Hand eczema

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Chapter

3

Evidence based dermatology – Hand eczema

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Key points

There is insufficient evidence on which to base a choice between short bursts of potent topical corticosteroids compared with continuous application of mild corticosteroids.

- There is insufficient evidence for oral immunosuppressants as maintenance therapy.
- There is little evidence of a steroid-sparing effect of emollients, although these are widely prescribed.
- PUVA and UVB are effective, but there is no evidence of a clinical advantage of one modality over the other.
- Oral retinoids appear to be effective and well tolerated in hand eczema, especially in hyperkeratotic hand eczema.
- There is insufficient evidence of an additive effect of iontophoresis.
- There is insufficient evidence for a low-nickel diet or chelating agents in hand eczema accompanied by nickel allergy.
- There is insufficient evidence of an additive effect of topical antibacterial agents.
- There is insufficient evidence of the superiority of topical calcineurin inhibitors to topical corticosteroids.
- Education for secondary and tertiary prevention seems to be effective; however, long-term data are needed.

Introduction

Definition

The term "hand eczema" implies an inflammation of the skin (dermatitis) that is generally confined to the hands, but sometimes the feet are involved as well. Clinically, the condition is characterized by signs of redness, vesicles (tiny blisters), papules, edema, scaling, fissures (cracks), erosions, and hyperkeratosis (callus-like thickening), all of which may be present at different points in time (Fig. 1). Itch, sometimes severe, is a common feature. Fissures and blisters might be painful and impair manual work. Microscopically, the disease is characterized by spongiosis with varying degrees of acanthosis, and a superficial perivascular infiltrate of lymphocytes and histiocytes.

Incidence and prevalence

Hand eczema is considered a common condition, with a point prevalence of 1–5% among adults in the general population, and a 1-year prevalence of up to 10%, depending on whether the disease definition includes more pronounced or mild cases.[1] The prevalence may be higher in some countries. Hand eczema is twice as common in women as in men, with the highest prevalence in young women. The reasons for this sex difference are unknown, although greater exposure of women to wet work is probably contributory. Reliable data on the incidence are scarce, and are mainly confined to estimates in particular occupational groups. The incidence of notified work-related cases is between 0.7 and 1.5 cases per 1,000 workers per year with much higher annual incidences among high-risk occupations, such as bakers and hairdressers.[2]

Etiology

The etiology is multifactorial. Contact irritants are the commonest external causes. Hand eczema caused by such irritants, or mild toxic agents, is known as irritant contact dermatitis. Water is a contact irritant, and thus an external causal or contributing factor. Causal factors that are less common than irritants are contact allergens. Hand eczema caused by skin contact with allergens is called allergic contact dermatitis. Ingested allergens (for example, nickel) may also provoke hand eczema. Being atopic (to produce immunoglobulin E (IgE) antibodies in response to ordinary exposures to allergens, usually proteins and, as a consequence, the tendency to develop asthma, rhinoconjunctivitis, or eczema) is a major predisposing factor responsible for hand eczema. A combination of the above-mentioned factors appears to play a role in many patients.

Hand eczema can be classified by etiology: irritant contact dermatitis, allergic contact dermatitis, atopic hand eczema, protein contact dermatitis, or a combination of these types. A morphological classification of hand eczema is: vesicular hand eczema (dyshidrotic,

pompholyx), hyperkeratotic hand eczema, fingertip dermatitis (pulpitis), nummular hand eczema, interdigital eczema, and dry fissured hand eczema.

Prognosis

When there is a single, easily avoidable contact allergic factor, the prognosis is good. Several studies, however, have suggested that hand eczema tends to run a long-lasting and chronic relapsing course, probably because of the multifactorial origin.

Diagnostic tests

The diagnosis is mainly based on history and clinical signs; there are no standardized diagnostic criteria. Patients are patch-tested to detect or rule out a contact allergy. In addition, prick tests or determination of specific IgE are performed to detect atopy, and skin scrapings are performed to rule out a mycotic infection. In the majority of cases, no relevant contact allergy can be detected. Specific prick tests of specific IgE are of additional value only in very special cases (contact urticarial reactions that can become eczematous: protein contact dermatitis).
Differential diagnostic psoriasis, mycosis, lichen planus, scabies, granuloma annulare, herpes simplex, and artefacts might be considered.

Treatment

The treatment of hand eczema is aimed at reducing clinical symptoms (including the disabling itch), preventing relapses, and reducing the burden of disease by allowing the resumption of everyday manual tasks. The outcome of the treatment can be assessed in dif¬ferent ways. Relevant outcome parameters include:

- the percentage of patients reporting a good/excellent response;
- the percentage of patients with an investigator-reported good/ excellent response;
- reduction in severity (patient-rated and physician-rated scoring systems);
- dose reduction;
- time until relapse.

Objectives

In daily practice, we often ask ourselves what treatment would be best for the patient with hand eczema who is sitting in front of us. This usually involves a comparison between dif-ferent treatment modalities. Against this background, we formulated 14 clinically relevant questions. Because of the tendency of hand eczema to develop a chronic or relapsing course, all of the questions are concerned with chronic hand eczema. In the context of this chapter, chronicity can arbitrarily be defined as a duration of more than 6 months.

Methods of search

Controlled trials dating back to 1977 were located by searching the Skin Group Specialized Register, Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, and Embase in February 2013 for original articles in English, French, German, or Dutch. Uncontrolled trials were discarded, unless systematic reviews and controlled trials were lacking on a specific subject. Also, papers studying different dermatoses and not specifically stating the results for the patients with hand eczema were ignored. The questions were formulated before the search, and only papers pertaining to these questions were included.

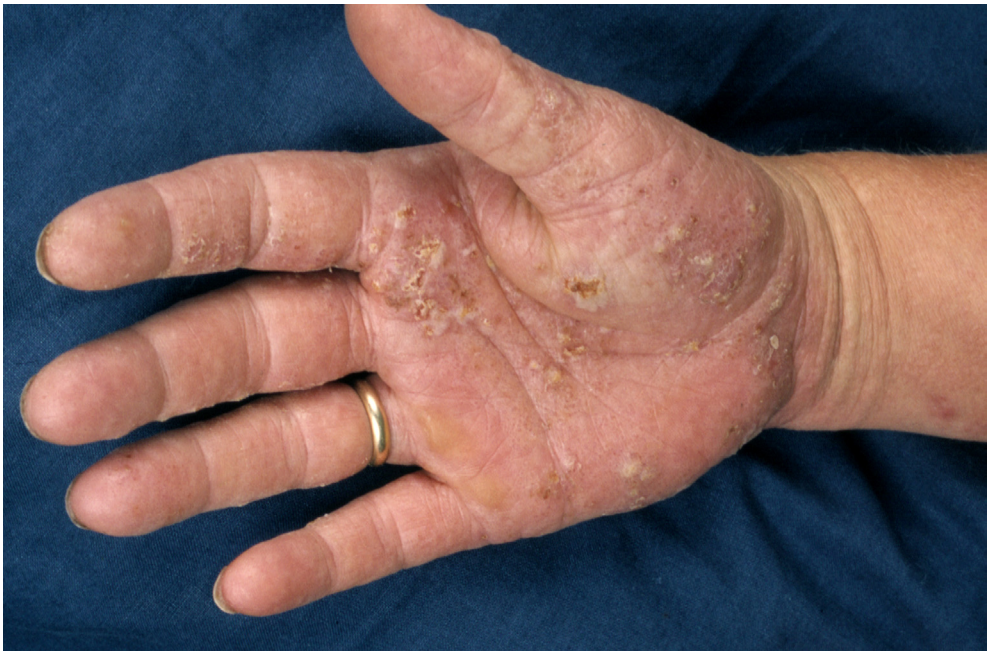

Fig. 1. Hand eczema: redness, erosions, and tiny blisters, accompanied by severe itching.

Questions

Because of the tendency of hand eczema to develop a chronic or relapsing course, all of the questions considered below deal with chronic hand eczema, arbitrarily defined as a duration of more than 6 months. Prescription of topical corticosteroids is at present the most common treatment; therefore, it is the major comparator in the questions listed below.

- In adults with chronic hand eczema, do topical coal-tar preparations lead to a better patient-rated or physician-rated reduction in symptom scores than topical corticosteroids?

- In adults with hyperkeratotic hand eczema, does dithranol lead to an improvement in patient-rated and physician-rated symptom scores and longer remission periods after clearance in comparison with topical corticosteroids?
- In adults with chronic hand eczema, do short bursts of potent topical corticosteroids (class 3 or 4) lead to better patient-rated or physician-rated symptom scores than continuous mild (class 1 or 2) topical steroids?
- In adults with chronic hand eczema, are oral immunosuppressive agents (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine) better in maintaining a long-term (more than 6 months) reduction of patient-rated or physician-rated symptom scores than topical corticosteroids?
- Is the treatment of chronic hand eczema with local psoralen– ultraviolet A (PUVA) or ultraviolet B (UVB) irradiation better in reducing patient-rated and physician-rated symptom scores than topical corticosteroids?
- In adults with chronic hand eczema, does treatment with PUVA irradiation (oral or topical psoralen) lead to a better reduction in patient-rated and physician-rated symptom scores and remission periods than UVB irradiation?
- In adults with chronic hand eczema, is oral treatment with retinoids better in terms of patient-rated and physician-rated symptom scores than topical corticosteroids?
- Is the treatment of chronic hand eczema with calcineurin inhibitors better in reducing patient-rated and physician-rated symptom scores than topical corticosteroids?
- In adults with dyshidrotic hand eczema, does iontophoresis lead to an improvement in patient-rated and physician-rated symptom scores in comparison with topical steroids or UVB/PUVA irradiation?
- In adults with relapsing vesicular hand eczema based on contact allergy to nickel, does dietary intervention or oral therapy with chelating agents lead to an improvement in patient-rated and physician-rated symptom scores in comparison with topical corticosteroids?
- Does the daily application of a bland emollient lead to dose reduction and/or frequency reduction of topical corticosteroids in adults with chronic hand eczema?
- In adults with chronic clinically active hand eczema, do protective or occlusive gloves or barrier creams lead to better patient-rated or physician-rated symptom scores than topical steroids?
- Does the addition of a topical antibacterial agent to topical corticosteroids result in better patient-rated or physician-rated symptom scores than topical corticosteroids alone?
- In patients with chronic hand eczema, is an educational intervention program effective for secondary and tertiary prevention on hand eczema compared with limited education as usual?

In adults with chronic hand eczema, do topical coal-tar preparations lead to a better patient-rated or physician-rated reduction in symptom scores than topical corticosteroids?

One clinical trial was identified on the effect of coal tar. Additional trials may be found in the older literature (pre-1977).

Efficacy

No systematic reviews were found.

Coal tar

In a self-controlled, randomized study, the efficacy of coal tar paste with zinc oxide paste was compared with betamethasone valerate 0.1% in 19 patients with a within-patient design. Coal tar gave significant improvement compared with baseline, but no significant difference was observed between the treatments.[3]

Drawbacks

Six participants dropped out because they experienced problems with wearing hand gloves (problems were not specified). One participant dropped out due to pompholyx as a result of contact allergy to 5% coal tar.

Comment

Small number of participants (n = 9) with relatively high drop-out rate (n = 7). The results are listed as overall mean scores and no exact data are given.

Implications for clinical practice

The scientific-based evidence for coal tar treatment is scarce; however, trials may be found in the earlier literature (pre-1977). Contrary to belief, coal tar is not associated with an increased risk of cancer.[4]

In adults with hyperkeratotic hand eczema, does dithranol lead to an improvement in patient-rated and physician-rated symptom scores and longer remission periods after clearance in comparison with topical corticosteroids?

No systematic reviews were found, and no trials (controlled or uncontrolled) of dithranol for any type of hand eczema were identified. Trials may be found in the earlier literature (pre-1977).

In adults with chronic hand eczema, do short bursts of potent topical corticosteroids (class 3 or 4) lead to better patient-rated or physician-rated symptom scores than continuous mild to moderate (class 1 or 2) topical steroids?

We found no studies comparing the effect of short bursts of strong (class 3 or 4) topical corticosteroids (for example, twice weekly, or at weekends only) with continuous application of milder (class 1 or 2) topical corticosteroids. One randomized controlled trial (RCT) compared thrice-weekly application versus weekend application of the same steroid, with limited evidence that the thrice-weekly application was better.

Efficacy

No systematic reviews were found.

Thrice-weekly versus weekend application

There is limited evidence of a preferential effect of thrice-weekly application of mometasone in a parallel group RCT with 106 participants in a 30-week maintenance phase (i.e., after induction of remission).[5]

Once-daily versus twice-daily application

In a controlled trial with once-daily halcinonide 0.1% versus twice-daily betamethasone dipropionate 0.05% both showed good efficacy in 53 participants during four weeks.[6] In half of the patients, once-daily halcinonide 0.1% was superior.

Two different concentrations

One left–right RCT of 2 weeks' duration comparing different concentrations of the same corticosteroid applied twice daily detected no difference in 46 participants.[2]

Class 2 versus class 3 corticosteroids

One RCT compared short-term (three weeks) application of fluprednidene acetate 0.1% cream (class 2) with betamethasone valerate 0.1% cream (class 3), both in a once-daily regimen in 76 participants.[7] There were no differences in the time to onset of effect or clinical efficacy.

Class 2 versus class 4 corticosteroids

In a double-blind left–right RCT with 61 participants, more patients remained free of relapses with clobetasol propionate than with fluprednidene acetate[8]. In addition, the time to relapse was longer with clobetasol propionate. Treatment initially and in case of recurrence was twice daily; in the maintenance phase, the application was twice weekly. The side effects were comparable between the two groups.

Drawbacks

Mild skin atrophy was reported in two studies.[5,8]

Comment

With the exception of the study on thrice-weekly versus weekend application, all of the studies were of short duration. The primary outcome was not always clearly stated, and some studies included patients in relapse. None of the studies investigated tachyphylaxis or atrophy. Earlier reports (pre-1977) may provide some insight into this issue.

Implications for clinical practice

The appropriate choice of an optimal topical steroid treatment schedule cannot be derived from the current literature on hand eczema trials. Evidence from studies on other eczematous diseases may have to be considered.

In adults with chronic hand eczema, are oral immunosuppressive agents (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine) better in maintaining a long-term (more than 6 months) reduction of patient-rated or physician-rated symptom scores than topical corticosteroids?

One RCT was identified, showing that cyclosporine was effective, but not significantly better in terms of clinical signs or quality of life. One RCT concluded that azathioprine is an effective adjunctive treatment option. We identified no RCTs studying other oral immunosuppressive agents.

Efficacy

No systematic review was found.

Cyclosporine versus topical betamethasone

An RCT compared cyclosporine with betamethasone dipropionate 0.05% twice daily in 41 participants.[9] The study had three phases, none of which showed a comparative advantage in terms of clinical signs, global assessment, or cumulative relapse rate. The first treatment phase was six weeks; the second and third amounted to 30 weeks.

Methotrexate

We identified no controlled trials. An uncontrolled case study showed low-dose methotrexate to be effective in five patients with recalcitrant palmoplantar pompholyx.[10]

Mycophenolate mofetil and azathioprine

We identified no controlled trials.

Azathioprine as adjunctive

One RCT compared the additional value of azathioprine to topical clobetasol propionate 0.05% cream with topical clobetasol propionate monotherapy in 108 patients with chronic hand eczema for 24 weeks.[11] This study reported a significant better improvement with regard to hand eczema severity index score and itch in the azathioprine group.

Drawbacks

Paresthesia ("tingling"), dizziness, facial edema, and increase in serum creatinine were reported during cyclosporine use. Surprisingly, no side effects were reported for azathioprine.

Comment

The comparator in the cyclosporine studies was a relatively strong corticosteroid.

Implications for clinical practice

Cyclosporine may be useful for achieving short-term control, but cannot be recommended for maintenance therapy. Long-term side effects such as blood dyscrasia, renal failure, increased blood pressure, and skin malignancies are of major concerns. Choices regarding systemic treatment of hand eczema cannot be derived from the current literature on hand eczema trials.

Is the treatment of chronic hand eczema with local psoralen+ultraviolet A or ultraviolet B irradiation better in reducing patient-rated and physician-rated symptom scores than topical corticosteroids?

We identified no trials explicitly comparing PUVA or UVB therapy with topical corticosteroids; only one RCT had ordinary topical treatment with emollients as the comparator. Several controlled trials were identified that compared the efficacy of PUVA, UVB, or UVA1 therapy with a control group or using a left–right design. There is insufficient evidence that PUVA or UVB therapy is more effective than conventional topical corticosteroid therapy.

Efficacy

No systematic reviews were found.

Topical psoralen+ultraviolet A

In a double-blind randomized within-patient trial of 15 patients with chronically relapsing vesicular hand eczema, topical PUVA and UVA treatment showed improvement of the severity score over the 8-week treatment period, but no statistical difference between the treated hands at any stage.[12] In a controlled clinical trial (CCT) with a left–right design, topical cream PUVA was compared with UVA1.[13] The study comprised 27 patients with

bilateral dyshidrotic hand eczema. Almost all patients showed a good response to both treatments, with a reduction of physician-rated scores of 50%. There were no statistically significant differences between the left and right hands. In an observer-blinded, left–right design, there was little difference between topical 8-methoxypsoralen (8-MOP) bath PUVA and topical 8-MOP lotion PUVA therapy in 24 patients with chronic hand or foot eczema; there was greater than 80% clearing with both modalities.[14] After one month, the most successful treatment was continued on both sides until the lesions cleared; there were no differences in the length of the relapse-free period. An open-label RCT with 158 participants showed that oral PUVA at home was equally effective as topical bath PUVA in the hospital.[15] In addition, it appeared to result in lower costs and less time off work. In a within-participant RCT with 15 participants, the effectiveness of middle-dose UVA1 irradiation was compared with topical cream PUVA therapy.[16] Treatment was given thrice weekly during a period of five weeks. Both groups improved, but there was no significant difference between the groups. An observer-blinded RCT in 29 participants showed no significant difference between topical and oral psoralen, although oral PUVA might be preferred in hyperkeratotic hand eczema.[17]

Ultraviolet A1

In a double-blind RCT with 28 patients with dyshidrotic hand eczema, five-times weekly irradiation with UVA1 was compared with placebo.[18] After 1 week of treatment, a significant difference was seen between the two groups, with greater efficacy for UVA1.

Ultraviolet B

Eighteen patients with chronic hand eczema resistant to potent topical corticosteroids were randomly divided into three treatment groups: UVB of the hands only, placebo irradiation, and whole-body UVB irradiation.[19] Local UVB irradiation of the hands was significantly better than placebo; whole-body UVB irradiation with additional irradiation of the hands was significantly better than continuing the local treatment alone (not specified), according to a simple clinical grading (cleared, improved, unchanged/worse). A 3-month follow-up period demonstrated fast relapse of the hand eczema. In an RCT with 48 patients with occupational hand eczema, UVB at home 5 days a week for 8 weeks was compared with nonspecific topical treatment.[20] Physician-rated scores and transepidermal water loss improved in both groups, although the improvement did not reach statistical significance for most parameters.

Drawbacks

Ultraviolet therapy can cause side effects such as burning episodes, subacute eczema, patchy hypopigmentation, and acute exacerbation of eczema. It may also induce skin cancer as a long-term effect.

Comment

In some studies, patients continued their topical medication or emollients. There are no studies comparing PUVA, UVA1, or UVB therapy with the conventional topical corticosteroid therapy. There is also no evidence that ultraviolet therapy is the most effective for hand eczema (see the next question).

Implications for clinical practice

PUVA and UVB are effective; UVA1 also appears to be effective. The choice of these treatment options is guided by considerations other than proven clinical superiority over other modalities.

In adults with chronic hand eczema, does treatment with psoralen+ultraviolet A irradiation (oral or topical psoralen) lead to a better reduction in patient-rated and physician-rated symptom scores and remission periods than ultraviolet B irradiation?

We identified two RCTs on oral PUVA and two CCTs on oral/topical PUVA. The controlled trial on topical bath PUVA demonstrated no comparative advantage, whereas the RCT on oral PUVA showed an effect in favor of PUVA.

Efficacy

No systematic review was found.

Topical bath psoralen+ultraviolet A versus ultraviolet B

A 6-week left–right design CCT including 13 patients showed that, although effective, topical bath PUVA was not better than UVB.[21]

Oral psoralen+ultraviolet A versus ultraviolet B

An RCT showed an effect in favor of oral PUVA in a 3-month study of 35 patients. In this study, only one hand was treated, but in most patients the untreated hand also improved.[22] In a 9-week RCT with left–right design, 15 patients were treated with local narrowband UVB or PUVA thrice a week. Both groups showed significant improvement compared with baseline and a local narrowband UVB phototherapy regimen is as effective as PUVA therapy in patients with chronic hand eczema of dry and dyshidrotic types.[23] A CCT comparing UVB used at home with PUVA at the clinic in 26 patients during approximately 10 weeks, showed no compara¬tive advantage.[24]

Drawbacks

Nausea caused by the oral psoralen was reported. Pain, burning, itching, and redness were

reported with both therapies, but slightly more from PUVA irradiation. In both PUVA and UVB, mild xerosis was reported, which responded to emollients.

Comment

Long-term adverse effects could not be assessed. Improvement of the untreated hand may be the result of compliance with topical emollients. More than 17 uncontrolled studies were identified, claiming a beneficial effect of ultraviolet treatment (PUVA or UVB), but there was no comparator in any of the studies.

Implications for clinical practice

PUVA or UVB is effective in treating hand eczema. The question of which modality is better remains unsolved.

In adults with chronic hand eczema, is oral treatment with retinoids better in terms of patient-rated and physician-rated symptom scores than topical corticosteroids?

We identified several trials on the use of retinoids in hand eczema; there were no trials comparing oral retinoids with corticosteroids. Both topical and oral treatment with retinoids appeared to be effective.

Efficacy

No systematic reviews were found.

Topical retinoid versus topical corticosteroids

In a symmetrical double-blind nonrandomized study, the efficacy of triamcinolone acetonide 0.1% cream was compared with the same cream containing, in addition, 0.25% retinoic acid.[25] The study included 18 patients with different types of eczema (12 with atopic dermatitis, four with allergic contact dermatitis, one with nummular eczema, and one with dyshidrosis); the palms and soles were involved in only five patients. The duration of treatment was planned for 2 weeks, with the option of extending the treatment to 3 weeks. No statistically significant differences were observed between the treatments. An open-label RCT with 55 patients compared bexarotene gel monotherapy (ligand for retinoid X receptors) with the same gel in combination with either mometasone furoate 0.1% ointment or with hydrocortisone acetonide 1% ointment.[26] The steroids were applied twice daily, whereas bexarotene gel was applied in an increasing regimen, starting at once every other day up to three times daily, unless adjustment was needed because of irritation. All groups showed a meaningful decrease in physician-rated scores, without significant differences between the groups.

Oral retinoids

An RCT including 29 patients with hyperkeratotic hand eczema compared once-daily 30 mg acitretin with placebo.[27] A significant improvement in comparison with the placebo group was seen in relation to hyperkeratosis, fissures, and scaling, but not in relation to itch, redness, or vesicles. The improvement occurred in the first four weeks, with no additional effect seen in the following four weeks. A multicenter, double-blind RCT assessed the efficacy of three different dosages of 9-cis-retinoic acid (alitretinoin) and placebo.[28] The 319 patients were equally randomized over four groups: oral alitretinoin 10 mg/day, 20 mg/day, 40 mg/day, and placebo. Alitretinoin led to a significant and dose-dependent improvement in the physician-rated score. In a large randomized trial alitretinoin (10 or 30 mg per day for up to 24 weeks) was superior to placebo in 1,032 patients with chronic severe hand eczema.[29] Of the patients treated with 30 mg alitretinoin, 40% rated their hand eczema as "clear" or "almost clear" at the end of therapy. In the 10 mg group this was 24% and in the placebo group 15%. In an extended open-label trial, 243 patients received 30 mg alitretinoin and the drugs remained well tolerated for overall treatment durations of up to 48 weeks.[30] In addition, the beneficial effects of alitretinoin over placebo were confirmed in a retreatment trial among a subgroup of 117 patients who had relapsed.[31]

Drawbacks

Topical use of retinoic acid plus corticosteroids is reported to cause significantly more subjective irritation than topical corticosteroids without retinoic acid.[25,26] Side effects of oral acitretin are common and almost all patients experience dry skin (especially the lips). The side effects were dose dependent; the most frequently reported were headache (14%, but this was also reported in the placebo group), mucocutaneous signs as dry lips (5%), and flushing (3%). Clinically insignificant increases in serum triglyceride, cholesterol, and creatinine kinase were reported in several trials on alitretinoin. Central hypothyroidism, with no clinical expression, was observed more rarely. Several papers studied the safety of oral alitretinoin, reporting comparable side effects.[32,33]

Comment

Oral 9-cis-retinioic acid appears to be a promising treatment option, but it remains to be demonstrated that this drug is more effective than conventional topical corticosteroids or UVB/PUVA therapy. In addition, evidence of the efficacy and safety of alitretinoin beyond 48 weeks and of the efficacy in vesicular hand eczema is lacking. A pregnancy prevention program is mandatory for women of fertile age because of the teratogenicity of oral retinoids.

Implications for clinical practice

Oral retinoids appear to be effective in hand eczema, especially in hyperkeratotic hand eczema. However, as there is no comparison with conventional therapy, it is unclear whether it should be a therapy of first choice.

Is the treatment of chronic hand eczema with calcineurin inhibitors better in reducing patient-rated and physician-rated symptom scores than topical corticosteroids?

Two RCTs were found that compared the efficacy of topical tacrolimus with mometasone furoate, which appeared to be equivalent and in two RCTs tacrolimus was significantly more effective than vehicle. Two RCTs compared topical pimecrolimus with vehicle cream.

Efficacy

No systematic reviews were found.

Tacrolimus

Sixteen patients were included in a left–right RCT comparing topical tacrolimus 0.1% ointment with mometasone furoate 0.1% ointment (a class III corticosteroid).[34] The treatment period was four weeks, with a follow-up period up to 8 weeks. Both treatments led to a statistically significant decrease in clinical severity, with no significant differences between the groups. In another RCT, topical tacrolimus 0.1% was compared with mometasone furoate in 30 patients for 90 days.[35] Both treatments showed similar therapeutic results. A randomized pilot study in 32 patients with moderate to severe hand eczema suggested that tacrolimus might prolong the time until relapse compared with vehicle cream during 14 weeks.[36] In an RCT, 28 participants with moderate to severe nickel sulfate-induced allergic hand eczema were treated with 0.1% tacrolimus ointment twice daily versus twice daily vehicle ointment during 14 days. The symptom scores were significantly lower in the tacrolimus group compared with the vehicle group during treatment and seven days afterwards.[37]

Pimecrolimus

In a multicenter RCT, 294 patients with hand eczema were allocated to up to 3 weeks' treatment with pimecrolimus 1% cream or to vehicle.[38] Twice-daily application of the study creams (evening application under occlusion) was continued until clearance or completion of three weeks' treatment. The efficacy of pimecrolimus 1% cream increased over time, while that of the vehicle stagnated after the second week. There were no statistically significant differences between the two groups, unless stratification for palmar involvement was applied; pimecrolimus 1% cream was superior in these patients. In a multicenter, double-blind, RCT 652 patients were treated for 6 weeks with pimecrolimus 1% or vehicle cream twice

daily with overnight occlusion, followed by a 6-week open-label pimecrolimus treatment.[39] There were no significant differences with regard to disease signs; however, pruritus relief was significantly better in the pimecrolimus group.

Drawbacks

Tacrolimus 0.1% ointment produced stinging upon application; with pimecrolimus 1% cream, however, this was uncommon (0.7% vs 2.1% in the vehicle group) or comparable to the vehicle cream.[39]

Comment

The effect of pimecrolimus 1% cream in comparison with the vehicle might have reached significance if the follow-up period had been longer, as the efficacy of pimecrolimus 1% cream increased over time. Pruritus relief was greater in the pimecrolimus group, but the other studies did not include patient-rated scores.

Implications for clinical practice

Topical tacrolimus is more effective than vehicles, but is at best equally effective as topical corticosteroids. Pimecrolimus is as effective as vehicles. With the present evidence, calcineurin inhibitors may be used for rotational therapy with topical corticosteroids, with potent corticosteroids for (severe) exacerbations and topical calcineurin inhibitors in the maintenance phase and for mild exacerbations.

In adults with dyshidrotic hand eczema, does iontophoresis lead to an improvement in patient-rated and physician-rated symptom scores in comparison with topical steroids or ultraviolet B/psoralen+ultraviolet A irradiation?

We identified only one RCT using iontophoresis in patients with dyshidrotic hand eczema, showing a significant improvement on the iontophoresis-treated side in comparison with the untreated side. We found no trials comparing iontophoresis with topical corticosteroids or UVB/PUVA therapy.

Efficacy

No systematic reviews were found.

Iontophoresis versus no treatment

In a randomized left–right comparison, the effects of tap-water iontophoresis in addition to steroid-free topical therapy were investigated in 20 patients with dyshidrotic hand eczema.[40] After three weeks (20 iontophoresis applications), the parameters "itching" and "vesicle for-

mations" scored significantly better on the iontophoresis-treated side than on the untreated side, but redness and desquamation did not differ significantly.

Drawbacks

Tap-water iontophoresis was always associated with subjective sensations such as stinging and discrete paresthesia ("tingling"). No severe side effects or possible harmful effects were reported.

Comment

We found insufficient evidence for the benefit of additional iontophoresis therapy in comparison with conventional corticosteroid or UVB/PUVA therapy.

Implications for clinical practice

Iontophoresis appears to be harmless, but has not been proved to be effective.

In adults with relapsing vesicular hand eczema based on contact allergy to nickel, does dietary intervention or oral therapy with chelating agents lead to an improvement in patient-rated and physician-rated symptom scores in comparison with topical corticosteroids?

We identified three small RCTs and one CCT. None of the studies compared the intervention with topical corticosteroids. An RCT on triethylenetetramine found no significant improvement of hand eczema. Another RCT, on tetraethylthiuram disulfide (disulfiram), found only very limited evidence in favor of this treatment. One controlled trial found no evidence that a low-nickel diet improves dyshidrotic hand eczema.

Efficacy

No systematic reviews were found.

Oral therapy with a nickel-chelating compound

In a multicenter, randomized, double-blind, crossover study, oral treatment with triethylenetetramine 300 mg daily for a 6-week period or placebo were given to 23 nickel-positive patients with chronic hand eczema.[41] No significant improvement occurred in hand eczema on the basis of either the patients' or the doctors' evaluations. The study was terminated prematurely because of literature reports on teratogenicity in rats. In a double-blind, placebo-controlled RCT, tetraethylthiuram disulfide at a gradually increased dosage was given for at least six weeks after the full dosage of 200 mg had been reached.[42] During the treatment period, the hand eczema healed in five of the 11 patients treated with tetraethylthiuram disulfide in comparison with two of 13 in the placebo group (not significant).

Using a semi quantitative scoring system, the results in favor of tetraethylthiuram disulfide were statistically significant for scaling and frequency of flares, but not for the sum of the parameters.

Low-nickel diet

In a nonrandomized trial including 24 patients with dyshidrotic hand eczema caused by nickel, the effects of a low-nickel diet for three months (eight patients) were compared with oral disodium cromoglycate for three months (nine patients) and with seven patients who did not give consent to the study and did not receive any treatment.[43] All 24 patients were evaluated blindly for itching and number of vesicles. The low-nickel diet did not lead to improvement in these patients, but those treated with disodium cromoglycate improved significantly and had fewer vesicles than the controls and the patients treated by diet.

Combination

A randomized placebo-controlled trial including 21 patients with chronic vesicular hand eczema with nickel sensitivity stated that the combination of low-nickel diet and short course of oral disulfiram therapy reduced severity of hand eczema statistically after four weeks.[44]

Drawbacks

One patient treated with disulfiram had toxic hepatitis after 8 weeks of treatment and two of 30 patients showed signs of hepatic toxicity.[42] Another RCT only noted slight, transient elevation of liver enzymes after four weeks.[44] The study on triethylenetetramine was ended prematurely due to a literature report on teratogenicity in rats.[41] No studies using a low-nickel diet assessed possible harmful effects.

Comment

None of the trials showed sufficient evidence for the benefit of either a low-nickel diet or a nickel-chelating compound. Only four CTs with small numbers of patients were carried out. On the basis of the harm and possible side effects, oral treatment with a nickel-chelating compound cannot be recommended. None of the trials compared treatments with conventional topical medication (for example, corticosteroids).

Implications for clinical practice

Given the side effects and the lack of efficacy, oral therapy with a nickel-chelating compound cannot be recommended. There is no evidence that a low-nickel diet improves pompholyx-type hand eczema.

Does the daily application of a bland emollient lead to dose reduction and/or frequency reduction of topical corticosteroids in adults with chronic hand eczema?

One RCT and two uncontrolled studies compared emollients with topical corticosteroids, showing better clinical assessments for emollients, albeit not significant.

Efficacy

No systematic review was found.

Emollient versus topical corticosteroids

A double-blind RCT of two weeks' duration compared twice-daily application of betamethasone valerate 0.1% with once daily application of betamethasone valerate 0.1% in addition to maintenance therapy with a 5% urea-containing moisturizer in 44 participants. Once-daily treatment combined with emollients showed a better clinical assessment (albeit not statistically significant) compared with twice-daily treatment, especially in the group of patients with a moderate eczema at inclusion.[45]

Versus each other

In one left–right RCT with 30 participants, using patient preference as the outcome parameter, there was limited evidence in favor of Aquacare-HP over Calmurid, both of which contain 10% urea.[46] An RCT in 32 participants confirmed that the frequent application of emollients resulted in better hand eczema scores.[47] However, a superior effect of emollient with ceramides versus a regular petrolatum-based emollient was not demonstrated.
This RCT showed that an emollient with ceramides was able to reduce the use of topical corticosteroids. The beneficial effect of emollients on hand eczema was also seen in a CCT comparing two bland emollients.[48] There was a decrease in transepidermal water loss, as well as an improvement in physician-rated and patient-rated severity scores. Uncontrolled studies noted a reduction in steroid use in patients treated with a moisturizing cream and in patients treated with a protective foam in 31 and 37 patients.[45,49]

Drawbacks

No major side effects were reported. Burning and worsening of the preexisting hand eczema were reported.[46] Patients were concerned about greasiness of their hands and with staining of objects they handled.

Comments

Several poor-quality uncontrolled studies were also identified, none of which had steroid dose reduction as the outcome parameter.

Implications for clinical practice

Despite the widespread use of emollients, there is only little evidence of any steroid-sparing or additive effect in the treatment of hand eczema. In general, there seems to be no harm either, apart from occasional contact allergy against an ingredient.

In adults with chronic clinically active hand eczema, do protective or occlusive gloves or barrier creams lead to better patient-rated or physician-rated symptom scores than topical steroids?

Information on avoidance of allergens or irritants on a case-by-case basis can be found in the major textbooks on contact dermatitis. The effect of emollients was covered in the previous question. One controlled trial on protective creams was found. We found a few uncontrolled, rather descriptive studies indicating some benefit of gloves and/or barrier creams, and one study used a within-patient left–right design.[50,51]

Efficacy

A number of issues in connection with this question are dealt with in a Cochrane systematic review on irritant hand eczema.[52] They concluded that industrial barrier creams may have a similar role as emollients in the prevention of occupational contact dermatitis; however, there is insufficient evidence that it has a long-term protective effect.

Barrier creams

In a randomized open trial in 53 patients a barrier-strengthening moisturizer (5% urea) seemed to prolong the disease-free interval in patients with controlled hand eczema compared with no treatment at all (20 vs 2 days).[53]

Comments

Protective gloves offer protection when manual (wet) tasks are performed; however, prolonged occlusion may be a risk factor for hand eczema.[54] Based on practical experience, supported by an experimental study on the healthy skin of volunteers, a cotton lining or inner glove is recommended.[55]

Implications for clinical practice

Insufficient evidence for long-term protective effect.

Does the addition of a topical antibacterial agent to topical corticosteroids result in better patient-rated or physician-rated symptom scores than topical corticosteroids alone?

No trials compared the additional effect of topical antibacterial agents with topical corticos-

teroids alone. Only one RCT comparing betamethasone cream with the addition of either fusidic acid or clioquinol was found, showing a similar effect on clinical severity.

Efficacy
No systematic reviews were found.

Addition of fusidic acid or clioquinol to betamethasone
In a multicenter open-label RCT with 120 patients, four weeks' twice-daily application of betamethasone 0.1% clioquinol 3% cream was compared with betamethasone 0.1% fusidic acid 2% cream.[56] The two preparations were equally effective in reducing the observer-rated severity score. However, the combination of betamethasone cream and fusidic acid produced a better bacteriological response.

Drawbacks
Betamethasone 0.1% fusidic acid 2% cream was considered more cosmetically acceptable than the preparation with clioquinol. The difference was statistically highly significant. Staining of the skin and clothing were the major problems.

Comment
Staphylococcal superantigens in infected areas elsewhere on the body, although the study protocol allowed them to be treated, might have had an effect on the hands.

Implications for clinical practice
There were no comparisons of a corticosteroid with a combination of corticosteroid and antibacterial agents. Evidence of an additional effect of antibacterial agents in patients with hand eczema is still lacking.

In patients with chronic hand eczema, is an educational intervention program effective for secondary and tertiary prevention on hand eczema compared with limited education as usual?

Several RCTs have been conducted on primary prevention, and a systematic review concluded that there is moderate evidence for the effectiveness of primary prevention programs. However, there is low evidence for the effect on improving clinical and self-reported outcomes.[57] We identified two RCTs, one CCT, and one controlled trial on secondary or tertiary prevention.

Efficacy

A Cochrane review concluded that, although the findings of the review were generally positive, there is insufficient evidence, at present, for the effectiveness of most of the treatments identified for primary prevention of occupation-induced hand eczema in the workplace.[52] No systematic reviews were identified on secondary or tertiary prevention.

Education programs

An RCT in 255 hospital workers with symptoms of hand eczema showed a beneficial effect of skin care education and individual counseling compared with care as usual (only topical steroids, emollients, and care by general practitioner) after six months.[58,59] In a CCT, 209 geriatric nurses with hand eczema received either care as usual by a dermatologist or a personalized secondary intervention program with education concerning barrier cream and gloves with lectures and hands-on training during four visits. After three months the hand eczema significantly improved in the intervention group. More nurses were able to continue their job because of the invention program compared with those without the program (96 vs 86%).[60] The Tertiary Individual Prevention study is a multicenter trial with an interdisciplinary, integrated inpatient rehabilitation measure with three weeks of inpatient treatment. The 1-year data from 1,617 individuals revealed a significant reduction in the severity of occupational skin diseases, the use of topical corticosteroids, and days of sick leave: 87.4% were able to return to work and to remain in the workforce.[61]

Integrated care

A multicenter RCT with 196 patients received usual care by a dermatologist or integrated care. The integrated care included allergo-dermatological evaluation by a dermatologist, occupational intervention by a clinical occupational physician, and counseling by a specialized nurse on optimizing topical treatment and skin care. After 26 weeks the intervention group scored significantly better on clinical effectiveness, but not on quality of life and days of sick leave.[62]

Drawbacks

Participation in the TIP study was voluntary, but patients were obliged to cooperate with the respective insurance organizations, which makes it difficult to compare this study with other countries.

Comment

In several studies, no comparator was used. It is difficult to compare different educational programs and to implement in daily practice. Three weeks of inpatient treatment might not be feasible in every setting.

Implications for clinical practice

Education and counseling seems to improve the effectiveness of hand eczema care and prevent relapse; however, long-term efficacy is still under investigation.

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chapter
3