Cyclosporine specific:

- Impaired renal function as indicated by a clinically relevant abnormal creatinine value (to be determined by investigator or treating physician)
- Uremia
- Hyperkalemia
- Hyperuricemia in patients with a medical history of gout

Recruitment and consent

Recruitment takes place at a university center Dermatology department, during specialized eczema consulting sessions every week. Several Dermatology departments in general hospitals are provided with the study protocol and asked to refer eligible patients. All referred hand eczema patients (by general practitioner or dermatologist) will visit the department several times for diagnostics (patch testing) and initial therapy. Only when these patients have a diagnosis of severe or very severe

recurrent vesicular hand eczema, prove refractory to standard therapy, and avoidance of irritants and allergens does not give significant improvement (i.e. meet the key inclusion criteria), they will be approached at the outpatient clinic to participate in the study. Patients will be extensively informed about the trial.

It is the responsibility of the investigator, or a person designated by the investigator, to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives and potential hazards of the study. It will also be explained to patients that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason. Patients will be given a period of one week to consider participation before they are asked to sign the informed consent form.

Treatment of subjects

Interventions

Group I will receive an oral *alitretinoin* capsule of 30mg once daily for a total of 24 weeks. In a dose-finding study, the effectiveness and tolerability of this dose was established and it is recommended to use this as the standard dose for the prescription of alitretinoin in hand eczema.[5, 6, 16]

Group II will receive oral *cyclosporine* tablets twice daily in a dose of 5mg/kg/day (split in 2 doses) and decrease this dose after 8 weeks to 3 - 3.5 mg/kg/day (split in 2 doses).[17]

Dosage reduction is allowed in both groups in case of abnormal findings on physical examination, laboratory markers, and/or adverse events. For alitretinoin, dose can be reduced from 30 mg/day to 10 mg/day, in accordance with the Summary of Product Characteristics (SPC) text.[16] For cyclosporine, in case of increased creatinine levels > 30% of baseline, laboratory measurement should be repeated after two weeks. If creatinine levels are still increased at least > 30%, dosage will be reduced with the recommended 30-50%.[15] Developing hypertension should be re-evaluated with at least 3 measurements (if necessary by the general practitioner). If repeated values of a systolic pressure > 160 mmHg or diastolic pressure > 105 mmHg are found, the general practitioner will be requested to start an antihypertensive drug (preferably calcium channel blockers). [15, 18]

Preparation and labelling of the study drugs will be carried out according to usual practice by the community pharmacy, honouring Good Manufacturing Practice guidelines. Medication will be dispensed and used in the same way as in routine clinical practice, according to (among other regulations) their marketing authorisations.

Use of concomitant medication

All patients will be given an emollient cream with instructions to apply it frequently (advice: minimum 2 times a day). One week before the first intake of study drugs, concomitant treatment with a topical class II corticosteroid (e.g. triamcinolone acetonide ointment 0.1%) at maximum is permitted when needed, with a maximum application of one finger-tip-unit (FTU) for each hand daily.[19] This also applies for concomitant topical corticosteroid therapy during the study period. High potency topical corticosteroids are not allowed as maintenance therapy.

Generally prohibited concomitant treatments during therapy comprise: systemic corticosteroids, other retinoids, any other systemic or topical anti-eczema therapy, phototherapy, immunosuppressive or cytostatic drugs.

Alitretinoin specific prohibited concomitant treatment: vitamin A supplements, tetracyclines and azole antimycotics. St John's wort should not be taken because of a possible interaction with hormonal contraceptive drugs. This could possibly result in a pregnancy, which is absolutely contraindicated because of the teratogenic nature of alitretinoin.[16]

Cyclosporine specific prohibited concomitant treatment: medicines that are substrates for the multidrug efflux transporter P-glycoprotein or the organic anion transporter proteins (OATP). This could result in elevated plasma concentrations which are associated with serious and/or life-threatening events, e.g. bosentan, dabigatranetexilate and aliskiren.

Inductors of CYP3A4 and/or P-glycoprotein will probably lead to a decrease of cyclosporine plasma concentrations. Examples of these are: barbiturates, carbamazepine, oxcarbazepine, phenytoin, nafcilline, intravenous sulfadimine, probucol, orlistat, St John's wort (Hypericum perforatum), ticlopidine, sulfinpyrazon, terbinafine, bosentan. Rifampicine induces metabolism of cyclosporine in the intestines and liver. Octreotide decreases oral absorption of cyclosporine.

Inhibitors of CYP3A4 and/or P-glycoprotein can increase cyclosporine plasma concentrations. Examples of these are: nicardipine, metoclopramide, methylprednisolon (high doses), allopurinol, cholic acid and derivatives, proteaseinhibitors, imatinib, colchicine, nefazodon.

Other drugs that increase cyclosporin plasma concentration are: macrolide antibiotics, azole antimycotics, verapamil, telaprevir, amiodarone, danazol, diltiazem, and lercanidipine. Furthermore, grapefruit and grapefruit juice can have an increasing effect on cyclosporine plasma concentration.

Also prohibited are drugs which result in an increased risk for nephrotoxicity when combined with cyclosporine, such as: aminoglycosides (including gentamycin, tobramycin), amphotericin B, ciprofloxacin, vancomycin, trimethoprim (+ sulfamethoxazole); fibric acid derivatives (e.g. bezafibrate, fenofibrate); NSAIDs (including diclofenac, naproxen, sulindac); melphalan, histamine H2-receptor antagonists (e.g. cimetidine, ranitidine), methotrexate.

The dosage of statins needs to be decreased when treatment with cyclosporine is started, because of a possible increase in plasma concentration of statins.[17]

Escape medication

In case of an exacerbation or postponed treatment effect, patients are allowed to receive a maximum of 3 courses of rescue medication: mometasone furoate once daily for 1 week, with a maximum application of one FTU for each hand daily.[19]

Outcome measures

Primary outcome measure

Severity of hand eczema

The PGA, based on a validated Photoguide developed by Coenraads et al, covers 5 degrees of severity (clear, almost clear, moderate, severe, very severe) and takes into account the intensity of clinical signs and percentage of hand surface involved.[14] Response to treatment is defined as an improvement of ≥ 2 steps on the PGA. Very severe hand eczema is defined as responding to treatment if a status of at least 'moderate' is achieved. Severe hand eczema is defined as responding to treatment if a status of at least 'almost clear' is achieved.

In this study the main endpoint is the between-group difference in response to treatment between baseline and 24 weeks of treatment.

Secondary outcome measures

Severity of hand eczema

- Between-group difference in response to treatment between baseline and 12 weeks of treatment.
- Between-group difference in mean change between baseline and week 4, 8, 12 and 24, assessed by the Hand Eczema Severity Index (HECSI) score.[20] The HECSI is an objective severity assessment based on clinical symptoms only. It includes erythema, fissures, vesicles, scaling, oedema, papules and measurement of the affected area. The score ranges from 0-360, with a score > 28 indicating severe hand eczema.
- Between-group difference in time to response (time to first PGA improvement of ≥ 2 steps). This is only measured at control visits so possible outcome is limited to 4, 8, 12 and 24 weeks. This will be corrected using statistical methods (see statistical paragraph).

Patient reported outcome measures (PROMs):

Quality of life

- Between-group mean change in quality of life between baseline and 12 and 24 weeks, assessed by the Quality Of Life in Hand Eczema Questionnaire (QOLHEQ). The QOLHEQ is a multi-domain disease specific instrument for hand eczema assessing impairments in quality of life. The score ranges from 0-120, with 120 indicating worst quality of life.[21, 22]

Patient reported improvement

- Between-group difference in patients reporting improvement as 'clear or almost clear' compared to baseline at week 12 and 24, assessed by Patient Global Assessment (PaGA). The PaGA takes signs and symptoms into account. It covers 6 degrees of improvement: 'clear or almost clear' (at least 90% clearing of disease signs and symptoms compared to baseline), 'marked improvement' (at least 75% clearing), 'moderate improvement' (at least 50% clearing), 'mild improvement' (at least 25% clearing), 'no change', or 'worsening'.[6]

Safety and tolerability

- Adverse events in both groups will be registered.

Cost-utility and cost-effectiveness

- Between-group difference in mean Quality Adjusted Life Years (QALYs) will be measured by the EQ-5D-5L score at baseline, week 12 and week 24. The EQ-5D-5L is a measure for Health Related Quality of Life (HRQoL) and utility values. The EQ-5D-5L questionnaire includes a descriptive system, which comprises 5 dimensions of health: mobility, self-care, usual

activities, pain/discomfort, and anxiety/depression. Moreover, it includes a visual analog scale (VAS), which records the respondent's self-rated health status on a graduated (0–100) scale.[23]

- Direct medical costs will be determined using standardized prices for consultation, treatment (medication; alitretinoin or cyclosporine, topical treatment with corticosteroids and emollients, if necessary oral or topical treatment with antibiotics), diagnostic tests, laboratory measurements, visits to the general practitioner for hand eczema and hospital admissions (inpatient and/or daycare). Included patients will be asked to keep track of how much they spend on over-the-counter medication and other products for their hand eczema (out-of-pocket costs). Direct non-medical costs, consisting of travel costs, will be determined using average travel costs to the hospital as determined by relevant Dutch guidelines on cost-studies in healthcare.[24, 25]
- Indirect costs, consisting mainly of productivity loss, will be also be calculated using tables from the guidelines with average income of Dutch workers stratified by age and gender, corrected for shift working / irregular working hours.[24]

Other study parameters

These comprise the following parameters: age, sex, body-mass-index, current and/or previous atopic dermatitis (both defined by U.K. Working Party criteria)[26], age of onset of atopic dermatitis, age of onset of hand eczema, work/activities (based on risk professions as named in the European Guideline on hand eczema)[4], current use of statins, current use of thyromimetics, currently smoking and amount of pack-years will be registered. Pack years are calculated by multiplying the total years smoked with the average packs per day smoked over these years.[27] For this, the online Smoking Pack Years Calculator, created by dr NJ Masters and C Tutt, will be used.[28]

Study procedures and overview

Procedures part of standard medical treatment

According to daily practice, a detailed patient history is obtained of all newly referred patients with hand eczema and they are planned for patch testing to exclude contact allergy. During this first period, patients are treated with topical corticosteroids and emollients. A structured education program by a nurse on provoking factors and treatment is provided. If a relevant contact allergy is

ruled out and the hand eczema proves to be refractory to topical therapy and/or UV therapy, the next step is systemic therapy. These patients are a candidate for the current study if they are diagnosed with severe or very severe recurrent vesicular hand eczema.

Laboratory analysis is performed to verify contra-indications for alitretinoin or cyclosporine. During therapy, standard monitoring of blood values is carried out, according to SPC texts and current guidelines. At every visit, the PGA for severity is determined and the hand eczema is scored using the HECSI, corresponding to daily practice. Furthermore, health related quality of life is scored with a Dutch version of the QOLHEQ at the start of therapy, at week 12 and week 24.

Standard laboratory tests to be performed include:
Alitretinoin: at week 0, 4, 8, 12 and 24, laboratory tests are carried out, including: full blood count, ASAT, ALAT, ALP, γ-GT, serum creatinine, cholesterol, triglycerides, HDL, TSH, T4 and glucose. Also, a urine pregnancy test will be carried out.
Cyclosporine: at week 0, 4, and 12 laboratory tests are carried out, including: full blood count, potassium, magnesium, ASAT, ALAT, ALP, γ-GT, bilirubin, LDH, albumin, serum creatinine, uric acid, cholesterol and triglycerides.
At week 4 and 12, cyclosporine trough levels will be determined.
At week 8 and 24, serum creatinine will be determined.

Procedures extra for this study

Patients will be given one week to consider participation. Due to this, a maximum of one extra visit is needed to randomize the patient and obtain baseline data. The PaGA one-item questionnaire will be obtained at week 12 and 24. This procedure is only extra in terms of obtaining a quantitative assessment of the qualitative report that a patient provides in daily practice.

Patients will be asked to keep track of out-of-pocket costs on products for their hand eczema. During each visit, patients will be asked for direct and indirect medical and non-medical costs. Furthermore, the EQ-5D-5L questionnaire is obtained at week 0, 12 and 24, which is extra compared to daily practice.

Serum Thymus and Activation-Regulated Chemokine (TARC / CCL17) will be determined at all visits to study whether this chemokine is a suitable biomarker for hand eczema severity and/or disease activity over time.

No diagnostic procedures or other treatments will be postponed for patients participating in this study.

In Table 1, a systematic overview of the study is presented.

Table 1. Study schedule

Visit	V-1 Screening	V0 Baseline	V1	V2	V3	V4
Week	**-1**	**0**	**4**	**8**	**12**	**24**
Screening/baseline						
Check for clinical eligibility (inclusion/exclusion)	x					
Sign informed consent	x					
Randomization		x				
Baseline data / demographics / medical history / baseline costs		x				
Laboratory exclusion criteria post randomization		x				
Start medication		x				
Treatment						
Escape medication assessment			x	x	x	x
If applicable: dosage alteration assessment			x	x	x	x
Efficacy						
Severity scoring PGA / HECSI		x	x	x	x	x
Quality of life questionnaire QOLHEQ		x			x	x
PaGA of improvement					x	x
Costs						
Cost assessment		x	x	x	x	x
Cost-utility questionnaire EQ-5D-5L		x			x	x
Safety						
Lab control		x	x	x	x	x
Concomitant medication		x	x	x	x	x
Adverse events			x	x	x	x
Blood pressure measurement (cyclosporine only)		x	x	x	x	x
If applicable: premature withdrawal assessment		x	x	x	x	x

HECSI, Hand Eczema Severity Index; PaGA, Patient Global Assessment; PGA, Physician Global Assessment; QOLHEQ, Quality Of Life in Hand Eczema Questionnaire

Patients are permitted to deviate from the schedule with a maximum of 7 days during week 0-8. From week 9 a maximum deviation of 14 days is permitted.

Safety

Alitretinoin

Main risks in the alitretinoin group are[16]:

- Teratogenicity of the study drugs
- Occurrence of allergic / anaphylactic reactions
- Depression with anxiety, mood changes and suicidal tendencies
- Sunburn
- Xerostomia, xerosis cutis
- Keratoconjunctivitis sicca, keratitis, blurred (night) vision, cataract. Care must be taken when driving a vehicle or when operating machines.
- Myalgia, arthralgia, increase of CK values
- Exostosis, ankylosing spondylitis
- Headache
- Blushing
- Increase of cholesterol and triglycerides, with ultimately pancreatitis
- Decrease of TSH and T4
- Increased liver transaminases
- Decrease in effective dose of simvastatin
- Change at scarring or dermatitis during therapy and 6 months after in case of aggressive dermabrasion or epilation
- Anemia
- Epistaxis
- Alopecia
- Benign intracranial hypertension (rare and most seen in combination with tetracyclines)
- Inflammatory bowel disease (rare)
- Vasculitis (rare)

Alitretinoin is a derivative of vitamin A. Alitretinoin has been administered in oncological clinical studies at dosages of more than 10-times of the therapeutic dosage given for chronic hand eczema. The adverse effects observed were consistent with retinoid toxicity, and included severe headache, diarrhea, facial flushing, hypertriglyceridemia. These effects were reversible.

It can be concluded that the (reversible) effects can be properly managed.

Cyclosporine

Main risks in the cyclosporine group are[17]:

- Renal toxicity
- Hepatotoxicity
- Hypertension, flushing
- Nausea/vomiting, abdominal discomfort
- Headache
- Diarrhea
- Anemia, thrombocytopenia
- Leucopenia
- Hyperlipidemia
- Hyperkalemia, hypomagnesemia, hyperuricemia, hyperglycemia
- Tremor, convulsions, paresthesia
- Hirsutism/hypertrichosis
- Acne
- Myalgia
- Muscle cramps
- Tiredness
- Gynecomastia
- Occurrence of allergic / anaphylactic reactions
- Pre-existing infections may also be aggravated and reactivation of polyomavirus infections may lead to polyomavirus-associated nephropathy or to JC virus associated progressive multifocal leukopathy. Serious and/or fatal outcomes have been reported.
- Increase risk of lymphomas and other malignancies (mainly when combining multiple immunosuppressive drugs)
- Increase risk of infections
- Decreased effect of live vaccinations

Experience with acute overdosage of cyclosporine is limited. Oral doses of cyclosporine of up to 10 g (about 150 mg/kg) have been tolerated with relatively minor clinical consequences, such as vomiting, drowsiness, headache, tachycardia and in a few patients moderately severe, reversible impairment

of renal function. However, serious symptoms of intoxication have been reported following accidental parenteral overdosage with cyclosporine in premature neonates.

In all cases of overdosage, general supportive measures should be followed and symptomatic treatment applied. Forced emesis and gastric lavage may be of value within the first few hours after oral intake. Cyclosporine is not dialysable to any great extent, nor is it well cleared by charcoal hemoperfusion.

It can be concluded that the (reversible) effects can be properly managed.

Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for medical reasons. Specific criteria for withdrawal are:

- Evidence of pregnancy
- Occurrence of serious adverse events
- Lack of efficacy at 12 weeks, defined as no improvement assessed by the PGA (at least 1 step improvement is necessary to continue treatment after 12 weeks)
- Use of prohibited concomitant therapy, or a need for their use
- The need for more than 3 courses of rescue medication
- Anaphylactic reaction or other severe systemic reaction to study drug intake
- Diagnosis of malignancy during study, excluding non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix
- Any infection that is opportunistic and other infections whose nature or course may suggest an immunocompromised status
- Administration of a living vaccine
- Developing hypertension (minimally 3 measurements). Systolic pressure > 160 mmHg or diastolic pressure > 95 mmHg, despite starting anti-hypertensive medication.[15]
- Severe laboratory abnormalities including:
    - ALAT and/or ASAT values > 300% of the upper limit of normal
    - Triglycerides > 9 mmol/l
    - Creatinine increase of > 30%, despite dose reduction
- Intercurrent severe illness or major surgery
- Protocol violations or if the requirements of the protocol are not respected

- Patient lost to follow up

Serious adverse events and suspected unexpected serious adverse reactions

A serious adverse event (SAE) is any untoward medical occurrence or effect at any dose that:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;

Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

Unexpected adverse reactions are suspected unexpected serious adverse reactions (SUSARs) if the following three conditions are met:

1. the event must be serious (see SAE);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in the SPC texts.

Randomization, blinding and treatment allocation

Randomization is carried out by a computer program (ALEA, http://www.aleaclinical.eu). Patients will be randomly assigned in a 1:1 ratio to the two treatment arms. We will use block randomization with a random block size of 4 or 6 (random generated blocks). No stratification will be done. This is a study with blinded efficacy assessors, who are unaware of treatment allocation. The participants and treating physician will be aware of treatment allocation. Efficacy assessment will be carried out by one main blinded assessor and a second assessor in case the first assessor is unable to be present. These assessors are trained by the primary investigator and are experienced in assessing hand

eczema by PGA and HECSI in daily practice. The first assessor is expected to perform around 95% of all assessments. Blinding will be broken after analyzing the data.

Statistical analyses

Hypothesis and sample size calculation

This trial is designed to demonstrate a superior response to cyclosporine compared to alitretinoin in the treatment of severe recurrent vesicular hand eczema. Response to treatment is defined as an improvement of ≥ 2 steps on the PGA, based on a validated Photoguide developed by Coenraads et al [14] at 24 weeks of treatment. A sample size of 31 in each group will have 80% power to be able to reject the null hypothesis of no difference between alitretinoin and cyclosporine, using a χ^2 test with a two-sided 0.05 significance level. In this calculation we use the following assumptions: randomization ratio is 1:1, and we expect the percentage of responders in the alitretinoin group to be 33%.[6] From a retrospective study and other case studies we estimate 68% responders in the cyclosporine group.[7] We anticipate a drop-out of maximally 15% of randomized patients; a small percentage prior to first application of study drugs due to excluding laboratory measurements and a larger percentage during follow up, mainly due to subjective side effects. We therefore plan to include 72 patients in total, 36 in the alitretinoin group and 36 in the cyclosporine group.

This was calculated with the sample size calculator of the Department of Statistics, University of British Columbia, Canada, available at http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html.

For all analyses we will use Bonferroni adjustment if necessary.

Primary analysis

Severity of hand eczema

Between-group difference in response to treatment between baseline and 24 weeks of treatment. For comparison of proportions in the alitretinoin and cyclosporine group a χ^2 test, or Fisher's exact test if appropriate, will be used. Presenting the data as odds ratios derived from logistic regression analysis will be considered as an alternative reporting method.

Secondary analyses

Severity of hand eczema

- Between-group difference in response to treatment between baseline and 12 weeks of treatment. For comparison of proportions in the alitretinoin and cyclosporine group a χ^2 test will be used.
- Between-group difference in mean change between baseline and week 4, 8, 12 and 24, assessed by the HECSI score. This will be reported graphically. For comparison of mean change between the alitretinoin and cyclosporine group at week 12 and 24, the Student's t-test or Mann-Whitney U-test will be used, depending on distribution of data.
- Between-group difference in time to response (time to first PGA improvement of ≥ 2 steps compared to baseline). Because this outcome measure is interval-censored, the cumulative incidence of 'response' will be analyzed using of actuarial life table analysis and weighted log-rank tests for interval censored data; in particular the group proportional hazards model[29] and a generalized Wilcoxon-Mann-Whitney test[30], which emphasizes early events. The exact permutation value for the scores of the group proportional hazards model will be calculated, along with Wilcoxon-Mann-Whitney tests and the non-parametric maximum likelihood estimate of the survival distribution function.[31]

Patient reported outcome measures (PROMs):

Quality of life

- Between-group mean change in quality of life between baseline and 12 and 24 weeks, assessed by the QOLHEQ. Clinically relevant improvement is defined as an absolute improvement of 15 points (theoretically corresponding to an improvement of ≥ 1 point on 50% of the questions) compared to baseline. For comparison of proportions of patients rated as having clinically relevant improvement in the alitretinoin and cyclosporine group, a χ^2 test will be used.

Patient reported improvement

- Between-group difference in patients reporting improvement as 'clear or almost clear' at week 12 and 24, assessed PaGA. For comparison of proportions of patients rated as 'clear or almost clear' in the alitretinoin and cyclosporine group, a χ^2 test will be used.

Safety and tolerability

- Descriptive statistics will be used to present adverse events.

Cost-utility and cost-effectiveness

- For both groups (alitretinoin and cyclosporine), the mean EQ-5D scores overall and of each dimension will be reported. Results from the descriptive system of the EQ-5D-5L will be converted to a utility index value, a population based (social) value specific for the Netherlands. With this value, Dutch utility values will be calculated in order to determine the QALYs over the study period. Mean values of the EQ-VAS will be reported with a 95% confidence interval. For comparison of means, the Student's t-test or Mann-Whitney U-test will be used, depending on distribution of data.
- The incremental cost-effectiveness ratio (ICER) will be calculated and reported as €/QALY.
- A regression model will be used to estimate the association between QALYs and the PGA.

Handling of missing data

All analyses will be based on the intention-to-treat principle to guard against attrition bias. Subjects might not only want to withdraw because the study drug works insufficient, they might also want to withdraw when their hand eczema is cured.

Missing values will be handled in a way that is dependent on assumptions about the missing data. If the extent and pattern of missing data is known (e.g. missing at random (MAR), missing completely at random (MCAR), missing not at random (MNAR)), an analysis will be chosen that is valid under a plausible assumption about the missing data (probably mixed models). This is according to a strategy proposed by White et al.[32]

Data handling

Data will be handled confidentially. Data derived from the questionnaires and other paper source documents will be coded using sequential administration numbers. A subject identification code list is used to link the data to the subjects. The code is not based on the patient initials and birth-date. The code will be safeguarded by the principal investigator, dr. M.L.A. Schuttelaar. The documents will be stored in a locked room. The digital source data will be saved in subsections of the subjects medical file. These data will be accessible to the principal investigator and the investigator, and also to other treating physicians. Data will not be accessed by the blinded efficacy assessors. All data will be recorded in electronic Case Report Forms (eCRFs) in Utopia (software for Electronic Data Capture)

developed by the Trial Coordination Center, linked to the University Medical Center Groningen. The eCRFs will only be accessible with the username and password of the responsible investigator.

Data will be saved for 15 years after completion of this study.

All the data will be saved in accordance with the Dutch Personal Data Protection Act.

Monitoring

A certified monitor will carry out monitoring of this study. The monitor will get read-only access to the digital and paper documents of participants. Goal of this monitoring is to review if:

- the rights and wellbeing of subjects are being protected
- the reported data is right and fully reproducible
- the execution of the study is in accordance with this protocol and relevant legal requirements.

Data Safety Monitoring Board

No Data Safety Monitoring Board (DSMB) is established, since this study will be conducted corresponding to daily practice. In case of life-threatening diseases usually the implementation of a DSMB is indicated from an ethical point of view. But hand eczema is a non-critical indication. Frequent laboratory assessments will reduce the possibility of serious adverse events to a minimum. The patient population in this clinical trial exists of legal competent adults and the study drugs alitretinoin and cyclosporine are well-investigated, well-characterized drugs.

Patient and public involvement

In the Netherlands there is no patient association exclusively for hand eczema patients. However multiple patients with hand eczema are member of the association of atopic dermatitis patients ('De Vereniging voor Mensen met Constitutioneel Eczeem', www.vmce.nl). This association has 1500 members and a website with up to 2000 hits a day. One committee member and two patients from this organization contributed to our study design by participating in a focus session concerning all aspects of our study, but in particular Patient Reported Outcome Measures, logistics from a patient perspective and patient-friendliness of the study. These patients also participated in composing and

refining the patient information material. Before and after the study, the website and newsletter of the patient association is used to announce start (drawing attention to the study) and end (announce results) of the study.

ETHICS AND DISSEMINATION

Ethics

This protocol was reviewed and approved by the Medical Ethical Review Board of the University Medical Center Groningen (reference METc 2015/375). The study will be conducted according to the principles of the Declaration of Helsinki (Seventh revision, Fortaleza, Brazil, October 2013), in accordance with the Medical Research Involving Human Subjects Act (WMO), and also in accordance with the International Conference on Harmonisation Good Clinical Practice Guidelines (ICH-GCP).

In this trial both groups are treated with a drug, known to be beneficial to hand eczema in a considerable amount of patients. So the intended benefit of both study drugs is to reduce the severity of hand eczema.

We hypothesize that cyclosporine has a superior efficacy compared to alitretinoin in severe chronic recurrent vesicular hand eczema. If this hypothesis is confirmed, there could be a practical, as well as a financial implication. Practically, more responding patients to cyclosporine leads to a greater beneficial effect on hand eczema in this patient group. Financially, cyclosporine is a lot less expensive than alitretinoin. If cyclosporine shows superior efficacy in severe recurrent hand eczema, this could lead to an official registration. This, in turn, could mean a decrease in financial burden for the treatment of severe recurrent vesicular hand eczema patients in the population.

We deem the overall risks for patients participating in this study to be acceptable because of the tight inclusion and exclusion criteria (ensuring a relatively healthy study population), combined with regular laboratory assessments to enhance safety monitoring. Furthermore, prior experience with both study drugs in daily practice has improved our capability to manage risks. The remaining risk is therefore small and does not differ from regular daily practice.

Dissemination

The study is designed honouring the Centrale Commissie Mensgebonden Onderzoek (CCMO) statement on publication policy. The results will be made public unreservedly; they will be offered for publication in a peer reviewed journal. In a publication all data will be handled anonymously.

Acknowledgements

The authors would like to thank K.M. Vermeulen for her valuable contributions to the health economics component of this protocol and the patient advisors that contributed to the design of the study.

References

1 Thyssen JP, Johansen JD, Linneberg A, et al. The epidemiology of hand eczema in the general population--prevalence and main findings, *Contact Dermatitis* 2010;62:75-87.

2 Mortz CG, Bindslev-Jensen C, Andersen KE. Hand eczema in The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS): prevalence, incidence and risk factors from adolescence to adulthood, *Br J Dermatol* 2014;171:313-23.

3 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.

4 Diepgen TL, Andersen KE, Chosidow O, et al. Guidelines for diagnosis, prevention and treatment of hand eczema, *J Dtsch Dermatol Ges* 2015;13:e1-22.

5 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;140:1453-9.

6 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, *Br J Dermatol* 2008;158:808-17.

7 Christoffers WA, Politiek K, Coenraads PJ, et al. Drug survival of cyclosporine in the treatment of hand eczema: a multicentre, daily use study, *J Eur Acad Dermatol Venereol* 2016;30:63-6.

8 Reitamo S, Granlund H. Cyclosporin A in the treatment of chronic dermatitis of the hands, *Br J Dermatol* 1994;130:75-8.

9 Granlund H, Erkko P, Eriksson E, et al. Comparison of cyclosporine and topical betamethasone-17,21-dipropionate in the treatment of severe chronic hand eczema, *Acta Derm Venereol* 1996;76:371-6.

10 Granlund H, Erkko P, Reitamo S. Long-term follow-up of eczema patients treated with cyclosporine, *Acta Derm Venereol* 1998;78:40-3.

11 Schmitt J. Ciclosporin versus alitretinoin for severe atopic hand dermatitis (TocyDD). Last updated 2014; Available at: clinicaltrials.gov/show/NCT01231854. Last accessed 2017.

12 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;21:606-19.

13 Menné T, Johansen JD, Sommerlund M, et al. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema, *Contact Dermatitis* 2011;65:3-12.

14 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;152:296-301.

15 Nederlandse Vereniging voor Dermatologie en Venereologie. Richtlijn Constitutioneel eczeem 2006, Updated 2007.

16 Anonymous. SPC text alitretinoin. Last updated 2015; Available at: http://db.cbg-meb.nl/IB-teksten/h100957.pdf. Last accessed 2017.

17 Anonymous. SPC text cyclosporine. Last updated 2015; Available at: http://www.medicines.org.uk/emc/medicine/1307. Last accessed 2017.

18 Cai J, Huang Z, Yang G, et al. Comparing antihypertensive effect and plasma ciclosporin concentration between amlodipine and valsartan regimens in hypertensive renal transplant patients receiving ciclosporin therapy, *Am J Cardiovasc Drugs* 2011;11:401-9.

19 Long CC, Finlay AY. The finger-tip unit--a new practical measure, *Clin Exp Dermatol* 1991;16:444-7.

20 Held E, Skoet R, Johansen JD, et al. The hand eczema severity index (HECSI): a scoring system for clinical assessment of hand eczema. A study of inter- and intraobserver reliability, *Br J Dermatol* 2005;152:302-7.

21 Ofenloch RF, Weisshaar E, Dumke AK, et al. 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;171:304-12.

22 Ofenloch RF, Oosterhaven JAF, Susitaival P, et al. Cross-Cultural Validation of the Quality of Life in Hand Eczema Questionnaire (QOLHEQ), *J Invest Dermatol* 2017;137:1454-60.

23 Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L), *Qual Life Res* 2011;20:1727-36.

24 Hakkaart-van Roijen L, Tan S, Bouwmans C. Handleiding voor kostenonderzoek, methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. College voor zorgverzekeringen. Geactualiseerde versie 2010.

25 Politiek K, Oosterhaven JA, Vermeulen KM, et al. Systematic review of cost-of-illness studies in hand eczema, *Contact Dermatitis* 2016;75:67-76.

26 Williams HC, Burney PG, Pembroke AC, et al. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation, *Br J Dermatol* 1994;131:406-16.

27 Weintraub WS, Klein LW, Seelaus PA, et al. Importance of total life consumption of cigarettes as a risk factor for coronary artery disease, *Am J Cardiol* 1985;55:669-72.

28 Masters N, Tutt C. Smoking Pack Years Calculator. 2017; Available at: http://www.smokingpackyears.com. Last accessed 2017.

29 Finkelstein DM. A proportional hazards model for interval-censored failure time data, *Biometrics* 1986;42:845-54.

30 Fay MP. Rank invariant tests for interval censored data under the grouped continuous model, *Biometrics* 1996;52:811-22.

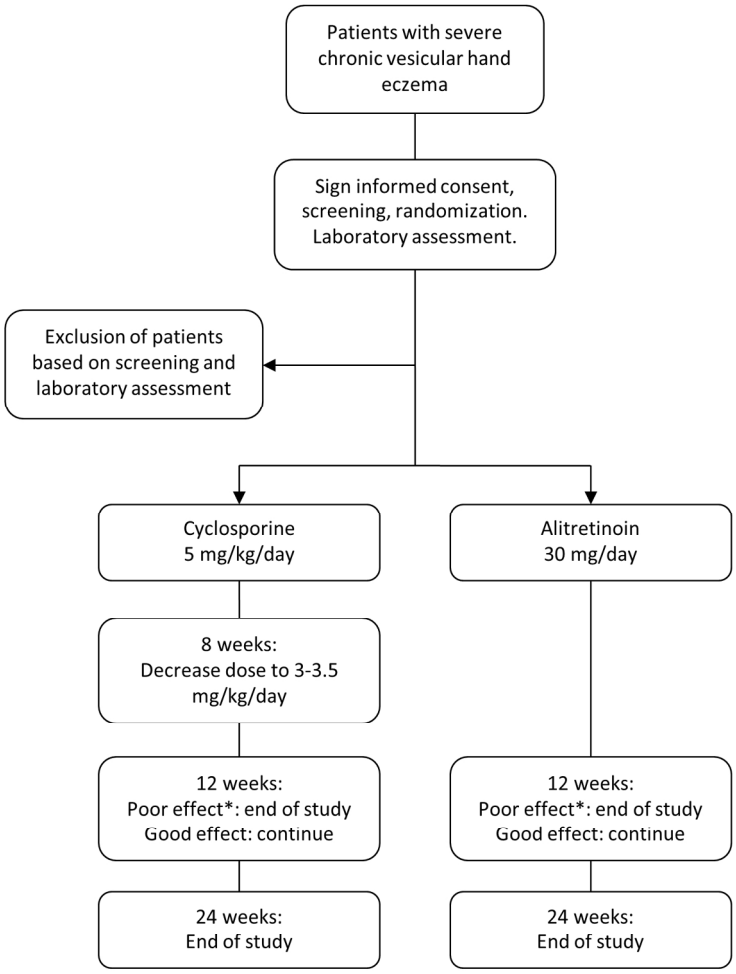
31 Fay MP. Interval: weighted logrank tests and NPMLE for interval censored data. R package version 0.1–1.1. 2014; Available at: https://cran.r-project.org/web/packages/interval/index.html. Last accessed 2017.

32 White IR, Horton NJ, Carpenter J, et al. Strategy for intention to treat analysis in randomised trials with missing outcome data, *BMJ* 2011;342:d40.

Figure legend

Figure 1. Study flow chart.

* Lack of efficacy defined as no improvement assessed by the Physician Global Assessment (Photoguide) (at least 1 step improvement is necessary to continue treatment after 12 weeks)



Study flow chart

165x174mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	Detailed within full protocol
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Not applicable
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not applicable

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5, 22
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	20-21
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Detailed within full protocol
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12-13
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	15-17 and Fig. 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	22
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	21
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	21, further detailed in protocol
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	21, further detailed in protocol
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	21, further detailed in protocol
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	21, further detailed in protocol
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Detailed within full protocol

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	24-25
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	22-24
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	22-24
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	24
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	25
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Detailed within full protocol
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Detailed within full protocol
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	1
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Detailed within full protocol

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	24-25, further detailed in protocol
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Detailed within full protocol
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Detailed within full protocol
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	26
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not detailed
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Detailed within full protocol
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	With Ethical Board application
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.