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REVIEW

Chronic Hand Eczema (CHE): A Narrative Review

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ABSTRACT

Chronic hand eczema (CHE) is a common and challenging skin condition, characterized by persistent hand dermatitis which lasts over 3 months or recurs at least twice a year. This condition is often multifactorial, involving genetic predispositions, environmental factors and triggers, such as irritants and allergens. Studies show a higher incidence in women, though prevalence estimates vary across different age groups. The pathogenesis involves complex immune mechanisms, particularly Th1/Th2 cell responses. Clinically, CHE presents in various forms, with symptoms such as redness, scaling and itching that significantly impact patients' quality of life. Treatment approaches are diverse. While emollients and topical corticosteroids have historically been the mainstay, new systemic therapies like JAK inhibitors and biologics are progressively being used for severe cases. Key molecular targets comprise interleukin (IL)-4 and IL-13, the JAK-STAT pathway, phosphodiesterase 4 (PDE4) and chemoattractant chemokines. Managing CHE effectively remains a challenge because of its chronicity and the variability in individual responses to treatment. However, emerging therapeutic strategies will help clinicians to offer more patient-centred approaches.

Keywords: Chronic hand eczema; Therapeutics; Atopic dermatitis; Hand dermatitis

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Key Summary Points
Chronic hand eczema (CHE) is defined as hand dermatitis lasting more than 3 months or occurring at least twice per year.
CHE has a great negative impact on patients' quality of life, especially work-related.
Conventional treatments include emollients and topical corticosteroids which often fail, or systemic treatments which come with a range of adverse events.
Emerging therapies targeting specific immune pathways of hand eczema include JAK inhibitors and biologics, which have increased efficacy and a higher safety profile.

INTRODUCTION

Chronic hand eczema (CHE) is a common skin disorder which often represents a challenge for both the patient and the clinician. The diagnosis is established on the basis of the persistence of hand dermatitis lasting for more than 3 months or causing at least two flares in a year. From a pathophysiological perspective, CHE is often multifactorial, with the clinical phenotype resulting from the interplay of various factors, including genetic predisposition, environmental factors and triggers, both allergic and irritant. A predominant role in the pathogenic cascade underlying CHE is played by Th1 and Th2 responses. It is possible to distinguish various clinical phenotypes of the disease. This subdivision reflects different sensitivities to the available therapies as well. For years, the mainstay of therapy has been represented by emollients and topical steroids. Recently, the introduction of an increasing number of drugs has significantly enriched the therapeutic arsenal available to clinicians. In this review, we aim to illustrate the different therapeutic strategies that clinicians have to manage this often-recalcitrant condition. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

EPIDEMIOLOGY

The incidence and prevalence rates of hand eczema (HE) are predominantly derived from Scandinavian studies and self-reported data collected via questionnaires. The Nordic Occupational Skin Questionnaire (NOSQ-2002) was developed by a Scandinavian team in 2002 to facilitate the collection of self-reported data on HE through straightforward questions, which have been validated in several studies [1]. According to these questionnaires, the incidence rates of HE ranges from 5.5 to 8.8 cases per 1000 person-years. The incidence rate is similar between adults and adolescents [2]. Although HE is rarely studied in the latter category and children, the 1-year prevalence can be estimated at between 5.2% and 10% [3]. The data also indicate that the incidence rate of HE is higher in women (7.1 per 1000 person-years) compared to men (4.0 cases per 1000 person-years), probably as a result of occupational exposure [4]. Although this gender difference disappears after the age of 30.

In terms of prevalence, Swedish population-based data from 1996 reported a 1-year prevalence of 9.7%, while a recent Norwegian study found a lifetime prevalence of 11.3% [2].

For what concerns the paediatric population, the 1-year prevalence from Scandinavian school children aged between 12 and 16 years old was 7%, while for adolescents aged between 16 and 19 years it was 10% [5].

A 2021 meta-analysis comprising 568,100 individuals demonstrated a lifetime prevalence of 14.5%, a 1-year prevalence of 9.1% and a point prevalence of 4% of HE in the general population [6]. This study also showed that approximately one third of patients suffered from a moderate to severe disease and a history of atopic dermatitis (AD).

PATHOGENESIS AND ETIOLOGY

CHE results from a complex interaction between genetic predisposition and exposome, both environmental and occupational. Moreover, epidermal barrier dysfunction is a key feature, translating into augmented transepithelial water loss (TEWL) and increased skin sensitivity [7]. The primary triggers for CHE include atopic predisposition, contact allergies, and irritants. However, it is often difficult to establish which etiological factor plays the most important role in the development of this condition. Indeed, irritative contact dermatitis (ICD) and allergic contact dermatitis (ACD) are often found to coexist together with an atopic substrate [8].

When it comes to genetics, mutations in certain genes, particularly the filaggrin (*FLG*) gene, are associated with increased susceptibility to CHE, especially in individuals with atopic conditions such as AD, allergic rhinitis and asthma [9]. However, it is worth highlighting that loss-of-function (LoF) mutations in the *FLG* gene do not seem to be associated with CHE in adults without atopic dermatitis [10].

Furthermore, it is well known that some lifestyle factors can impact significantly the severity of HE. For instance, in a prospective study performed by Brans and colleagues, smoking emerges as an important aggravating factor of CHE in an occupational setting, both conferring a bad prognosis and interfering with the outcome of prevention programs [11]. On the other hand, no conclusive nor convincing evidence was found regarding other lifestyle factors, such as body mass index (BMI), physical activity and alcohol consumption [12].

It is relatively easy to define CHE from a temporal perspective. Indeed, it can be defined as a dermatitis that persists more than 3 months and/or relapses at least twice per year [13].

However, it is often complex to classify HE. Different classifications have been proposed. Recent approaches rely on etiological factors or clinical subtypes. The latest European guidelines suggest distinguishing between ACD, ICD, protein contact dermatitis/contact urticaria and atopic HE on an etiological basis [14]. Regarding clinical features, the same guidelines propose to differentiate between acute recurrent vesicular HE, hyperkeratotic HE, nummular HE, and pulpitis [13]. Another factor complicates this matter: indeed, two or more diagnoses can coexist, and even the sub-diagnoses might change with time.

It is evident that CHE should be regarded more as a group of related conditions, rather than a single disease. This complexity reflects the immunological landscape which can underlie CHE. ICD is characterized by a predominance of the Th1/Th17 axes, which translates into activation of interleukin (IL)-1α, IL-1β, IL-8, tumour necrosis factor alpha (TNFα) and granulocyte–macrophage colony stimulating factor (GM-CSF) [15]. On the other hand, the immune signature of ACD varies according to the nature of allergens, as demonstrated by Dhingra and colleagues [16]. In particular, nickel showed preferential increase of Th1/interferon-γ (IFNγ) and activation of innate immunity, as a result of binding to Toll-like receptor (TLR)-4. Furthermore, this metal was demonstrated to induce significant polarization towards Th17 and Th22 phenotypes. By contrast, fragrances, and less significantly rubber, seem to elicit a Th2-biased response, with a minor but yet important contribution from Th17. In the skin of patients with AD there is overexpression of Th2 and Th22, which produce a great amount of IL-4, IL-5, and IL-13. The main effects of these cytokines consist in immunoglobulin class switch towards immunoglobulin (Ig) E and increased Th2 $CD4^+$ lymphocyte survival, besides a decrease of some antimicrobial peptides (AMPs), such as human cathelicidin peptide LL37 and human beta-defensin (HBD)-2 [13]. Lastly, from a structural perspective, skin in both AD and HE is characterized by defective production of ceramides, besides reduction in expression of enzymes that are involved in lipid metabolism. Lipid synthesis is also altered by cytokines, such as those released by Th2 and Th22 cells. Moreover, these lymphocyte subsets determine downregulation of tight junctions and inhibition of AMPs, thus compromising skin barrier function [17]. Hyperkeratosis is one of the key features of CHE, and it derives from the release by keratinocytes of cytokines such as TNFα [13]. Besides, epidermal proliferation is promoted by IL-17, produced by

both Th1 and Th2, through induction of IFNγ and IL-4 respectively [18].

In patients with an atopic diathesis, the Janus kinase (JAK) signalling pathways play an important role [7], as well as Th2-released IL-31, which is a major contributor to pruritus in this category [17].

CLINICAL PRESENTATION

As mentioned above, CHE is defined by more than 3 months persistence or by at least two relapses per year after its initial occurrence, and complete clearance between those relapses. The longer the eczema persists, the most likely it is to become chronic, even in those cases where the causative agents have been withdrawn. Histological findings include perivascular lymphocyte infiltrates in the upper dermis and sometimes also into the epidermis, and intercellular edema, spongiosis and parakeratosis in the epidermis.

Acutely, HE manifests with erythematous and oedematous lesions, with papules and vesicles, and less frequently also bullae. Chronically, the disease presents with crusts, lichenifcation, hyperkeratosis, scaling and fissures. The most common symptom in all kinds of CHE is pruritus, but its intensity and frequency can vary according to the different kinds of CHE, for example patients with atopic HE present higher itch sensation. Other symptoms are burning and stinging sensations that can lead to high levels of pain.

The most common manifestation sites of CHE are the palms (especially in atopic CHE) and the interdigital spaces, even though CHE can also manifest on the dorsal part of the hand and on the wrists. The clinical picture can vary over time despite the etiology remaining the same. The higher the diseased area extension, the worse the prognosis is [19].

According to a consensus-based recommendation from the European guideline on HE, hand eczema is divided into etiological subtypes and clinical subtypes. The etiological subtypes are irritative contact dermatitis (ICD), ACD, atopic HE and contact urticarial.

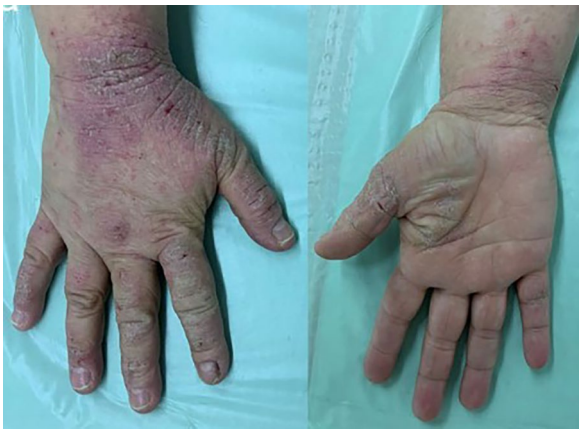

Fig. 1 Atopic hand eczema [19]. Nummular HE: coin-shaped plaques develop on the dorsal side of the hands and sometimes on the backs and sides of the fingers. The plaques are scaly or with peripheral vesicles. Pulpitis sicca: erythema and xerosis with desquamation develop on the tips of most fingers, leading to painful fissure on the fingertips, sometimes together with vesicles. The condition is usually correlated with AD and therefore becomes worse in the winter period. This kind of HE can be occupational/allergic; in the latter case just the fingers would be involved. Interdigital eczema/finger web eczema is characterized by erythema and desquamation. Hyperkeratotic HE. Acute recurrent vesicular HE [20]

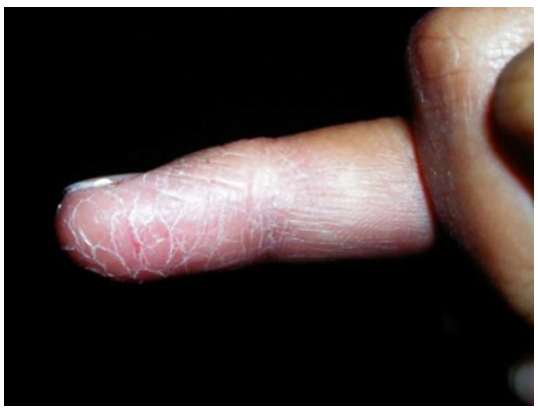

Fig. 2 Pulpitis variant of CHE [21]

The clinical subtypes are shown in Figs. 1, 2 and 3.

Differential diagnoses of CHE are psoriasis, lichen planus, scabies, drug reactions, secondary syphilis, cutaneous T cell lymphoma, pityriasis

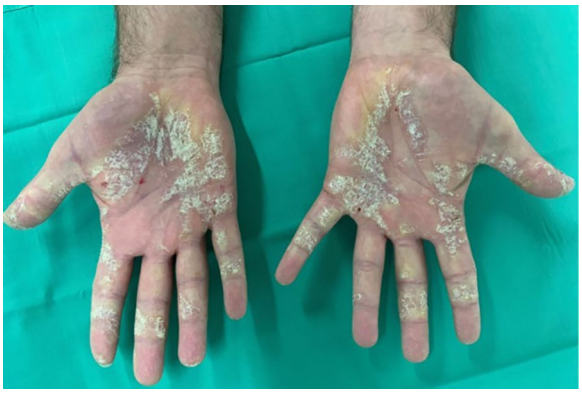

Fig. 3 Hyperkeratotic CHE [19]

rubra pilaris, Bowen's disease, porphyria cutanea tarda and palmoplantar keratodermas [20].

TREATMENT

Because of the great number of involved factors and the complexity of pathogenetic landscape, the management of HE tends to be very challenging for clinicians. Indeed, no single pathway can be targeted to improve patients' clinical picture.

The treatment of choice depends on the morphology, etiology, localization and severity of HE. Acute HE should be treated promptly, in order to avoid chronicization. Moreover, it is mandatory to identify and to avoid exogenous causative agents, either irritants or allergens [14].

The literature agrees that the correct approach to CHE is multimodal [7, 14, 22].

Conventional Therapies: Topical Therapies

Since disruption of epithelial barrier function plays a key role in the pathogenesis of CHE, use of emollients to restore this function and skin hydration represents the basis of the management of this disease. Nonetheless, evidence of their efficacy is limited. A Cochrane review performed by Christoffers et al., considering two small studies, failed to draw significant conclusions supporting the use of emollients in CHE [23]. However, further studies suggest that moisturizers may reduce itch and severity [24, 25]. Existing allergies and the patient's preferences must be taken into consideration when choosing a specific moisturizer.

Topical Steroids (TCS)

Topical glucocorticoids (TCS) have been cornerstone in the management of CHE for years [14]. They exist in different formulations and potency. Some of the most powerful ones, such as clobetasol, are suitable for managing the acute phase of the disease. However, they cannot be applied chronically, because of their profile of tolerance. Indeed, continuous use of these drugs is associated with skin atrophy, steroid-dependent dermatitis and risk of secondary infections [26]. The aforementioned skin atrophy is partially due to inhibition of stratum corneum repair, through filaggrin degradation [27]. Some topical steroids, such as mometasone, show fewer adverse effects, despite being moderately potent [19]. In order to minimize the risk of cutaneous side effects, it is possible to combine topical glucocorticoids and topical inhibitors of calcineurin, such as tacrolimus and pimecrolimus. Moreover, a further option consists in alternating these two categories of drugs [28].

Topical Inhibitors of Calcineurin (TCIs)

The topical inhibitors of calcineurin (TCIs) pimecrolimus and tacrolimus are approved as treatments for AD, while not being licensed for CHE of other etiologies. This category of drugs blocks transcription of several inflammatory cytokines released from T lymphocytes and mast cells. TCIs target nuclear kappa B pathway and calcineurin activity, thus exhibiting potent—yet aspecific—anti-inflammatory activity [29]. A Cochrane review on TCI use in HE highlights conflicting data regarding efficacy of pimecrolimus 1%, which seems to be similar to placebo [23]. This might be due to the different permeability of skin on the palmar and dorsal surfaces of hands [14].

Other Topical Therapies

Another therapeutic option is crisaborole, a phosphodiesterase 4 (PDE4) inhibitor. Promoting the degradation of cyclic adenosine monophosphate (cAMP), this drug inhibits the synthesis of inflammatory cytokines. Unlike TCIs, a key feature of crisaborole is its small molecular weight, which facilitates its absorption through the skin. A retrospective chart review considering 251 patients suggests that crisaborole might be effective in CHE, with 61.1% of them being "clear or almost clear" [30].

Calcipotriol is a topical vitamin D_3 derivative. It acts on epidermal keratinocytes by inhibiting proliferation, cytokine synthesis, angiogenesis and regulating immune responses [15]. However, its use is limited by common cutaneous side effects, consisting mainly of skin dryness, irritation and scaling [27]. Its effectiveness is supported by several case reports [31, 32]. Moreover, a prospective randomized controlled study (RCT) performed by Juntongjin and Pongprasert showed comparable efficacy for calcipotriol 0.005% ointment and topical steroids [33].

Conventional Therapies: Physical Therapies

UV Phototherapy

Physical therapies have been used as second-line treatments for CHE in clinical practice as well. Among these, psoralen plus ultraviolet A (PUVA) and UVA1 phototherapy are the most frequently used. A Cochrane systematic review considering 10 studies on UV therapies showed a similar effectiveness for PUVA performed as bath or cream [34]. UVA1 phototherapy represents a valid alternative, despite its often limited available [14]. Local acute adverse events consist of burning of the skin and erythema. On the other hand, chronic use is associated with an increased risk of non-melanoma skin cancer (NMSC) [35]. Furthermore, the need for frequent visits to ensure treatment success is an important limitation [36].

Conventional Therapies: Systemic Therapies

Topical therapies have frequently insufficient effectiveness in severe CHE, which thus requires systemic treatments. This category comprises systemic steroids, retinoids and immunosuppressive agents, including cyclosporine, methotrexate, mycophenolate mofetil (MMF) and azathioprine.

Systemic Steroids

Oral steroids are often used to treat flares, while their long-term use is limited by adverse events. Moreover, they might lead to immediate disease relapse when discontinued [19]. Thus far, there are no RCTs about systemic steroids in CHE [23]. Treatment is typically started with prednisone (or equivalent dose of other systemic steroids), at a dose of 0.5–1 mg/kg/day (up to a maximum of 60 mg/day), for 7 days [21]. A gradual tapering, as well as daily treatment with super-potent steroids in the following 2 weeks is essential, in order to avoid disease relapse.

Retinoids

Alitretinoin (9-*cis*-retinoic acid) is a vitamin A derivative which has received approval for CHE refractory to topical therapies, in different European countries, South Korea and Canada [37]. The molecular targets of this drugs are represented by retinoic acid receptors A and X. Binding to these receptors, alitretinoin regulates keratinocyte proliferation, apoptosis and angiogenesis, besides having immunomodulating properties. Different placebo-controlled studies demonstrated alitretinoin efficacy. Furthermore, a daily dosage of 30 mg was notably more effective than 10 mg [23]. The latter dosage is reserved for cases when the 30-mg dose is not tolerated or when impacting side effects, such as hyperlipidaemia. The most common side effect of alitretinoin is headache, particularly with the greater dose. Further adverse effects include hypercholesterolaemia and hypertriglyceridaemia, as well as a compromised thyroid function. Like with all retinoids, photosensitivity and teratogenicity are to be taken into consideration.

Alitretinoin seems to be more effective in the hyperkeratotic subtype of CHE. This drug is approved for 3–6 months of treatment, and it should be discontinued if no response is observed after 3–4 months [37].

In case of failure of alitretinoin, another retinoid—acitretin—can be used. Nevertheless, this drug is not licensed for this purpose. Moreover, data about its efficacy are limited [14]. Unlike alitretinoin, acitretin binds specifically to retinoic acid receptors. This drug is particularly useful in the hyperkeratotic form of CHE. In a single-blind placebo-controlled trial performed by Thestrup-Pedersen et al., a dosage of 30 mg/day of acitretin afforded a 51% reduction of all symptoms and signs after 4 weeks of treatment, including fissuring, hyperkeratosis, vesicle and erythema. On the other hand, no further improvement was observed over other 4 weeks [38]. Like alitretinoin, acitretin has teratogenic potential. There is no consensus about a specific dosing and duration for CHE treatment. Acitretin is usually administered at a dosage of 0.3–0.5 mg/kg/day, divided into two doses for 4–8 weeks. After this period, it is possible to continue with acitretin 0.5–0.8 mg/kg for other 3–4 months. Once complete healing is obtained, acitretin can be discontinued [19].

Cyclosporine

Cyclosporine is an orally administered calcitonin inhibitor. It acts by inhibiting T lymphocyte-mediated immune responses. Despite being licensed for AD in several countries, this drug does not have specific approval for CHE. Cyclosporine is characterized by a rapid onset of action. However, its chronic use is associated with side effects such as hypertension and nephrotoxicity [39]. An open-label study performed by Granlund and Reita highlighted a 1-year success rate of 74% in patients with CHE treated with cyclosporine at a dosage of 3 mg/kg/day [40]. Through a retrospective study comparing treatments with alitretinoin (30 mg/day) and cyclosporine (3–5 mg/kg/day) for 24 weeks, Jang et al. report responder rates of 68.2% and 40.9% for alitretinoin and cyclosporine respectively [41]. However, cyclosporine should be avoided in patients with compromised renal function, uncontrolled hypertension and malignancies. Moreover, potential adverse events include nephrotoxicity, headache, increased blood pressure, risk of infections, gastrointestinal manifestations and hyperlipidaemia. If no effect is described by 8 weeks, cyclosporine should be discontinued [14].

Azathioprine

Azathioprine is an immunosuppressive agent that acts by inhibiting purine synthesis and IgM and IgG production. By inducing the accumulation of 6-thioguanine nucleotides in lymphocytes, azathioprine decreases the expression of endogenous inflammatory molecules, e.g. α4-integrin, TNF receptor superfamily member 7 (TNFRSF7) and TNF-related apoptosis inducing ligand [17]. Treatment with azathioprine may be associated with side effects, including lymphocytopenia and other alterations in cell count [42]. Patients with deficiency of thiopurine S-methyltransferase (TPMT) enzyme activity are at high risk of myelosuppression and therefore azathioprine should be avoided. To date, this drug has not yet received approval for CHE [14]. However, a single-blind RCT comparing topical clobetasol versus clobetasol plus azathioprine 50 mg/day showed better outcomes in the combination group [43]. The initial dosage might be established at 1 mg/kg/day per os, and it can be increased up to 3 mg/kg/day for at least 3 months. Furthermore, this drug might be used as long-term treatment, once the minimum effective dosage is defined [19].

Methotrexate

Methotrexate (MTX) is a molecule that specifically works in the S-phase of the mitotic cycle. Its effects involve interfering with DNA synthesis, targeting and the inhibiting dihydrofolate reductase enzyme. Moreover, MTX works on the adenosine pathway, thus exerting an anti-inflammatory action [42]. Its toxicity is mainly due to its action on cells which have a high turnover rate, e.g. epidermal keratinocytes, the gastrointestinal (GI) tract, the hair matrix and bone marrow [44]. Like cyclosporine and

azathioprine, MTX has no license for use in CHE. Besides, there are no RCTs assessing its efficacy in this disease [14]. A Dutch retrospective study seems to suggest some effectiveness of MTX in the treatment of CHE, with a small number of patients showing "almost clear" skin after 12 months. Furthermore, MTX may be effective mainly in patients with hyperkeratotic subtype of CHE [45]. MTX might be started at a dosage of 7.5 mg per os per week, and then it can be titrated up to 25 mg orally [19].

JAK-STAT PATHWAY

JAK inhibitors target the JAK-STAT (signal transducer and activator of transcription factors) pathway, which is one of the main players in the pathogenesis of many immune-mediated conditions, such as AD. Although it is not completely known if JAK inhibitors directed towards AD will also be directed towards HE, the suppression of the Th2 pathways potentially benefits allergic contact dermatitis because various allergens have been shown to cause Th2-skewed immune activity [46, 47].

The JAK family is composed of JAK1, JAK2, JAK3 and non-receptor tyrosine kinase 2 (TYK2). JAKs bind intracellularly the cytokine receptor and activate STAT, which are intracytoplasmic transcription factors and include STAT1, STAT2, STAT3, STAT4, STAT5A/STAT5B and STAT6. Once activated, STAT proteins dimerize and move into the nucleus where they regulate the expression of specific genes [7]. JAK1, JAK2 and TYK2 are omnipresent in mammals, while JAK3 is more restricted in its expression, associated mainly with haematopoietic cells. Overall, JAK activation induces cell migration, differentiation, proliferation and apoptosis. Therefore, JAK inhibitors exert immunomodulatory and antiproliferative effects. The first generation of JAK inhibitors are tofacitinib, ruxolitinib, baricitinib and oclacitinib. Second-generation agents have a higher selectivity for certain JAK isoforms, for example abrocitinib and upadacitinib are more selective for JAK1. JAK1 plays an fundamental role in the expression of IL-4, IL-5, IL-13 and IL-31, all of which are associated with the pro-inflammatory signalling pathways of AD [46, 47].

Topical JAKi

Delgocitinib

Delgocitinib is a pan-JAK inhibitor which exerts its effect on all members of the JAK family (JAK1, JAK2, JAK3 and tyrosine kinase [TYK]2), thus modulating Th1, Th2, Th17 and Th22 immune responses. Through these mechanisms, this drug acts on several cytokines, including IL-4, IL-6 and IL-22. The efficacy of topical delgocitinib ointment 30 mg/g was assessed in a randomized, double-blind, phase IIa study [48]. In this trial, patients were assigned to receive delgocitinib or vehicle for 8 weeks. At week 8, the delgocitinib group reached an adjusted mean Hand Eczema Severity Index (HECSI) score significantly lower than the placebo group. It is worth highlighting that no plateau of efficacy was described, thus suggesting that long-term treatment might be associated with further improvement. Moreover, the efficacy of delgocitinib in a cream solution was evaluated in a 16-week randomized phase IIb study [49]. In this trial, 258 patients were randomized to receive one of four different doses or placebo: 1, 3, 8 or 20 mg/g. This study demonstrated efficacy of delgocitinib cream, as well as a dose-dependent relationship. Adverse events (AEs) observed in delgocitinib-treated patients included headache, nasopharyngitis and wound infections after biopsy. The most important clinical trials that demonstrated the efficacy of delgocitinib in CHE were DELTA 1 (NCT04871711) and DELTA 2 (NCT04872101) [50]. These are two identical multicentric, randomized, double-blinded and placebo-controlled studies in which adult patients were randomly assigned to placebo or delgocitinib cream twice daily. Efficacy was evaluated in terms of Investigator's Global Assessment for Chronic Hand Eczema (IGA-CHE) at week 16. Treatment success was defined as IGA-CHE score of 0 ("clear skin") or 1 ("almost clear skin"). This result was achieved in a significantly greater proportion in the treatment groups versus placebo, both in DELTA 1 (20% vs 10%) and in DELTA 2 (29% vs

Table 1 Main clinical trials currently ongoing in CHE as listed on https://ichgcp.net/clinical-trials-registry (as of 29 November 2024)

NCT number	Title	Participants (*N*)	Intervention	Age (years)	Phase	Primary outcome	Blinding	Study completion (estimated)
NCT05355818	Efficacy and safety of delgocitinib cream in adolescents 12–17 years of age with moderate to severe chronic hand eczema (DELTA TEEN)	92	Delgocitinib cream 20 mg/g	12–17	3	IGA-CHE treatment success at week 16	Both participants and investigators (double)	December 17, 2024
NCT03861455	Efficacy and safety of dupilumab chronic hands eczema refractory to highly potent topical corticosteroids (DUPECZEMAIN)	94	Dupilumab	≥ 18	2	Severity score mTLSS (modified Total Lesion Symptom Score) at week 16	Both participants and investigators (double)	June 1, 2024
NCT05682859	Treatment of chronic hand eczema with oral roflumilast (HERO)	40	Roflumilast	18–75 (adult, older adult)	4	HECSI-75 at week 16 when compared to HECSI at baseline	Both participants and investigators (double)	April 1, 2026

7%) [50]. At present, there is a clinical trial ongoing assessing the efficacy of twice-daily treatment with delgocitinib cream in adolescent subjects (12–17 years). A two-arm, phase III study has been recently completed, demonstrating the superiority of delgocitinib cream (twice-daily regime) versus alitretinoin orally [51] (Table 1).

Ruxolitinib

Ruxolitinib targets JAK1 and JAK2, and is a potent inhibitor of both. This drug can be administered orally or topically. The former option has been used for years in the treatment of haematopoietic dyscrasias, such as polycythemia vera (PV) and myelofibrosis (MF) [52]. Topical ruxolitinib has been assessed in different dermatological conditions, like AD, vitiligo, psoriasis and alopecia areata (AA). This drug is significantly effective in AD. In a phase II study, different posologies of topical ruxolitinib (RUX) 1.5% were compared to vehicle or triamcinolone cream 0.1% [53]. All RUX regimens were demonstrated to be effective at week 4. The maximum improvement in terms of Eczema Area and Severity Index (EASI) (71.6% vs 15.5%; $p<0.0001$) and Investigator's Global Assessment (IGA) was described in the group treated with ruxolitinib twice daily (BID) (38.0% vs 7.7%; $p<0.001$). This drug is effective in reducing pruritus in AD as well. The efficacy of topical ruxolitinib in CHE had been evaluated in two phase III clinical trials (TRuE-CHE1 and TruE-CHE2). However, these studies were stopped for economic reasons [54].

Systemic JAKi

Gusacitinib

Gusacitinib exerts its action by blocking the pathways of spleen tyrosine kinase (SYK) and all Janus kinases (JAK1, JAK2, JAK3 and TYK2) [55]. It is administered orally. By these mechanisms, this drug inhibits the signalling of Th17, Th1, Th2 and Th22 lymphocytes. Gusacitinib shares the same toxicity profile as other systemic JAKi, including lymphopenia, anaemia, hypertriglyceridaemia, hypercholesterolaemia and increased risk of thromboembolism. A double-blind, placebo-controlled, multicentre phase II study has evaluated the efficacy and safety of gusacitinib in 97 patients with CHE [56]. Patients were randomized to receive gusacitinib 40 mg, gusacitinib 80 mg or placebo once daily, for 12 weeks (phase A). In the following phase (phase B), all patients received the drug, up to week 32. Both treatment groups experienced a significant improvement of their condition. Moreover, patients receiving gusacitinib 80 mg showed a 69.9% reduction in Total Lesion Symptom Score (TLSS), greater than the lower dose group (49%). The most common adverse events comprised upper respiratory tract infections (URTIs), nausea and headache. Furthermore, five patients experienced serum creatine phosphokinase (CPK) elevation.

Upadacitinib

Upadacitinib is an oral JAKi which acts specifically on JAK1. It is currently licensed for the treatment of moderate-to-severe AD. In an observational cohort study (BioDay registry), upadacitinib led to significant improvements in 32 patients with mild-to-moderate CHE and concomitant AD [57]. HECSI-75 was described in 59.3% patients, while 74.1% achieved "almost clear skin". Side effects associated with upadacitinib include acne, URTIs, urinary tract infections (UTIs), herpes zoster, oral herpes and increased CPK. Upadacitinib is available in 15 mg and 30 mg doses.

Baricitinib

Baricitinib is an oral, reversible inhibitor of JAK1 and JAK2, while shows a lower affinity for TYK2 and JAK3. This drug is approved for the management of AA and AD, at doses of 2 mg and 4 mg. Side effects are the same as described for upadacitinib. A potential role of baricitinib in CHE is suggested by some case reports [58]. Nevertheless, there is currently no formal clinical study assessing its efficacy in HE.

Abrocitinib

Abrocitinib is a JAK1 inhibitor, and it is orally administered. It is licensed for

moderate-to-severe AD. The phase III studies JADE MODO I and JADE MODO II demonstrated superiority of both abrocitinib 100 mg and abrocitinib 200 mg to the vehicle in patients with AD [56]. Data analysis and extrapolation from the phase III study JADE DARE highlighted that a greater proportion of patients with AD and concomitant CHE treated with abrocitinib 200 mg experienced hand healing compared to those treated with dupilumab 300 mg [47].

Emerging Therapies: PDE4 and cAMP

Cyclic adenosine monophosphate (cAMP) is an intracellular second messenger which regulates cellular metabolism and energy homeostasis. In particular, cAMP induces the expression of IL-10 which is an anti-inflammatory cytokine. Therefore IL-10 will suppress the expression of cytokines such as TNFα and INFγ, which are pro-inflammatory and also involved in CHE and several other diseases (e.g. psoriasis). cAMP is degraded by PDE4 [59]. Therefore, drugs targeting both cAMP and PDE4 have been recently studied. At present, there are both topical PDE4 like roflumilast and crisaborole, and systemic PDE like apremilast [22].

Apremilast

Apremilast is an oral drug which exerts its action by inhibiting PDE4. It is licensed for dermatological diseases such as moderate-to-severe psoriasis, psoriatic arthritis (PsA) and Behçet syndrome. A relevant indication is represented by severe comorbidities (e.g. oncological history) and important infectious conditions [60]. In a randomized, observer-blinded comparative study, 77 patients with hyperkeratotic HE were divided into two treatment groups [61]: one group received mometasone furoate 0.1% cream with orally administered apremilast 30 mg twice daily, while the other was treated with mometasone furoate 0.1% cream alone. The results analysed after 3 months highlighted significant decreases in HECSI, Visual Analogue Scale (VAS) for pruritus and Quality of Life in Hand Eczema Questionnaire (QOLHEQ), in both study groups. A more detailed comparison between the two arms showed that those receiving apremilast achieved significantly better improvement in the third month in terms of IGA and Physician Global Assessment (PGA). Furthermore, they developed fewer flares during the observation period.

Roflumilast

Roflumilast is a topical inhibitor of PDE4. It has been used in psoriasis as a local treatment [62]. A randomized, placebo-controlled phase IIa clinical trial has assessed efficacy of roflumilast 0.5% cream in subjects with AD [63]. Nonetheless, no statistically significant improvement of EASI was described. On the other hand, roflumilast produced an important amelioration of NRS pruritus scale score. A multicentre, double-blinded, placebo-controlled RCT (HERO) is currently ongoing, aiming to test both efficacy and safety of orally administered roflumilast 500 mg/tablet in CHE [64]. However, no preliminary data are available yet.

Emerging Therapies: IL-4/13 Axis

Exposure to inflammation, bacteria and viruses can lead to the disruption of epidermal skin barrier, allowing the penetration of allergens through the tissues. Allergens possessing protease activity can compromise the tight junction proteins of epithelial cells, allowing them to access submucosal dendritic cells (DCs). Damaged epithelial cells release alarmins such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, which subsequently activate innate lymphoid cells (ILCs) and DCs. Activated DCs move to local lymph nodes where they present the allergen peptides to naïve T cells via major histocompatibility complex (MHC) class II molecules. Here, IL-4 and IL-13 play an essential role in the Th2 immune activity in AD, contributing to both immune activation as well as skin barrier dysfunction [2].

Indeed, the role of IL-4 is to induce the differentiation of naïve T cells into Th2 cells. Once primed, Th2 cells release many inflammatory cytokines such as IL-4, IL-13, IL-5, IL-9 and

chemokines such as eotaxin 1/2/3. IL-4 and IL-13 are crucial for long-term maintenance of Th2 cells and their continuous cytokine synthesis. IL-4 and IL-13 are also responsible for recruiting eosinophils and mast cells which then release inflammatory and allergic mediators. Moreover, they are involved in stimulating B cells and inducing IgM class switching towards IgE.

Recently it has been found that IL-4 and IL-13 also promote neurogenic itch by interacting with IL-31 and therefore directly acting on pruritogenic sensory fibres.

Furthermore, IL-4 and IL-13 induce hyperplasia and reduced differentiation of keratinocytes, arresting their full maturation, and downregulate filaggrin, a protein fundamental to keeping the ability of the skin to adequately retain moisture and therefore protect against allergens and pathogens.

IL-13 uniquely downregulates matrix metalloproteinase (MMP)-13 of dermal fibroblasts, which therefore will decrease collagen degradation. This will result in fibrosis and thickening of the dermis, giving typical lichenified AD lesions [65].

Dupilumab

Dupilumab is a human monoclonal IgG4 antibody (mAb) which targets the shared α-subunit of IL-4 receptor (IL-4Rα), thus inhibiting both IL-4 and IL-13 pathways. This drug is currently approved for treatment of AD. Furthermore, dupilumab was shown to be effective in patients with AD and concomitant CHE [66]. However, the hyperkeratotic phenotype of CHE seems to be particularly resistant to this treatment [67]. This drug has been suggested to be useful to address ACD as well, because of the overlapping immune mechanisms shared by AD and ACD, since some allergens seem to elicit both innate and adaptative immune responses. There is an ongoing phase II clinical trial (DUPECZEMAIN) assessing the efficacy and safety of dupilumab in patients with CHE that is refractory to highly potent topical steroids [68]. Moreover, several observational studies and clinical reports support the effectiveness of off-label dupilumab in CHE [69, 70]. The most relevant adverse effect is dupilumab-induced ocular surface disease. This condition is more frequent in patients with AD when compared to patients with asthma, eosinophilic esophagitis or chronic rhinosinusitis with nasal polyps [71]. However, not much is known about the precise mechanism underlying this manifestation.

Tralokinumab

Tralokinumab is a human monoclonal antibody specifically directed against IL-13, not involving IL-4. It is currently licensed for use in AD. Nevertheless, data about its effectiveness in CHE are poor. There is a case-report describing a patient with AD and concomitant CHE receiving tralokinumab for his disease. Despite a good response in the first 7 months of treatment, the treatment was withdrawn because of the development of paradoxical psoriasis. This might be explained by a switch from Th2 immune response to a Th1-biased one [72]. Conversely, one of the authors describes a patient with CHE and AD confined to small areas of face and trunk, who responded well to tralokinumab treatment. The most frequent side effects include URTIs and conjunctivitis.

Emerging Therapies: Chemoattractant Cytokines

A 2021 article by Shibuya et al. [73] proposed that the CCL2−CCR2 signalling pathway may play a significant role in the development of skin inflammation in irritative contact dermatitis. The chemokine CCL2 interacts with several receptors, including CCR1, CCR2, and CCR3, with CCR2 being its primary receptor. This receptor is predominantly found on skin macrophages and blood monocytes. CCL2 is also already recognized for its involvement in inflammatory conditions such as atherosclerosis, rheumatoid arthritis, allergic asthma, psoriasis and AD, and it also appears to contribute to wound healing. Beyond its role in chemotaxis, CCL2 has diverse immunomodulatory effects on both lymphoid and myeloid immune cells. Additionally, nonimmune cells, such as endothelial cells, fibroblasts and epithelial cells, are known to produce CCL2. Within the skin, CCL2 secretion facilitates the recruitment

Table 2 Summary of available treatments in CHE

Drug/therapy category	Drug/therapy	Usual dosage	Notes	Adverse effects	Efficacy
Topical steroids	Mometasone, clobetasol	Q24h or Q12h, depending on steroid potency	Not suitable for chronic use	Atrophy, steroid-dependent dermatitis and risk of secondary infections	Significant variability of data and difficulties in comparison between different drugs
Topical inhibitors of calcineurin (TCIs)	Pimecrolimus, tacrolimus	Q24h	Licensed for AD, not for HE of other etiologies	N/A	Conflicting data on pimecrolimus, which has similar efficacy to placebo in CHE
Other topical drugs	Crisaborole	Q24h	N/A	N/A	Clear or almost clear skin in 61.1% patients with CHE [30]
	Calcipotriol	Q24h	N/A	Skin dryness, irritation and scaling	Several case reports; a prospective RCT indicates a similar efficacy for calcipotriol 0.005% ointment and topical steroids [33]
UV therapy	PUVA, UVA1	There are no standardized regimens	UVA1 phototherapy often has limited availability; need for frequent visits	Burning and erythema of the treated skin; long-term increased risk of non-melanoma skin cancer (NMSC)	Mean reduction in HE score of 41% [45]; similar efficacy for PUVA and UVA1

Table 2 continued

Drug/therapy category	Drug/therapy	Usual dosage	Notes	Adverse effects	Efficacy
Systemic steroids	Prednisone, betamethasone etc.	There are no standardized regimens; typically, prednisone 0.5–0.1 mg/kg/day per day (up to a maximum of 60 mg/day) for 7 days	Risk of disease relapse when discontinued; gradual tapering is strongly recommended; suitable for use during flares of CHE, not for chronic phases	Fluid retention, hyperglycaemia, osteoporosis, myopathy, bone fractures, skin atrophy, acne, mood changes, insomnia, psychosis, peptic ulcers, increased risk of infections, cataracts, glaucoma	There are no RCTs about systemic steroids in CHE; there are difficulties in obtaining affordable data about efficacy
Retinoids	Alitretinoin	30 mg/day; 10-mg dose is available for cases when the latter is not tolerated or in case of impacting AE	Alitretinoin is approved for CHE in several European countries; 3–6 months of treatment; it should be discontinued if no response is observed after 3–4 months	Headache, hypercholesterolaemia, hypertriglyceridaemia, compromised thyroid function; photosensitivity and teratogenicity	There are several RCTs supporting the efficacy of alitretinoin; Ruzicka et al. showed responses in up to 48% of patients, vs 17% for placebo [37]
	Acitretin	There is no consensus about a specific dosing and duration for CHE; usually administered at a dosage of 0.3–0.5 mg/kg/day divided into two doses, for 4–8 weeks; then it is possible to use a dosage of 0.5–0.8 mg/kg/day for further 3–4 months	Acitretin is not licensed for use in CHE; it is particularly effective in hyperkeratotic forms of CHE	Headache, hypercholesterolaemia, hypertriglyceridaemia, compromised thyroid function; photosensitivity and teratogenicity	There are limited data about efficacy. Thestrup-Pedersen et al. demonstrated a 51% reduction of all symptoms and signs after 4 weeks of treatment, with no further improvement over other 4 weeks [38]

Table 2 continued

Drug/therapy category	Drug/therapy	Usual dosage	Notes	Adverse effects	Efficacy
Traditional immunopressant agents	Cyclosporine	3–5 mg/kg/day divided into two doses; cyclosporine should be discontinued if no effect is observed by 8 weeks	Despite being approved for AD in several countries, this drug does not have specific approval for CHE; rapid onset of action; cyclosporine should be avoided in patients with compromised renal function and malignancies	Hypertension, nephrotoxicity (both especially with chronic use), headache, risk of infections, gastrointestinal impairment and hyperlipidaemia	A retrospective study performed by Jang et al. showed responder rates of 68.2% and 40.9% for alitretinoin and cyclosporine respectively [37]
	Azathioprine	Initial dosage might be 1 mg/kg/day per os, and it could be increased up to 3 mg/kg/day for at least 3 months. This drug might be used as a long-term treatment	Not approved for CHE; azathioprine should be avoided in patients with defective TPMT enzyme activity because of their higher risk of myelosuppression	Lymphocytopenia and other alterations in cell count	An RCT comparing topical clobetasol versus clobetasol plus azathioprine 50 mg/day showed better outcomes in the combination group [43]
	Methotrexate	It might be started at a dosage of 7.5 mg per week per os, with the possibility to be titrated up to 25 mg	Has no license for use in CHE	Nausea, vomiting, diarrhoea, stomatitis, bone marrow suppression (anaemia, leukopenia, thrombocytopenia), transaminitis, hepatotoxicity, cirrhosis, pneumonitis, pulmonary fibrosis, alopecia, photosensitivity, increased risk of infections, nephrotoxicity, headache, dizziness	There are no RCTs assessing efficacy in CHE. A retrospective study seems to suggest some effectiveness, with a small number of patients reaching "almost clear" skin after 12 months [45]

Table 2 continued

Drug/therapy category	Drug/therapy	Usual dosage	Notes	Adverse effects	Efficacy
Topical JAK inhibitors (JAKi)	Delgocitinib	Delgocitinib cream 20 mg/g Q12h	No plateau of efficacy has been observed	Headache, nasopharyngitis, wound infections after biopsy	DELTA 1 and DELTA 2 demonstrated efficacy of delgocitinib, with IGA-CHE 0/1 reached in 20% (DELTA 1) and 29% (DELTA 2) of participants, significantly greater than in the placebo group (10% and 7% respectively) [50]
Ruxolitinib	No established dosage	N/A	N/A	Redness, itching and flushing at the application site, headache	The efficacy of topical ruxolitinib in CHE had been evaluated in two phase III clinical trials (TRuE-CHE1 and TRuE-CHE2), which have been withdrawn for economic reasons [54]

Table 2 continued

Drug/therapy category	Drug/therapy	Usual dosage	Notes	Adverse effects	Efficacy
Systemic JAKi	Gusacitinib	No established dosage; in phase II clinical trials, 40 mg and 80 mg/day have been tested	N/A	Lymphocytopenia, anaemia, hypertriglyceridaemia, hypercholesterolaemia, increased risk of thromboembolism, URTIs, nausea, headache, CPK elevation	In a phase II clinical trial, patients receiving gusacitinib 80 mg Q24h experienced a 69.9% reduction in TLSS, greater than the lower group (49%) [56]
	Upadacitinib	15 mg or 30 mg/day	Currently approved for the treatment of moderate-to-severe AD	Acne, URTIs, UTIs, herpes zoster, oral herpes, increased CPK	In an observational cohort study, HECSI-75 was described in 59.3% of patients, whereas 74.1% achieved "almost clear skin" [57]
	Baricitinib	2 or 4 mg/day	Currently licensed for the management of AD and AA	The same as described for upadacitinib	Possible effectiveness suggested by some case reports, while there is no current formal clinical study evaluating its efficacy in CHE [58]
	Abrocitinib	100 or 200 mg/day	Licensed for moderate-to-severe AD	The same as described for upadacitinib	The phase III study JADE DARE showed that a greater proportion of patients with AD and concomitant CHE treated with abrocitinib 200 mg experienced hand healing compared to those treated with dupilumab 300 mg [47]

Table 2 continued

Drug/therapy category	Drug/therapy	Usual dosage	Notes	Adverse effects	Efficacy
PDE4 inhibitors	Apremilast	30 mg twice daily per os, with the usual titrating scheme	Relevant indication is represented by severe comorbidities (e.g. oncological history and important infectious conditions)	Weight loss, diarrhoea, nausea	In a randomized, observer-blinded comparative study, patients who received mometasone furoate 0.1% cream with orally administered apremilast 30 mg twice daily reached better outcomes than who received mometasone furoate alone [61]
	Roflumilast	Roflumilast 0.5% cream	Topical inhibitor of PDE4	Weight loss, diarrhoea, nausea, application site pain	In a phase IIa RCT, roflumilast 0.5% failed to afford a statistically significant improvement of EASI. However, it led to an important amelioration of NRS pruritus rating scale [64]

Table 2 continued

Drug/therapy category	Drug/therapy	Usual dosage	Notes	Adverse effects	Efficacy
Inhibitors of IL-4/IL-13 axis	Dupilumab	300 or 200 mg Q2W, depending on the body weight	IL-4RA antagonist; it is currently approved for treatment of AD, whereas its use for CHE is off-label. The hyperkeratotic phenotype seems to be particularly resistant	Dupilumab-induced ocular surface disease, dupilumab facial dermatitis	DUPECZEMAIN is a phase II RCT that is assessing the efficacy and safety of dupilumab in patients with AD that is refractory to highly potent topical steroids [68]. Several observational studies and clinical reports support the effectiveness of dupilumab in CHE [69, 70]
	Tralokinumab	300 mg Q2W	IL-13 antagonist; currently approved for use in AD	URTIs and conjunctivitis	Data about its effectiveness in CHE are poor. There is a case report of a patient who had experienced an initial improvement, before losing effect. One of the authors of this review describes a patient with CHE and AD confined to small areas of trunk and face, who responded well to tralokinumab

Table 2 continued

Drug/therapy category	Drug/therapy	Usual dosage	Notes	Adverse effects	Efficacy
Chemoattractant cytokines inhibitors	AFX5931		Investigational small molecule directed against CCL2 and CCL5		In a phase 4 RCT evaluating the effectiveness of topical AFX5931, the active comparator group experienced a decrement of HECSI from 22.67 to 20.6 at day 28, while in the vehicle group mean HECSI changed from 25.6 to 21

Qxh/w (from Latin) every *x* hours/weeks, *AD* atopic dermatitis, *CHE* chronic hand eczema, *RCT* randomized controlled trial, *PUVA* psoralen plus ultraviolet A, *UVA1* ultraviolet A1, *AE* adverse events, *TPMT* thiopurine *S*-methyltransferase, *JAK* Janus kinases, *PDE4* phosphodiesterase 4, *URTIs* upper respiratory tract infections, *UTIs* urinary tract infections, *IL-4/IL-13* interleukin-4 and Interleukin-13

of inflammatory monocytes, DCs and memory T cells. As such, targeting the CCL2–CCR2 axis locally may offer a potential therapeutic approach for irritative contact dermatitis [22, 74].

AFX5931

AFX5931 is an investigational small molecule which directly targets CCL2 and CCL5, cytokines which are important in the major subtypes of CHE [75]. A phase 4 randomized controlled study has evaluated the efficacy of topical AFX5931 in 20 patients with CHE [76]. In the active comparator group, mean HECSI decreased from 22.67 to 20.6 at day 28, while in the vehicle group mean HECSI changed from 25.6 to 21.

CONCLUSIONS

Hand eczema is a persistent and difficult condition to manage, with significant psychological and economic impact as for all the spectrum of atopic disorders. Indeed, CHE significantly impairs patients' work life, leading to missed workdays, reduced productivity, and difficulties in performing job-related tasks. Topical treatments often fall short for severe cases, and although systemic therapies can be effective, they come with significant adverse effects. However, emerging treatments for AD, including new biologics and systemic therapies—such as JAK inhibitors—are beginning to be used for HE. Additionally, new therapeutic targets, such as chemoattractant cytokines, are being thoroughly studied. A growing collection of innovative systemic therapies targeting the molecular mechanisms of HE are becoming available (Table 2). These new treatments not only show increased efficacy but have improved safety profiles as well, making them attractive additions to the clinician's toolkit. It is crucial for both clinicians and patients to stay informed about these advancements, since the pace of progress in hand eczema treatment is without precedent. In the near future, this evolving landscape will ensure a more effective and patient-centred approach to managing this challenging condition.

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