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Update on Chronic Hand Eczema

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Introduction

Hand eczema is an inflammatory skin disease that often has a chronic course. Chronic hand eczema (CHE) is defined as eczema on the hands with a disease duration of longer than three months or two or more relapses per year.[1] During the COVID-19 pandemic, hand eczema gained attention due to the increased risk of developing particularly irritant contact dermatitis in the context of a change in hand hygiene habits and frequency of hand washing.[2]

This has once more highlighted how important skin protection continues to be for prevention of the disease. Beyond this, new and updated guidelines are available,[1,3] and a multitude of high-quality studies on hand eczema prevalence, pathogenesis and treatment have furthered our understanding of the disease and its management.

This article aims to provide an overview on recent information about hand eczema with a focus on epidemiology, quality of life, and new treatment options.

Epidemiology

Two recent systematic reviews and meta-analyses provide updated estimates on the prevalence and incidence of hand eczema in the general population[4] and in healthcare workers.[5] Their results show that healthcare workers are at a higher risk of developing hand eczema, with pooled lifetime (33.4%), 1-year (27.4%) and point prevalence (13.5%) numbers higher than the results in the general population (14.5%, 9.1%, 4.0%, respectively).[4,5] In addition, the incidence rate of hand eczema was found to be higher in healthcare workers with 34 cases/1000 person-years compared to 7.3 cases/1000 person-years in the general population.[4,5]

Knowledge about hand eczema in children and adolescents is limited, although many adult patients describe onset of their disease early in life. Pediatric hand eczema is common, although reports about frequency of hand eczema in children vary (lifetime prevalence: 6.5%–13.3%; 1-year prevalence 5.2%–10.0%).[6] Allergic contact dermatitis is a contributing factor in the development of pediatric hand eczema with the most commonly reported allergens being nickel, methylisothiazolinone, and methylchloroisothiazolinone.[6]

Sources of exposure specific for the young age group include toys, slime, and bubble solutions.

A recent study from Denmark explored hand eczema among 15-19-year olds and found point-prevalence in this cohort to be 4.9%, with 1-year prevalence of 12.1% and lifetime prevalence of 18.3%.[7] A total of 60.2% of the adolescents were working either part-time or full-time and 38.2% of the participants with hand eczema believe that occupational exposures were contributing to their skin disease.[7] Silverberg *et al* described sixfold higher odds of developing hand

	Mechanism of action	Route of administration
Delgocitinib	Pan-JAK inhibitor	Topical
Ruxolitinib	JAK 1/2 inhibitor	Topical
Dupilumab	IL-4/IL-13 inhibitor	Subcutaneous injection
Tralokinumab	IL-13 inhibitor	Subcutaneous injection
Upadacitinib	JAK 1 inhibitor	Oral
Gusacitinib	JAK/spleen tyrosine kinase (SYK) inhibitor	Oral

Table 1. Selection of treatments studied for hand eczema (not exhaustive); *courtesy of Sonja Molin, MD.*

eczema in children and adolescents in the context of employment.[8] These results emphasize the need for early promotion of skin care and protection to prevent development of eczema in young workers.

Impact on Quality of Life

Quality of life is significantly impacted by hand eczema, which is a result of limited hand function, visible skin lesions and associated stigma, and negative consequences of not being able to fully participate in life or work.

Several recent studies analyzed quality of life impairment in people living with hand eczema as well as the presence of anxiety and depression.[9-11] A Finnish study confirmed a significant association of (self-reported) hand eczema and symptoms of anxiety and depression in a working age general population cohort.[10] A study from Poland measured the quality of life impairment in 100 hand eczema patients using the Dermatology Life Quality Index (DLQI) and found a mean value of 11.62, which translates into "very large effect on patient's life".[11] The severity of anxiety and depression in patients was linked to hand eczema severity.[11] A nationwide cross-sectional study from Denmark sent questionnaires about hand eczema to a random sample of 100,000 adults. In a group of 2,176 respondents with current hand eczema, they observed moderate impairment in several domains of the questionnaire that was used (Quality Of Life in Hand Eczema Questionnaire, [QOLHEQ]) including symptoms, treatment, and prevention. The authors report that severe, chronic and work-related eczema, as well as female sex were strongly associated with moderate-to-severe impairment of quality of life.[9] The most bothersome symptoms related to hand eczema are itch and pain. Zalewski *et al* studied the prevalence and characteristics of itch in hand eczema patients, itching was reported by 81.0% of the participants and pain in 53.0% during the three days before the examination.[12] They found both itching and pain more frequently among female participants, and both correlated positively with the severity of hand eczema.[12] Treatment approaches for hand eczema need to target these key symptoms and ideally provide fast relief.

New Treatment Options for Hand Eczema

Traditional treatment of hand eczema included topical moisturizing creams, topical steroids and systemic agents for severe cases. With new therapeutic targets emerging, and some of the advanced therapies for atopic dermatitis (AD) starting to cross over for use in hand eczema it is likely that our approach to the management of the disease will change significantly in the nearer future. Interleukin (IL)-4/IL-13 inhibitors and Janus kinase (JAK) inhibitors are two classes of drugs emerging for the treatment of CHE. The following paragraph highlights some of the newer data relevant for management of hand eczema without raising the claim of completeness. It will discuss delgocitinib, dupilumab and upadacitinib in more detail. More compounds are currently in clinical development for hand eczema and further results are to be expected (**Table 1**).

Topical treatment options for hand eczema are limited and topical corticosteroids (TCS) are still considered the gold standard for management of flares. Long-term use of TCS is limited by their safety profile.[13] A recent study from Denmark reported that in their cohort, 76.4% of hand eczema patients would prefer a nonsteroidal topical treatment.[14] Steroid fatigue is common in patients with chronic inflammatory skin diseases and these results emphasize the need for steroid-free treatment options to broaden the therapeutic armamentarium.

The topical pan-JAK inhibitor delgocitinib is currently being studied for hand eczema. Its Phase 3 clinical trial program has been completed and the regulatory approval process is underway in several countries. The role of JAK inhibitors in the development of hand eczema is not yet fully understood. They are relevant in immune cell signalling and activation of

keratinocytes and the skin's inflammatory response.[13] It was reported that topical delgocitinib application may contribute to improvement of skin barrier function by suppressing STAT3 activation and the subsequent increase in levels of barrier proteins like filaggrin.[15]

In a pooled data analysis from the Phase 3 trials with twice daily application of delgocitinib cream 20 mg/g compared to cream vehicle in adults with moderate to severe CHE, a greater proportion of delgocitinib-treated patients achieved treatment success (IGA [Investigator's global assessment] -CHE score of 0 or 1 with an improvement of at least 2 points from baseline) versus cream vehicle at week 16 (24.3% vs 8.4%; P<0.001). For the evaluation of these results, it is important to know that 'clear/almost clear' would only allow for no/barely perceptible erythema and no other signs of hand eczema.[16]

Adverse events leading to treatment discontinuation were reported in 0.5% of delgocitinib-treated patients compared to 3.4% in the cream vehicle group. The most frequent adverse events (≥ 2% in any treatment group) were COVID-19 infection (delgocitinib: 11.1%, vehicle cream: 10.6%) and nasopharyngitis (delgocitinib: 6.9%, vehicle cream: 7.5%).[16]

The reported serious adverse events (delgocitinib: 1.7%, vehicle cream: 1.9%) were all assessed as unrelated to the study drug. No adverse events of special interest (ie. eczema herpeticum, deep vein thrombosis, or pulmonary embolism) were observed, with no changes or differences of clinical relevance between treatment groups in laboratory parameters, vital signs, or electrocardiogram.[16] The pooled data analysis showed statistically significant improvement in health-related quality of life measured by DLQI and EQ5-D (EuroQol-5 Dimension) in patients treated with delgocitinib compared to cream vehicle.[17,18] A significant mean reduction in itch was detected 1 day after the first application of delgocitinib cream and for pain 3 days after the first application of delgocitinib cream.[19]

Moderate and severe hand eczema can be challenging to treat and might require systemic treatment. Recent data on systemic treatments used for AD like IL-4/IL-13 inhibitors and oral JAK inhibitors confirms their potential for use in patients with hand eczema. IL-4/IL-13 inhibition moderates the TH2 response to improve pruritic immune-mediated inflammatory skin diseases and has been shown to be effective in AD.[13] A recent Phase 3 multicentre trial studied dupilumab in adult and adolescent patients with atopic hand and foot dermatitis compared to placebo.[20] The mean duration of atopic hand/foot dermatitis in all participants (n=133) was 15.6 years. This underlines how long-lasting the course of the disease is for many patients. At Week 16, a significant number of patients reached the primary endpoint (HF [hand foot]-IGA 0/1) with dupilumab (40.3%) compared to placebo (16.7%).[20] The adverse events and safety profile were consistent with those of previous reports on the use of dupilumab in AD.[20]

Treatment of patients with atopic hand eczema with the selective JAK1 inhibitor upadacitinib at a daily dose of 15 mg or 30 mg compared to placebo was studied over 16 weeks in the context of two Phase 3 multicentre trials.[21] Efficacy was measured by change in the Hand Eczema Severity Index (HECSI). A 75% or greater HECSI improvement was observed in both dosing groups compared to placebo, with short timelines and maximum improvement already achieved after 4 weeks.[21] The adverse event and safety profile were consistent with those of previous reports on the use of upadacitinib in AD.[21]

Perspective

Chronic hand eczema continues to be a bothersome disease with significant impact on patients' quality of life and work productivity, and effective treatment options are needed to expand our therapeutic armamentarium. New treatments are emerging that will likely change our approach to the disease and allow the clinician to move away from the topical steroid-only approach.

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