


Drugs for the Treatment of Chronic Hand Eczema: Successes and Key Challenges

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Abstract: Chronic hand eczema (CHE) is a common and burdensome inflammatory skin condition seen in up to 10% of the population, more often in high-risk occupational workers. Topical therapeutics comprise the standard of care, but up to 65% of cases do not resolve after treatment, and moderate-to-severe cases are often resistant to topical therapeutics and require systemic options instead. To date, there are no systemic therapeutics approved to treat CHE in the United States, but several drugs are under investigation as potential treatments for CHE. The primary focus of this review is on the novel therapeutics, topical and systemic, that are under investigation in recently completed or currently ongoing trials. This review also briefly outlines the existing treatments utilized for CHE, often with limited success or extensive adverse effects. CHE represents a major challenge for physicians and patients alike, and efforts to improve the minimally invasive diagnostic tools and treatment paradigms are ongoing. In the near future, CHE patients may benefit from new topical and systemic therapeutics that specifically target abnormally expressed immune markers.

Keywords: AFX5931, chronic hand eczema, delgocitinib, dupilumab, gusacitinib, roflumilast

Introduction

Chronic Hand Eczema Prevalence and Clinical Presentation

Chronic hand eczema (CHE) is an inflammatory skin condition with a 10% prevalence in the general population.¹⁻⁴ CHE is most common in people who work in high risk occupations with consistent water exposure to the hands, including health care workers, hair dressers, cooks, cleaners, and others working in manufacturing involving direct hand work.^{1,5} There is an enormous psychosocial burden of disease and the functional impairment from HE has been identified as a major cause of morbidity and employment-related financial hardships.^{2,6-8} Recent studies reported that up to 82% of CHE patients had to change their work situation, 48% had taken sick leave for several days at a time, and at least 15% were on unemployment or disability pension.^{2,6-8} Further, CHE has an overwhelming impact on quality of life due to repercussions from the pain and itch symptoms for work and social activities, as well as the psychological stress due to visibility of the hands.^{2,9} CHE is diagnosed in individuals with hand eczema of more than 6 months duration. Clinically, hand eczema is characterized by cutaneous fissures and vesicles in the setting of erythema, often associated with scaling and hyperkeratosis, and symptoms of itch and pain. The morphology can be confused with other skin conditions such as psoriasis, mycosis, and atopic dermatitis, among others.^{4,9}

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CHE Etiologies and Pathogenesis

CHE is a heterogeneous condition, with a wide range of etiologies and clinical manifestations that are in large part due to a multifactorial pathogenesis. Most cases of hand eczema are caused by a combination of etiologies. There are three main etiologic classifications of hand eczema: irritant contact dermatitis (ICD), allergic contact dermatitis (ACD), and atopic hand eczema, which accounts for over 50% of cases.^{4,9-12} ICD is due to prolonged exposure to skin irritants such as detergents, solvents, sweat, and frequent exposure to water, which compromises the skin barrier and causes a contact allergy.^{4,9,13,14} Atopic hand eczema is a delayed type IV hypersensitivity reaction to a chemical substance, typically nickel, chromate, rubber, or preservatives. This form of hand eczema can be diagnosed with patch testing.^{4,9,15} Atopic hand eczema is the most common etiology of hand eczema, accounting for over 50% of cases.^{4,12,16,17} Further, atopic dermatitis (AD) is the most important risk factor for chronic hand eczema, and up to one half of patients with CHE have other atopic conditions including asthma, allergic rhinitis, elevated IgEs, and atopic dermatitis.^{9,18-20}

The pathogenesis of CHE is dependent upon the primary etiology of the eczema. Each etiology has a unique immune signature that should, ideally, be targeted for effective treatment of the condition. Irritant contact dermatitis has a Th1/Th17 immune profile that results from the activation of IL-1 α , IL-1 β , TNF- α , GM-CSF, and IL-8 from keratinocytes upon exposure to an irritant.²¹⁻²³ This immune activation causes damage to the keratinocytes, which promotes cellular infiltrate from inflammatory cells such as neutrophils and mast cells.²¹⁻²³ ACD shows a variable immune signature, dependent upon the allergen at play. Metal-induced ACD typically presents with a Th1/Th17 immune profile, with elevated markers of innate immunity and expression of IL-1 β , IL-6, IFN- α 1, CXCL1, CXCL2, CXCL9, CXCL10, and CXCL11.^{15,21,24} Fragrance and rubber-induced ACD typically presents with a Th2/Th22 immune profile, inducing cytokines such as IL-5, IL-13, IL-22, IL-32, CCL5, CCL13, CCL17, CCL18, and CTLA4.^{15,21,24} Atopic hand eczema, like other atopic conditions, presents with a Th2/Th22 immune profile, in conjunction with endogenous factors such as tight junction defects and an increase in transepidermal water loss (TEWL), thereby compromising the integrity of the epidermal barrier.^{1,25-28} Atopic hand eczema lesions are characterized by increased Th2

activation and production of IL-4, IL-13, IL-31, CCL17, CCL18, and CCL22, and T-cell activation that produces IL-22. IL-4/IL-13 also induce increased IgE synthesis, which characterizes many CHE cases.^{21,22,29}

CHE Treatment Paradigm

There is a large unmet need for effective therapeutics for long-term control of CHE, particularly moderate-to-severe cases, as there are currently no FDA-approved treatments for chronic hand eczema.³⁰ Up to 65% of patients continue to experience recurrent episodes of HE after 5 years of treatment with topicals.^{1,6} Patients with mild to moderate CHE are often treated with hydration, emollients, or high potency topical steroids or calcineurin inhibitors, but these options are often unsatisfactory.^{1,2,4,31-33} New immune-targeted treatments are being investigated in clinical trials. Topical pan-Janus Kinase (JAK) inhibitor delgocitinib has shown promising data for treating mild-to-severe CHE in a completed Phase 2 trial – it was efficacious and well tolerated, showing clearance of CHE after 8 weeks of treatment compared to placebo.^{34,35} There are also ongoing studies with phosphodiesterase type 4 inhibitors (PDE4) and inhibitors of highly inflammatory chemokines CCL2 and CCL5 for the treatment of mild to moderate CHE.^{1,35-38} These are all important targets that have been found to be dysregulated across CHE etiologies.

Still, moderate-to-severe cases are often refractory to topical treatments. Thus far, alitretinoin is the only systemic therapy approved for the treatment of severe hand eczema, but it is approved only in Europe, Canada, Israel, and South Korea.³⁹⁻⁴¹ While no systemic therapies have been approved in the United States, several are being investigated in clinical trials, including existing oral immunosuppressants such as cyclosporine and azathioprine, which have shown some efficacy in treating moderate-to-severe CHE, but they are limited by the side effect profile.⁴²⁻⁴⁵ Other systemic options, including oral JAK/spleen tyrosine kinase (SYK) inhibitors and injectable biologics, namely gusacitinib, a JAK/SYK inhibitor, and dupilumab, a monoclonal antibody towards IL-4R α that is approved for the treatment of moderate-to-severe atopic dermatitis, are being investigated in clinical trials. A phase 2 trial of gusacitinib in CHE has reported initial promising results, with dose-dependent improvements in hand eczema compared to placebo, and several case and observational studies of Dupilumab have similarly shown significant improvements in moderate-to-severe CHE.⁴⁶⁻⁴⁹ Dupilumab specifically targets Th2 cytokines and has

a highly favorable safety profile, and gusacitinib targets several cytokine axes that may be involved in CHE, making them potentially promising treatment options, but both are still in early stages of investigation.^{49–53}

The heterogeneity of CHE and the lack of approved systemic treatments advocates for a more precise and efficacious approach to long term disease management. This review will focus on novel topical and systemic treatments in a current or recently completed clinical study investigation for chronic hand eczema, with a review of several of the most relevant existing drugs approved for other conditions that have also been investigated through clinical study for CHE (summarized in Table 1). To identify treatments to review in this article, we conducted a thorough search using the United States Clinical Trials database (clinicaltrials.gov) and searched for all trials using the key terms “chronic hand eczema,” “hand eczema,” and “hand dermatitis.” In addition to outlining the successes in treating CHE, this review also highlights the key challenges still faced in CHE drug development and clinical management.

Existing Topical Therapeutics

Calcipotriol, a topical Vitamin D3 derivate that has been studied for the treatment of several skin diseases, has also been evaluated as a treatment for hand eczema.^{39,54,55} Calcipotriol affects epidermal cells by prohibiting proliferation, angiogenesis, and cytokine production, and regulates hapten-induced immune responses by dendritic cells,^{1,39,54} but its widespread use is limited by common side effects such as skin scaling, dryness, and irritation.^{55,56} Case reports of several patients have shown improvements in hand eczema after treatment with topical calcipotriol,^{39,54} and a recent prospective, randomized trial found that 0.005% calcipotriol was as effective as topical steroids in improving clinical severity of hand eczema.⁵⁵

Calcineurin inhibitors, another class of existing topicals, are frequently used in the treatment of mild to moderate chronic hand eczema.^{9,57–59} They inhibit the transcription of various inflammatory cytokines released from T-cells and mast cells by affecting the nuclear factor kappa B pathway and blocking calcineurin phosphate activity, and therefore function as potent, but non-specific, anti-inflammatories.^{1,59,60} Pimecrolimus, a topical calcineurin inhibitor, has widely been used in the treatment of atopic dermatitis and chronic hand eczema.^{57,58} Three trials have evaluated the efficacy of

1% pimecrolimus cream for the treatment of CHE,^{58,61,62} and have found that patients experience significant improvement in clinical severity and symptomatology (Table 1).^{61,63} Tacrolimus, another topical calcineurin inhibitor, has previously been approved to treat atopic dermatitis but has less skin penetration than pimecrolimus.⁶⁴ Though it has been efficacious in improving distressing inflammatory symptoms in patients with CHE,^{59,65} one prospective study found it only achieved complete clearing of disease in 44% of participants.⁶⁴

Topical steroids, in various formulations, are another class of drugs utilized for the treatment of CHE, as they are effective anti-inflammatory, anti-mitotic, and immunosuppressive medications that are easy to administer.^{66–68} However, topical steroid use is limited by several side effects seen with prolonged use, including tachyphylaxis and dermal atrophy, among others.^{69,70} Topical clobetasol propionate, is an old, high potency corticosteroid that has been utilized in mild to moderate cases of chronic hand eczema. An open-label study of the efficacy of clobetasol propionate 0.05% foam found improvement in 96.7% of subjects after 15 days of use, concluding that clobetasol propionate foam is an effective and safe treatment for chronic hand eczema (Table 1).^{71,72} Triamcinolone acetonide is another combination topical steroid investigated for the treatment of CHE,⁷³ and it has also been evaluated for the treatment of allergic and irritant contact dermatitis, for which it has shown variable efficacy in reducing clinical severity.⁷⁴ Halometasone is a glucocorticoid recently investigated as a combination formula with antibacterial, triclosan, for the treatment of CHE.^{75,76} This topical serves as an effective combination, functioning as an antiseptic and anti-inflammatory to improve microbial colonization with *Staphylococcus aureus* (*S. aureus*) in affected skin as well as inflammation.^{76,77}

Though there has been modest success in the treatment of CHE with existing topical drugs, their use is limited to mild-to-moderate cases and long-term they are associated with several side effects. This has advocated for the development of novel treatments that are efficacious and well tolerated across the spectrum of clinical severity.

Novel Topical Therapeutics Small Molecule Drugs

Small molecule drugs are a new class of treatments that have previously been shown to be effective therapeutics for atopic dermatitis.^{78–81} Due to their small size, they can

Table 1 Relevant Clinical Trials for the Treatment of Chronic Hand Eczema

	Agent	Target / Mechanism	Clinical Trial Status	Clinical Trial Number	Reference
Topical	LEO 19,123	Calcipotriol	Completed in 2007	NCT00404196	LEO19123 Cream in the Treatment of Hand Eczema. In: https://ClinicalTrials.gov/show/NCT00404196 . ¹⁴⁸
	Pimecrolimus	Calcineurin/ FKBP	Completed in 2008	NCT00226707	Pimecrolimus Cream 1% in Patients (18 Years of Age and Over) With Mild to Moderate Chronic Hand Dermatitis. In: https://ClinicalTrials.gov/show/NCT00226707 . ⁶³
	Tacrolimus	Calcineurin/ FKBP	Completed in 2008	_____	Schliemann, et al Tacrolimus ointment in the treatment of occupationally induced chronic hand dermatitis. Contact dermatitis. 2008;58(5):299–306. ⁶⁴
	Clobetasol propionate	Corticosteroid	Completed in 2012	NCT00828464	Study to Evaluate Safety, Efficacy and Tolerability of Clobetasol Propionate for Chronic Hand Dermatitis. In: https://ClinicalTrials.gov/show/NCT00828464 . ⁷¹
	Triamcinolone acetonide	Corticosteroid	Completed in 2012	NCT00890968	Safety and Efficacy Study of Triamcinolone Acetonide DuraPeel to Treat Hand Dermatitis. https://ClinicalTrials.gov/show/NCT00890968 . ⁷³
	Halometasone triclosan	Corticosteroid	Completed in 2018	NCT03246776	Microbial Colonization and Change of Chronic Keratinized Hand Eczema After Using Halometasone Triclosan. In: https://ClinicalTrials.gov/show/NCT03246776 . ⁷⁷
	Delegocitinib (LEO 124,249)	Pan-JAK	1. Completed in 2018 2. Completed in 2020	1. NCT02664805 2. NCT03683719	1. Proof of Concept, Twice Daily Applications of LEO 124,249 Ointment in the Treatment of Chronic Hand Eczema. In: https://ClinicalTrials.gov/show/NCT02664805 . ⁸³ 2. Phase 2b Dose-ranging Trial to Evaluate Delegocitinib Cream 1, 3, 8, and 20 mg/g Compared to Delegocitinib Cream Vehicle Over a 16-week Treatment Period in Adult Subjects With Chronic Hand Eczema. In: https://ClinicalTrials.gov/show/NCT03683719 . ⁸⁴
	Roflumilast (ARQ-252)	PDE4	Ongoing Phase 1/2b	NCT04378569	Safety and Efficacy of ARQ-252 Cream in Subjects With Chronic Hand Eczema. In: https://ClinicalTrials.gov/show/NCT04378569 . ³⁷
	AFX 5931	CCL5/CCL2	Completed in 2019	NCT03703895	A Study for a Topical Medication Versus Placebo in Patients With Hand Dermatitis. In: https://ClinicalTrials.gov/show/NCT03703895 . ³⁸

Systemic	Alitretinoin	Vitamin A derivative	Approved in EU, Canada, Israel, and South Korea	1. NCT00124475 2. NCT00817063	1. Ruzicka, et al Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. <i>British Journal of Dermatology</i> . 2008;158(4):808–817. ⁹⁹ 2. Fowler et al. A phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of alitretinoin (BAL4079) in the treatment of severe chronic hand eczema refractory to potent topical corticosteroid therapy. <i>Journal of Drugs in Dermatology</i> . 2014;13(10):1198–1204. ¹⁰³
	Acitretin	Vitamin A derivative	Completed in 2014	NCT01545284	Pilot Study on the Use of Acitretin for the Treatment of Severe Chronic Hand Dermatitis. In: https://ClinicalTrials.gov/show/NCT01545284 . ¹¹³
	Cyclosporine	Calcineurin/NFAT	Ongoing Phase 3	NCT03026946	Alitretinoin vs Cyclosporine in Severe Recurrent Vesicular Hand Eczema. In: https://ClinicalTrials.gov/show/NCT03026946 . ¹¹⁴
	Azathioprine	DNA synthesis	Ongoing Phase 3	NCT03026907	Alitretinoin vs Azathioprine in Severe Non-hyperkeratotic Hand Eczema. In: https://ClinicalTrials.gov/show/NCT03026907 . ¹¹⁵
	Gusacitinib (ASN002)	JAK/SYK	Completed in 2020	NCT03728504	Study to Evaluate ASN002 in Subjects With Moderate To Severe Chronic Hand Eczema. In: https://ClinicalTrials.gov/show/NCT03728504 . ⁵⁰
	Dupilumab	IL-4Ra	Ongoing Phase 2	NCT03861455	Efficacy and Safety of Dupilumab Chronic Hands Eczema Refractory to Highly Potent Topical Corticosteroids. In: https://ClinicalTrials.gov/show/NCT03861455 . ⁵²

penetrate the epidermal barrier, allowing them to function as both topical and systemic treatments for CHE. Though there have been only few mild reported side effects from these treatments, due to their being topical drugs, patient compliance may be limited by the fact that hands are utilized and washed frequently throughout the day, which could compromise the efficacy of the treatment. Several clinical trials are currently ongoing to assess the efficacy and safety of these molecules in the treatment of CHE.

Delgocitinib

One of the most exciting advances in the treatment of CHE has been the positive data seen from the use of pan-JAK inhibitor delgocitinib. Delgocitinib is a small molecule pan-JAK inhibitor that non-selectively modulates Th2 signaling via blockage of JAK1, JAK2, and JAK3.^{1,34,35,82} It is able to do so by blocking the signaling of several inflammatory cytokines such as IL-4, IL6, IL-13, IL-22, IL-31, and IFN γ , thereby suppressing the inflammatory cascade and preventing the downregulation of important barrier genes.^{1,15,21,34,36} Targeting the JAK signaling pathways is an effective way to achieve a therapeutic response in a majority of patients, as it targets multiple cytokine pathways involved in CHE.^{15,21} One phase 2 proof-of-concept trial completed in 2016 evaluated the use of delgocitinib ointment for eight weeks in 91 patients with chronic hand eczema compared to placebo.⁸³ Delgocitinib was found to improve disease severity in 45.7% of patients receiving the active treatment, compared to 14.9% in those receiving the placebo vehicle – this significant difference was seen in both irritant contact hand dermatitis as well as nonirritant type, suggesting its role as a therapeutic across CHE subtypes.³⁴ Further, it was deemed both safe and effective, as only three treatment-related adverse events were reported and none were serious. Such mild adverse events of delgocitinib include nasopharyngitis and headache, seen in a small minority of patients.³⁴ A more recent phase 2 randomized parallel assignment trial, completed in 2020, investigated the use of delgocitinib versus placebo in 258 patients with mild to severe chronic hand eczema over 16 weeks. The primary endpoint of this trial was to assess symptom improvement via the Investigator’s Global Assessment (IGA) score.⁸⁴ Results have not yet been published of this most recent trial.

Roflumilast

Roflumilast is a high potency selective inhibitor of the PDE4 receptor, which functions by degrading cyclic adenosine monophosphate (cAMP).^{85,86} Blocking the

PDE-4 receptor allows cAMP to signal the transcription of immune function genes such as anti-inflammatory IL-10, while simultaneously reducing the production of inflammatory cytokines such as TNF α and IFN γ , which have been identified as possible involved in CHE.^{15,87,88} Roflumilast has been investigated as a topical therapeutic for AD, but showed little to no efficacy.⁸⁹ It is currently being evaluated in a Phase 1/2b randomized parallel assignment trial involving 221 patients with chronic hand eczema.³⁷ Patients were randomized to receive one of two doses of topical roflumilast cream (ARQ-252) cream, 0.1% or 0.3%, or topical placebo for 2 weeks (phase 1) and 12 weeks (phase 2b). The primary outcome measures are safety and IGA score of either 0 “clear” or 1 “almost clear” skin after 12 weeks. This trial was recently started and is still ongoing, and results have not yet been published (Table 1).^{37,90}

AFX5931

Another investigational small molecule treatment targets cytokines directly to decrease the heightened inflammation involved in CHE. A recently developed topical anti-inflammatory, AFX5931, directly targets CCL5 and CCL2, two key inflammatory cytokines involved in the pathogenesis of allergen and irritant contact dermatitis.^{91–93} One Phase 4 clinical trial completed in 2019 compared the use of this topical anti-inflammatory to placebo.³⁸ In a 3:1 randomization, 15 subjects received the active treatment while 5 subjects received the vehicle placebo, and efficacy was assessed using the Investigator’s Global Assessment and Hand Eczema Severity Index. Phase 4 results have not yet been published (Table 1).³⁸

Existing Systemic Therapeutics

Systemic therapeutics are often needed to control moderate-to-severe CHE that is refractory to topicals. However, there are no FDA approved systemic treatments for CHE. Several systemic drugs are currently under clinical investigation, holding promise for the treatment of CHE. Systemics may require less frequent and precise patient compliance,⁹⁴ but they are often associated with a higher side effect profile, which can be a deterrent for patients.

One systemic therapeutic, alitretinoin, a retinoid vitamin A derivative, is approved for moderate-to-severe CHE in Europe, Canada, Israel, and South Korea,^{95–98} showing efficacy in treating refractory CHE in several large studies, as below. Retinoids are systemic vitamin A derivatives

that treat CHE by targeting the retinoic acid receptors A and/or X, which have been found to be downregulated in CHE skin.^{98,99} Targeting these receptors decreases inflammation by inhibiting keratinocyte-derived vascular endothelial growth factor, inhibiting keratin gene expression, and decreasing levels of IgE, Th2, and Th17 cells, while also increasing levels of Treg cells.^{1,100–102} Several studies have shown alitretinoin to be efficacious in the treatment of CHE.^{99–101,103–106} The most recent large Phase 3 trial completed internationally studied the safety and efficacy of oral alitretinoin in 1032 patients randomized to receive 10mg alitretinoin, 30mg alitretinoin, or a placebo pill once a day for 24 weeks. Improvement was measured by PGA, and 48% of participants achieved a score of “clear” (0) or “almost clear” (1) after 30mg of alitretinoin every day compared to only 17% of participants receiving placebo, with a dose-dependent response as well as a dose dependent side effect profile, including headaches, mucocutaneous events such as cheilitis and dry skin, hyperlipidemia, and decreased TSH and free thyroxine.⁹⁹ Though this trial and others internationally have shown therapeutic efficacy with its use, alitretinoin has a barrage of adverse effects including teratogenicity, xerosis, alopecia, cheilitis, myalgias, suicidality, headaches, and serum abnormalities such as elevated lipids and LFTs, and leukopenia.^{99–101,107–109} The possible side effects of this medication make it a suboptimal option as a long-term treatment for chronic hand eczema.⁹⁷

Another systemic retinoid, acitretin, has been approved for psoriasis and has shown some efficacy in severe CHE as well.^{96,110,111} Acitretin differs from alitretinoin in that it targets specifically the A retinoic acid receptors, but it has a similar effect of decreasing cellular differentiation, keratinization, and inflammation, and reducing Th1 and Th17 cell infiltration.^{96,112} Clinical trials conducted in Europe have assessed the use of acitretin, and though a reduction in symptoms was seen in patients compared to placebo, a lower percentage of patients experienced complete clearing of eczema than other systemic therapeutics.^{112,113} Like alitretinoin, the severe adverse effects likely outweigh the therapeutic efficacy - one review found that 43.1% of patients discontinued treatment with acitretin in the first few months of use due to adverse effects, such as xerosis or dermatitis.^{96,110} Due to their side effect profile, retinoids are an undesirable option for long-term treatment of CHE.

Two systemic broad immunosuppressants have also been tested as therapeutic options for moderate-to-severe CHE: cyclosporine and azathioprine.^{114,115} Both are oral

medications that suppress systemic inflammation, and both have been previously been explored as treatment options for atopic dermatitis. Systemic immunosuppressants have a variety of adverse effects and are often poorly tolerated, and further, they are non-specific and therefore are not as efficacious as other targeted systemics.^{78,116–120} Apremilast, a small molecule systemic drug that has showed a good safety profile in the treatment of psoriasis,^{121–123} has also been seen in clinical case series to successfully treat CHE, showing 90% clearance and a reduction in pruritus.^{124,125}

Methotrexate and systemic corticosteroids have also been empirically used for the treatment of moderate-to-severe chronic hand eczema.^{82,126–129} Although smaller scale studies, case reports, and retrospective reviews have found modest efficacy in their use, neither has been formally investigated in a registered clinical trial for the treatment of CHE.^{82,126,130,131}

Novel Systemic Therapeutics

The successful use of biologics and JAK-inhibitors in several inflammatory skin diseases, such as AD and psoriasis, is currently also being adopted for the treatment of severe CHE, with several drugs under investigation.

Small Molecules

Gusacitinib

A recent addition to the systemic treatments used for chronic hand eczema is gusacitinib (ASN002), an oral medication that blocks the JAK and SYK signaling pathways.^{132,133} Blocking SYK effectively inhibits IL-17 signaling, while blocking JAK inhibits Th1, Th2, and Th22 signaling, all of which are implicated in the immune pathogenesis of CHE across its various etiologies.^{133,134} As a JAK/SYK inhibitor, gusacitinib can have immunosuppressant side effects such as lymphocytopenia. Further, though it is often well tolerated by patients, mild-to-moderate adverse events have been reported, including headaches, nausea, diarrhea, and mild hypertension.^{135–137} A phase 2b clinical trial recently completed in mid-2020 evaluated the efficacy, safety, and tolerability of once daily oral gusacitinib in 97 participants with moderate-to-severe chronic hand eczema otherwise refractory to topical therapeutics.⁵⁰ Participants were randomized to receive 40mg of gusacitinib, 80mg of gusacitinib, or a placebo tablet for 32 weeks, and symptomatic change from baseline was measured using the mTLSS and PGA (Table 1).⁵⁰ Topline results from this trial showed dose-dependent improvements in mTLSS and PGA from baseline

in patients receiving both 80mg and 40mg of gusacitinib, compared to placebo, after 16 weeks. They also found that the drug was safe and well-tolerated.⁴⁷

Biologics

Dupilumab

Dupilumab is a monoclonal antibody that directly inhibits IL-4 and IL-13, two crucial cytokines in the Th2 signaling immune pathway that are implicated in the pathogenesis of allergic contact hand dermatitis and atopic hand dermatitis.^{21,46,138,139} Not only does dupilumab directly decrease Th2 signaling, it also indirectly decreases Th17 and Th22 signaling, and decreases epidermal proliferation while increasing epidermal differentiation.¹³⁸ Dupilumab is FDA approved to treat atopic dermatitis, and generally has a favorable safety profile, though injection-site erythema, conjunctivitis, and, rarely, head and neck dermatitis have been frequently reported.^{140–142} Of note, though dupilumab is more costly than some older systemic drugs, such as cyclosporine or methotrexate, the longer term safety profile and significant efficacy in clearing severe disease increase the cost efficacy of dupilumab use.^{143,144}

Dupilumab has been seen in several case studies to improve severe CHE that is otherwise refractory to highly potent topical therapeutics.^{49,53,139} Also, observational studies of AD patients with comorbid hand eczema on dupilumab have seen significant improvements in hand eczema, as measured by the hand eczema severity index (HECSI-75) and quality of life measures.⁴⁶ The findings in these case and observational studies have motivated an ongoing phase 2 clinical trial involving 94 participants with moderate-to-severe CHE.⁵² Participants were given a 300mg dose of dupilumab IM every 2 weeks or a placebo injection every 2 weeks, after a 600mg loading dose, for a total of 16 weeks. Change in clinical severity was assessed using the modified Total Lesion Symptom Score (mTLSS) change from baseline as a primary endpoint, with pruritis, pain, quality of life, sleep loss, IGA, PaGA, EASI, and IgE levels as secondary endpoints (Table 1).⁵² The study is ongoing and preliminary results have not yet been published, but the emerging anecdotal evidence of its efficacy in CHE makes dupilumab a possible treatment option for moderate-to-severe resistant CHE.

Conclusion

Chronic hand eczema (CHE) is a common skin condition that affects up to 10% of the population.^{1–4} It carries a significant burden, as affected individuals are often

unable to work or struggle to complete some activities of daily living due to the impact of CHE on their hands.^{2,6–8} Despite some similarities to AD, it is a heterogenous disease with a pathophysiology that is not yet fully studied. The multi-faceted immune profile of chronic hand eczema across its different etiologies complicates the process of developing a single treatment regimen with a high safety profile, that can work across all etiologies.

Thus far, several topical and systemic therapeutics have been proposed for the treatment of moderate as well as moderate-to-severe CHE, but, still, with few compelling results. Topical steroids – particularly higher potency steroids such as clobetasol propionate – have long demonstrated efficacy, particularly for mild-to-moderate cases, but are associated with adverse effects.^{33,69,145–147} The adverse effects associated with topical steroids, including skin atrophy and tachyphylaxis, hinder longer term use, which is often required for the treatment of CHE.^{69,70,146} Non-steroidal topical treatments such as calcineurin inhibitors and calcipotriol have also shown limited efficacy, but current treatment regimens are not standardized.^{33,61,64,148,149} Of note, a unique challenge of treating CHE with any topical drug is ensuring patients' compliance due to difficulty of keeping the therapy on the hands entirely, as hands are used and washed throughout the day, which may detract from the efficacy of a topical treatment. They are also limited in that they are used for mild-to-moderate hand eczema only, and more severe cases are typically resistant to topical therapies. Recent advances have been made with the topical pan-JAK inhibitor delgocitinib. It has emerged as a potential treatment for mild-to-severe disease, showing high efficacy with a favorable side effect profile.

Positive data for moderate-to-severe CHE has been shown outside of the US through the utilization of alitretinoin, which is a relatively cost-effective systemic drug that has shown efficacy in treating refractory, chronic moderate-to-severe cases of hand eczema.^{99–101,103,147,150} However, it has safety concerns, particularly for women of childbearing age who must adhere to strict birth control measures.^{100,104,151} Gusacitinib and dupilumab are emerging as possible effective treatment options for CHE,^{34,35,46,49,53,125,132,138} but are still in early phases of study and are financially costly for patients.^{143,144}

The significant disease burden of chronic and moderate-to-severe cases, in combination with the frequent lack of response of such cases to topical therapeutics, advocates for a new treatment paradigm. Previous research on other

inflammatory skin conditions, including AD and psoriasis, have made massive strides in developing effective, safe, and highly targeted treatments through the use of biomarkers that helped define disease patho-mechanisms. In CHE, such an approach is similarly needed, perhaps through minimally invasive biomarkers, such as tape strips. Tape strips are becoming more frequently used to study biomarker expression in skin diseases allowing for a more comprehensive understanding of its pathogenesis and paving the way for future treatment development.^{152–157} Increasing the understanding of underlying immune profiles of the different CHE phenotypes will allow for the development of valuable therapeutics and continued investigation of immune-based therapeutics such as delgocitinib, gusacitinib, and dupilumab.

Clinical Perspective and Future Directions

While the spectrum of therapeutic options for CHE has expanded in recent years, this condition is still an open challenge for physicians and patients alike. The limited number of effective therapeutics, the relapsing-remitting course of the disease, along with the low compliance to therapy, represent unmet needs with deleterious impacts on patients' quality of life. In light of the multiple pathogenetic factors at play in CHE (for example, atopic and non-atopic types), the therapeutic flowchart encompassing topical, phototherapy, and systemic treatments should be actively followed by the physician in order to ensure an effective intervention. Physicians should also encourage simultaneous preventative and hygiene measures, including hand moisturizing, avoiding excessive washing, and using mild-strength soaps and washes. These measures are synergistic with the use of topical and systemic drugs.

The heterogeneity of CHE can also hinder a timely diagnosis due to the wide range of CHE causes. This delay leads patients to be discouraged from pursuing treatment and causes a drop off in therapeutic adherence. The negative impact that this condition has on patients goes beyond the physical impairment caused by the eczema. Patients are often unable to work, have difficulty sleeping, and experience social embarrassment and shame around the appearance of their hands. This takes both a financial and emotional toll on patients. The enormous psychological burden of the condition makes CHE incredibly challenging to treat, as it is crucial to balance treatment trial and error with patient quality of life.

Thus, while topical treatments still find space in the treatment of mild CHE, systemic therapy should be discussed at the early stage with moderate-to-severe CHE patients, before the condition worsens. The broad immunomodulators azathioprine and cyclosporine, in addition to retinoids, are accepted as off-label treatments of CHE, but their use is compromised by severe long-term side effects. With the advent of more targeted therapies such as small molecules and biologics, we can modify the treatment paradigm of CHE, but more research into their efficacy across CHE phenotypes is needed.

In order to develop these targeted treatments, it is important to identify the molecular and cellular aspects that differentiate the various immune phenotypes of this condition. Due to the unique features of the hands, a minimally invasive diagnostic tool that is well-tolerated by patients and does not increase risk of infection or scarring would be ideal. Major strides have been made in the field of dermatology through the use of tape strips to characterize the immune and barrier gene profiles in various skin conditions – such an approach should be similarly applied to CHE. Future studies in CHE should focus on identifying the immune and barrier abnormalities of the condition that differentiate the various clinical phenotypes. The identification of specific upregulated biomarkers may also reveal reliable markers for clinical monitoring. This methodology would allow for an improvement in the process of drug development and encouraging treatment adherence. It is conceivable that in the next several years, other therapeutics – both topical and systemic – will be developed that are specifically tailored to the underlying pathogenesis of a given CHE etiology.

Abbreviations

ACD, allergic contact dermatitis; CHE, chronic hand eczema; ICD, irritant contact dermatitis; JAK, janus kinase; SYK, spleen tyrosine kinase.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

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