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Review

Chronic Hand Eczema: From Nosological Ambiguity to Therapeutic Identity in the Era of Targeted Topical JAK Inhibition

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Abstract

Chronic hand eczema (CHE) is a persistent and relapsing inflammatory dermatosis characterized by substantial functional impairment, psychosocial distress, and occupational disability. Although epidemiologically common and clinically burdensome, CHE has long suffered from nosological ambiguity, frequently interpreted as a localized manifestation of atopic dermatitis, psoriasis, allergic contact dermatitis, or cumulative irritant dermatitis. The recent regulatory approval of topical delgocitinib, a pan-Janus kinase (JAK) inhibitor specifically indicated for moderate-to-severe CHE inadequately controlled by topical corticosteroids, has reshaped both therapeutic strategy and conceptual framing of the disease. The introduction of a targeted therapy dedicated to CHE has reinforced its clinical identity while simultaneously highlighting its internal biological heterogeneity. Beneath the umbrella term "chronic hand eczema" lie distinct phenotypes characterized by variable barrier dysfunction, immune polarization, and environmental interaction. This review integrates current knowledge on epidemiology, pathophysiology, diagnostic stratification, therapeutic algorithms, phase III registrative evidence, emerging real-world data, and the central role of barrier restoration. Particular attention is devoted to the hand as a specialized barrier organ and to the interplay between inflammation and epidermal structural integrity. In the era of targeted therapy, precise diagnostic framing and barrier-oriented management are indispensable to optimize outcomes.

Keywords: chronic hand eczema; skin barrier; delgocitinib; JAK inhibitors; occupational dermatitis; barrier repair; real-world evidence; cosmetic dermatology

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1. Introduction

The recent marketing authorisation of a topical therapy specifically indicated for chronic hand eczema represents far more than the addition of a new drug to the dermatological armamentarium [1]. It marks a conceptual transition in how this disease is understood, framed, and managed. For decades, chronic hand eczema has occupied an uncertain position within dermatology: highly prevalent, clinically impactful, yet diagnostically fluid. It has been defined operationally as eczema localised to the hands persisting for more than three months or recurring at least twice within a year, but this definition has always been descriptive rather than pathobiological [2,3].

Historically, CHE has been interpreted as a localised expression of other inflammatory dermatoses. In some patients, it has been considered a manifestation of atopic dermatitis

restricted to the hands. In others, particularly those with hyperkeratotic palmar plaques, it has overlapped clinically with palmoplantar psoriasis. In occupational contexts, cumulative irritant dermatitis or allergic contact dermatitis have been invoked as primary aetiologies [3,4]. This interpretative variability has shaped therapeutic strategies: treatments have been extrapolated from other diseases, and CHE has rarely been approached as a condition with its own immunological architecture [5,6].

The approval of topical delgocitinib, a pan-JAK inhibitor evaluated in large phase III trials and specifically indicated for moderate-to-severe CHE inadequately controlled by topical corticosteroids, has altered this landscape [7]. Regulatory recognition confers legitimacy. When a therapy is approved for a defined indication, it implicitly affirms that indication as a distinct clinical entity. Yet this therapeutic milestone has also illuminated a deeper reality: under the umbrella term "chronic hand eczema" lies substantial biological heterogeneity [3].

CHE is not a monolithic disease. Hyperkeratotic-fissured forms, vesicular (pompholyx-like) variants, pulpitis, and mixed phenotypes likely represent convergent clinical expressions of partially distinct pathogenic pathways [8–10]. Some patients display Th1/Th17-dominant signatures reminiscent of psoriasis, whereas others show Th2 skewing typical of atopic inflammation [9]. Environmental factors, including irritant exposure, wet work, and allergen contact, further modulate disease expression. Thus, CHE may be best conceptualised not as a single disease but as a barrier-centred inflammatory platform characterised by phenotypic diversity [11,12].

In the era of targeted therapy, this heterogeneity has practical significance. Broad immunosuppressive strategies can obscure underlying mechanistic differences; targeted modulation requires a more precise understanding of inflammatory drivers [3]. The availability of a pan-JAK inhibitor does not simplify diagnosis—it intensifies the need for accurate clinical framing. Patch testing, occupational assessment, and careful morphological evaluation remain foundational [7].

From a cosmetic dermatology perspective, the renewed focus on CHE is equally significant. The hand is a uniquely exposed barrier organ, subject to mechanical stress, environmental insult, and social visibility. Barrier dysfunction is not merely a secondary phenomenon but a central pathogenic event. Therefore, any modern therapeutic strategy must integrate anti-inflammatory modulation with active barrier restoration [13–16].

This review explores chronic hand eczema through this expanded lens: as a clinically unified yet biologically heterogeneous disorder at the intersection of immune dysregulation and barrier failure, now entering an era of therapeutic precision.

2. Epidemiology and Clinical Burden

Hand eczema is among the most prevalent inflammatory skin disorders, with lifetime prevalence estimates ranging from 14% to 15% and annual prevalence between 4% and 10% [9–11]. A substantial proportion evolves into chronic disease, with persistent or recurrent symptoms reported in up to half of patients five years after onset [10].

CHE accounts for approximately 80–90% of occupational dermatoses in Europe [12]. High-risk professions include healthcare workers, hairdressers, food handlers, cleaners, and metalworkers, where repetitive exposure to water, detergents, disinfectants, and irritants—collectively termed "wet work"—plays a pivotal role [13,14].

The functional and psychosocial burden is considerable. The hands are instruments of interaction, labor, and identity. Fissures, pain, pruritus, and hyperkeratosis impair manual function and social confidence. Dermatology Life Quality Index (DLQI) scores in moderate-to-severe CHE are comparable to those observed in psoriasis [7,15]. Indirect

socioeconomic consequences include work absenteeism, job modification, and in severe cases occupational change [12].

3. The Hand as a Specialized Barrier Organ

The palmar skin is one of the most structurally specialised regions of the human integument. Its architecture reflects evolutionary adaptations to repetitive mechanical stress, tactile precision, and environmental exposure. Unlike most body sites, palmar skin lacks pilosebaceous units and exhibits a markedly thickened stratum corneum, compact orthokeratosis, and distinct keratin expression patterns, including high levels of keratins K6, K16, and K17 under stress [16,17]. The density of eccrine sweat glands is particularly elevated, contributing to thermoregulation and grip while also influencing hydration dynamics and local pH.

The stratum corneum of the palm is not merely thicker; it is biophysically distinct. Corneocytes are densely packed and embedded within a highly organised lipid matrix composed predominantly of ceramides, cholesterol, and free fatty acids, arranged in lamellar bilayers [18]. This lipid organisation is essential for controlling permeability, maintaining mechanical cohesion, and preventing transepidermal water loss (TEWL). The corneodesmosomal network provides structural integrity, while natural moisturising factors (NMF), derived largely from filaggrin degradation, maintain hydration and flexibility.

However, this specialization carries a cost. The absence of sebaceous glands reduces endogenous lipid supply, making palmar skin more reliant on intrinsic barrier integrity and exogenous moisturisation. Repetitive friction, pressure, microtrauma, and exposure to detergents or solvents can disrupt corneodesmosomal cohesion and alter lipid lamellar organisation. Wet work further induces repetitive swelling and contraction of corneocytes, mechanically destabilising the barrier.

In chronic hand eczema (CHE), these structural vulnerabilities are exacerbated. Studies have shown alterations in ceramide subclass composition, reduced long-chain ceramides, and impaired lamellar organisation, even in patients without classical atopic dermatitis [19,20]. Reduced filaggrin expression, whether genetically determined or cytokine-mediated, compromises NMF production and stratum corneum hydration. Elevated TEWL confirms functional barrier impairment [21].

Mechanical stress also activates intracellular signalling pathways in keratinocytes. Mechanotransduction induces the release of pro-inflammatory mediators, oxidative stress, and upregulation of stress keratins. Reactive oxygen species generated by environmental exposure further disrupt lipid membranes and protein structures. Thus, the palmar barrier in CHE is not simply passively damaged; it is actively involved in inflammatory amplification.

Another emerging dimension is the cutaneous microbiome. Altered barrier function modifies microbial composition, potentially favouring dysbiosis. Although microbiome data specific to CHE remain limited, parallels with atopic dermatitis suggest that barrier disruption may facilitate colonisation by pro-inflammatory microbial communities, further enhancing immune activation.

From a cosmetic and translational perspective, the hand must be understood as a highly specialised barrier interface whose structural resilience depends on lipid integrity, hydration equilibrium, mechanical cohesion, and immune homeostasis. In CHE, structural failure is not secondary to inflammation alone; it is both a trigger and a perpetuator of disease. Effective management must therefore target not only cytokine signalling but also the restoration of lamellar lipid architecture and corneocyte cohesion.

4. Pathophysiology: The Barrier–Immune Axis

Chronic hand eczema arises from a complex and dynamic interaction between epidermal barrier dysfunction and immune dysregulation. Rather than a unidirectional inflammatory cascade, CHE represents a self-reinforcing bidirectional loop in which structural fragility and immune activation mutually perpetuate.

Barrier disruption initiates the process (Figure 1). Mechanical microfissures, lipid disorganisation, and increased TEWL expose deeper epidermal layers to environmental irritants, allergens, and microbial antigens. Keratinocytes respond not merely as structural cells but as active immunological sentinels. Upon stress, they release epithelial-derived alarmins, including thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 [22]. These cytokines activate Langerhans cells and dermal dendritic cells, promoting polarisation of naïve T cells.

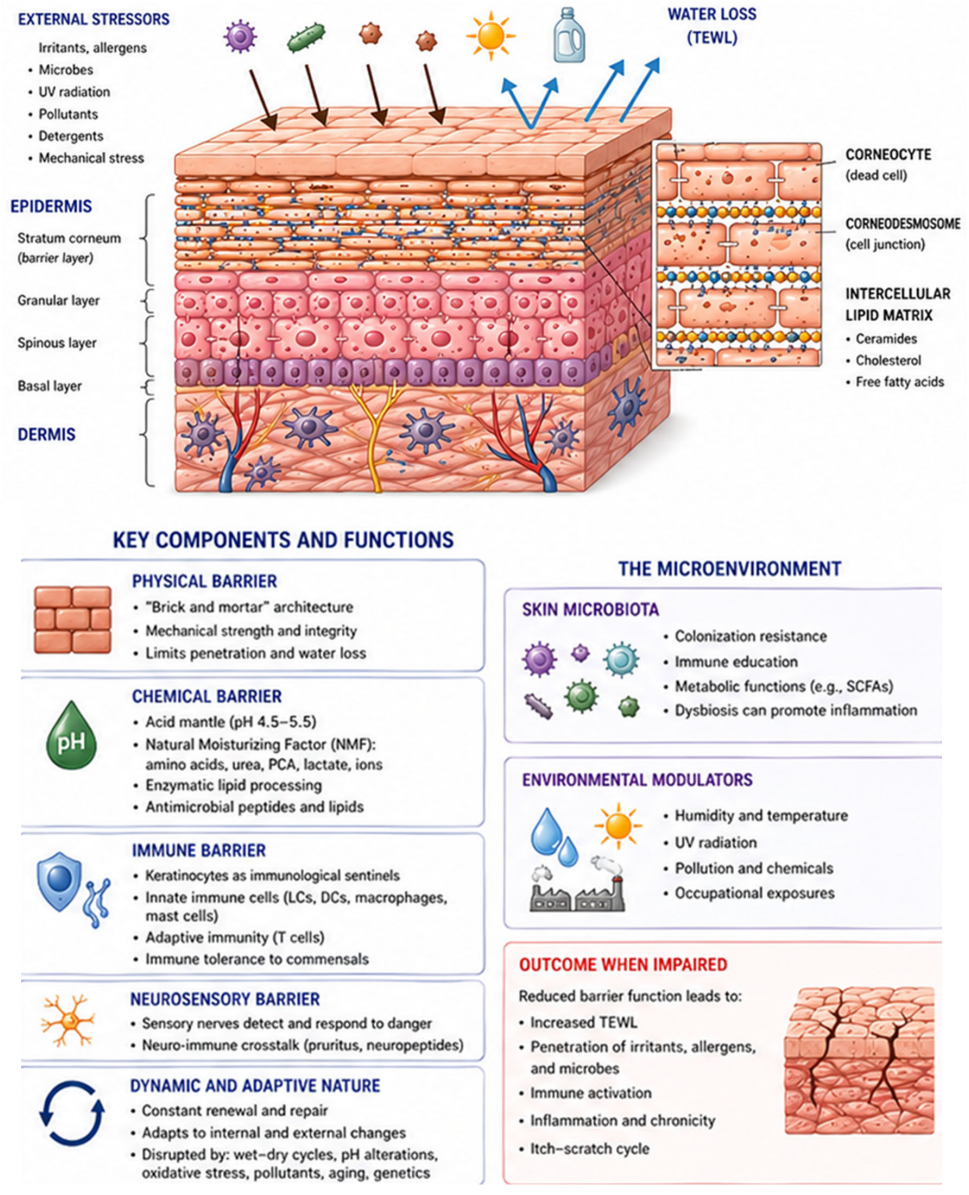


Figure 1. The complexity of the skin barrier: The skin barrier is a multilayered, dynamic defense system integrating physical, chemical, immune, and neurosensory components. Its integrity depends on coordinated interactions between structural lipids, keratinocytes, microbiota, and environmental factors. Barrier disruption leads to increased transepidermal water loss (TEWL), enhanced penetration of external agents, and initiation of inflammatory processes.

Immune polarisation in CHE is heterogeneous. Hyperkeratotic phenotypes frequently show enhanced Th1 and Th17 signatures, with increased expression of IFN-γ, IL-17A, and IL-22 [23]. In particular, IL-22 promotes keratinocyte hyperproliferation and abnormal differentiation, contributing to scaling and thickening. In contrast, vesicular or pompholyx-like variants often show stronger Th2 skewing, characterised by upregulation of IL-4 and IL-13 [24]. Mixed phenotypes display overlapping signatures, reflecting the convergence of multiple inflammatory axes.

This heterogeneity underscores a central concept: CHE is not defined by a single immune pathway but by convergence at key signalling nodes(Figure 2). Many cytokines are implicated in CHE signalling through the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway. IL-4 and IL-13 activate JAK1/JAK3; IFN-γ signals through JAK1/JAK2; and IL-22 engages JAK1/TYK2 [25]. This shared intracellular machinery explains why pan-JAK inhibition can modulate diverse inflammatory polarisations simultaneously.

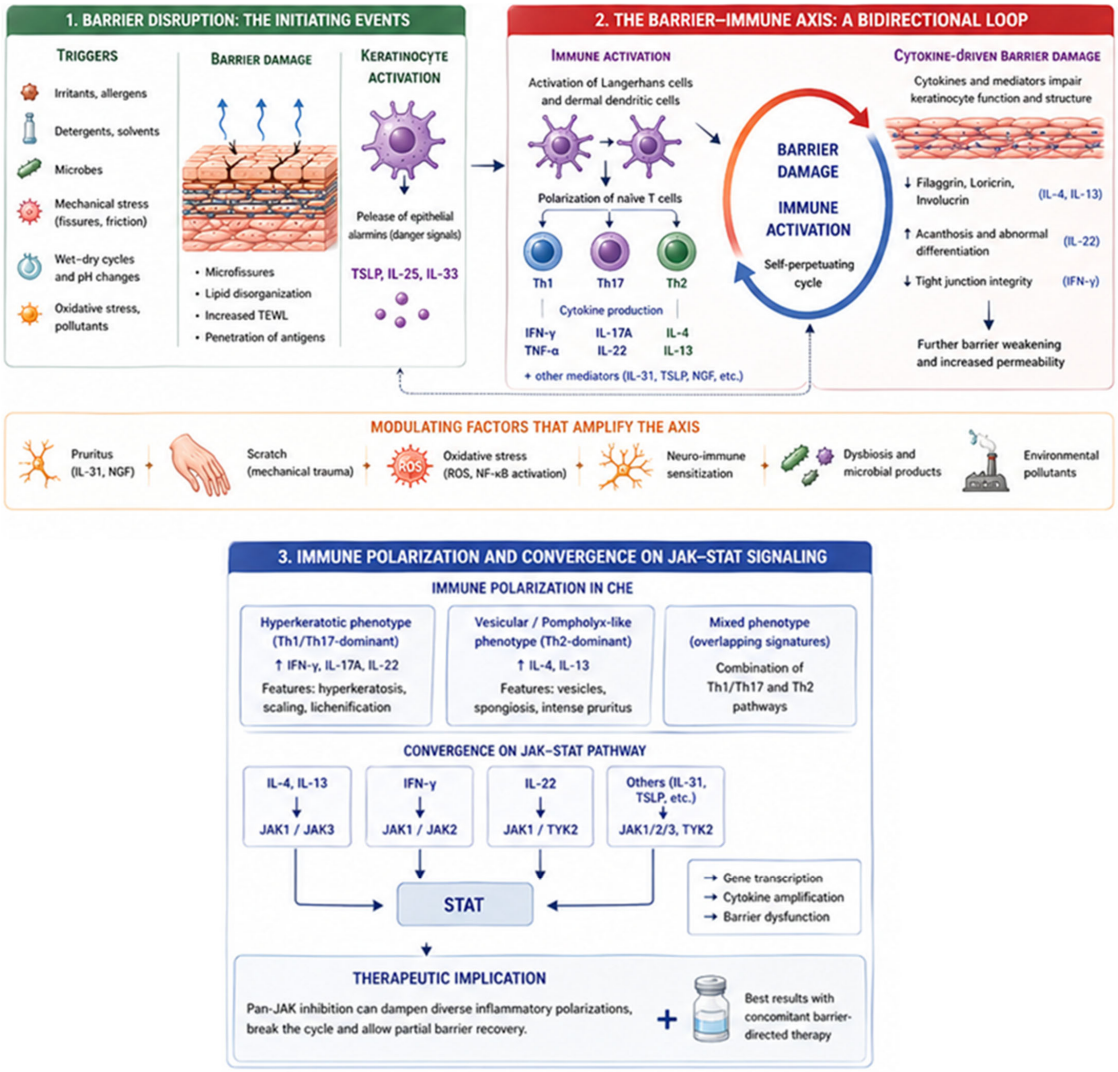


Figure 2. The skin barrier–immune axis in chronic hand eczema (CHE): Chronic hand eczema is driven by a bidirectional, self-perpetuating loop between barrier dysfunction and immune activation. Barrier disruption triggers keratinocyte-derived alarmins (TSLP, IL-25, IL-33), leading to immune polarization (Th1/Th17 or Th2). Cytokines further impair barrier integrity via effects on differentiation, tight junctions, and lipid organization. Multiple cytokines converge on the JAK–STAT pathway, providing a key therapeutic target.

Chronic cytokine exposure further damages the barrier. IL-4 and IL-13 downregulate expression of filaggrin, loricrin, and involucrin, weakening terminal differentiation [26]. IL-22 induces acanthosis and disrupts normal keratinocyte maturation [27]. IFN-γ compromises tight junction integrity. Thus, immune activation feeds back to impair structural resilience, perpetuating the barrier–inflammation loop.

An additional layer involves the neuroimmune axis. Pruritus in CHE is not merely symptomatic; scratching causes further mechanical trauma, thereby amplifying barrier disruption. Cytokines such as IL-31 and nerve growth factor enhance sensory nerve activation, thereby contributing to the itch–scratch cycle.

Oxidative stress and environmental pollutants also modulate this axis. Reactive oxygen species can activate NF-κB signaling in keratinocytes, enhancing cytokine production. Repeated wet–dry cycles alter epidermal pH, affecting enzymatic lipid processing and further destabilizing the barrier [24].

Viewing CHE as a barrier–immune axis disorder has direct therapeutic implications. Broad immunosuppression may dampen inflammation but does not necessarily restore structural lipid organisation. Conversely, emollient therapy alone cannot suppress cytokine-driven immune amplification. Targeted JAK inhibition occupies an intermediate mechanistic position: by suppressing upstream cytokine signalling, it may permit normalisation of keratinocyte differentiation and partial structural recovery [25]. However, full restoration of lamellar lipid architecture likely requires concomitant barrier-directed interventions.

In this light, CHE can be viewed as a disorder of failed resilience. The palmar barrier, subjected to extraordinary mechanical and environmental demands, becomes structurally compromised. Immune activation, once triggered, reinforces fragility. Effective therapy must therefore interrupt inflammatory signaling while simultaneously rebuilding structural competence.

5. Diagnostic Framing in the Era of Targeted Therapy

Historically, therapeutic escalation in CHE followed a severity-based approach. With the availability of targeted agents, stratification must now incorporate both aetiologic and phenotypic characterisation.

Patch testing remains essential to exclude allergic contact dermatitis [5]. A detailed occupational history identifies cumulative irritant exposure. A full-body examination differentiates psoriasis from generalised atopic dermatitis. Histopathology may assist but often lacks specificity [2].

The presence of a targeted topical JAK inhibitor does not obviate this framework. Instead, it underscores the need for accurate classification. Misdiagnosis risks suboptimal outcomes and therapeutic misalignment. Precision dermatology in CHE demands integration of clinical morphology, exposure assessment, and immunological inference.

6. Therapeutic Evolution: From Broad Immunosuppression to Targeted Modulation

For many years, therapeutic management of CHE followed a relatively linear, severity-based escalation. High-potency topical corticosteroids were a first-line therapy and remain effective for short-term control in a substantial proportion of patients. Their anti-inflammatory efficacy is rapid and broad, suppressing multiple cytokine pathways simultaneously. However, this breadth is accompanied by limitations. Relapse after discontinuation is common, and chronic use carries risks of cutaneous atrophy, telangiectasia, and barrier thinning—ironically exacerbating structural fragility in an already compromised tissue.

Phototherapy, including PUVA and narrowband UVB, has been used in refractory cases. Although effective in selected patients, logistical constraints, cumulative exposure risks, and limited accessibility limit its widespread applicability [28].

Oral alitretinoin marked the first systemic therapy specifically approved for severe CHE refractory to topical corticosteroids. In the pivotal BACH trial, approximately 48% of patients in the 30 mg arm achieved clear or almost clear status after 24 weeks [29]. This was a major advance. Yet systemic exposure introduces monitoring requirements and adverse events, including headache, dyslipidemia, mucocutaneous dryness, and strict teratogenic precautions. The delayed onset of maximal response—often requiring several months—contrasts with patient expectations for rapid improvement in a functionally disabling condition.

The introduction of topical delgocitinib fundamentally alters this therapeutic landscape. By targeting the JAK-STAT pathway—a nodal signalling hub for multiple cytokines, including IL-4, IL-13, IL-22, and IFN-γ—it provides upstream modulation across diverse immune polarisations. Unlike corticosteroids, it does not induce epidermal atrophy. Unlike alitretinoin, it avoids systemic teratogenicity and the need for laboratory monitoring [30].

The comparative positioning of therapies can therefore be conceptualised along three axes: breadth of immunomodulation, systemic exposure, and impact on barrier integrity. Corticosteroids provide broad suppression but may compromise structural resilience with chronic use. Alitretinoin exerts systemic immunomodulatory and differentiation effects, albeit with systemic adverse events. Delgocitinib provides targeted upstream modulation with minimal systemic absorption and theoretical advantages in preserving epidermal architecture.

This shift underscores the need for individualised therapeutic decision-making. In moderate disease unresponsive to topical steroids, delgocitinib may now be considered before systemic retinoids. In severe hyperkeratotic cases with extensive involvement, systemic therapy may still be appropriate. The era of "one algorithm fits all" has given way to therapeutic stratification.

7. Registrative Evidence: DELTA 1 and DELTA 2

The development programme of topical delgocitinib for chronic hand eczema represents the first large-scale, rigorously conducted effort to evaluate a targeted topical immunomodulator specifically in this disease population [7]. The pivotal DELTA 1 and DELTA 2 trials were randomised, double-blind, vehicle-controlled phase III studies enrolling adult patients with moderate-to-severe CHE inadequately controlled by potent topical corticosteroids. Importantly, the inclusion criteria required prior failure or insufficient response to corticosteroids, thereby positioning delgocitinib in a clinically meaningful therapeutic setting rather than as first-line therapy [7].

The primary endpoint in both trials was Investigator's Global Assessment for Chronic Hand Eczema (IGA-CHE) success at week 16, defined as clear or almost clear skin with at least a two-grade improvement from baseline. This composite endpoint integrates both absolute disease status and relative change, thus reflecting clinically meaningful improvement rather than marginal variation [7].

In both DELTA 1 and DELTA 2, the proportion of patients achieving IGA-CHE success at week 16 was significantly higher in the delgocitinib arm than in the vehicle arm. The magnitude of the difference was robust and consistent across trials, supporting the reproducibility of efficacy. Beyond statistical significance, the clinical relevance of the response deserves emphasis. CHE is a functionally disabling condition, and achieving "clear" or "almost clear" status corresponds not merely to cosmetic improvement but to restoration of manual function and reduction of fissure-related pain [7].

Secondary endpoints provided additional granularity. The Hand Eczema Severity Index (HECSI), a quantitative measure incorporating erythema, vesiculation, fissuring, scaling, and extent of involvement, showed significant reductions in the active treatment group. Improvements in HECSI scores were detectable as early as week 4, indicating a relatively rapid onset of action. In a disease historically characterised by protracted therapeutic courses—particularly with systemic retinoids—the early separation from vehicle is clinically meaningful.

Pruritus, often underestimated in CHE but frequently severe and sleep-disrupting, was significantly reduced in patients receiving delgocitinib. The temporal pattern of itch reduction mirrored overall inflammatory improvement, suggesting effective interruption of cytokine-mediated neuroimmune signalling.

Quality-of-life outcomes further reinforced efficacy. DLQI scores improved significantly versus vehicle, reflecting functional and psychosocial benefit. Given the occupational implications of CHE, improvements in daily functioning are as critical as objective lesion clearance.

Safety outcomes are particularly relevant in long-term management. The majority of adverse events were mild application-site reactions, such as transient burning or irritation. Importantly, systemic exposure was minimal, and no clinically meaningful laboratory abnormalities were observed. Unlike systemic immunosuppressants or retinoids, delgocitinib did not require laboratory monitoring. No signal for systemic JAK-associated adverse effects emerged in the registrative programme [31].

Long-term open-label extension studies provided insight into durability of response and cumulative safety. Patients who responded in the double-blind phase generally maintained improvement with continued use. No new safety signals were identified over extended treatment periods. The absence of tachyphylaxis or late-emerging adverse events strengthens the therapeutic profile for chronic use [31].

An important nuance concerns phenotypic responsiveness. Subgroup analyses suggested efficacy across hyperkeratotic and vesicular phenotypes, although dedicated stratified analyses remain limited. Given the heterogeneity of CHE, demonstration of cross-phenotype efficacy is encouraging and consistent with the upstream position of JAK signaling in multiple cytokine pathways.

Notably, registrative trials did not incorporate instrumental barrier function measurements such as TEWL or lipidomic profiling. However, clinical reduction of fissuring and scaling implies structural normalization of the stratum corneum. Future trials integrating objective barrier metrics would further elucidate the structural impact of JAK inhibition in CHE.

8. Real-World Evidence: Translating Trial Efficacy into Clinical Practice

While randomized controlled trials establish internal validity, real-world evidence determines external validity. Early observational data and post-marketing cohorts provide preliminary but important insight into how delgocitinib performs outside the controlled conditions of phase III trials [32].

Initial real-world reports describe rapid reduction in HECSI scores within the first 4–8 weeks of treatment, mirroring trial kinetics. Importantly, real-world populations often include patients with longer disease duration, multiple prior treatment failures, and greater phenotypic variability. The observation that response rates remain clinically meaningful in such settings supports generalizability.

Adherence patterns in routine practice appear favorable. The absence of systemic adverse effects and laboratory monitoring reduces patient burden. In contrast to systemic retinoids, which may be discontinued due to mucocutaneous side effects or laboratory abnormalities, topical delgocitinib demonstrates high persistence rates in early cohorts.

One of the most relevant real-world observations concerns hyperkeratotic CHE [30]. Historically, this phenotype has been considered particularly refractory. Preliminary observational data suggest that delgocitinib achieves meaningful reduction in hyperkeratosis and fissuring, although complete clearance may require longer treatment duration. The mechanistic rationale—suppression of IL-22 and Th17-associated pathways—supports efficacy in this subgroup.

Comparative real-world data between delgocitinib and alitretinoin are emerging but remain limited. Retrospective analyses suggest that delgocitinib may offer faster onset of symptomatic relief, particularly regarding pruritus and fissure pain, whereas alitretinoin may induce more profound keratolytic effects in selected hyperkeratotic cases. However, systemic adverse event profiles often limit long-term retinoid use. Direct head-to-head prospective studies would be valuable to clarify positioning.

From an occupational medicine perspective, real-world cohorts emphasize functional restoration. Patients report improved ability to perform wet work, reduced absenteeism, and enhanced manual dexterity. These outcomes, rarely captured in controlled trials, are critical in CHE.

Safety findings in routine practice are consistent with trial data. Application-site reactions remain the most common adverse event and are generally transient. No systemic safety concerns have been reported to date. Continued pharmacovigilance remains necessary, particularly given class-wide attention to JAK inhibition in systemic formulations, although topical exposure differs substantially in pharmacokinetics.

Real-world data also underscore the importance of integrated management. Patients receiving concomitant barrier-repair regimens—ceramide-rich emollients, occupational skin protection programs—demonstrate more sustained remission. This observation reinforces the concept that anti-inflammatory modulation must be coupled with structural restoration [33].

Limitations of current real-world evidence include relatively short follow-up periods, absence of standardized outcome measures across cohorts, and potential selection bias. Prospective registries incorporating objective barrier assessments, phenotypic stratification, and long-term follow-up are needed (Table 1).

Table 1. Comparative overview of therapeutic strategies and key evidence in chronic hand eczema (CHE).

Therapy/Study	Study Design	Population	Efficacy Outcomes	Onset of Action	Safety Profile	Key Limitations
Alitretinoin (BACH trial)	Phase III, randomized, double-blind, placebo-controlled trial	Adults with severe refractory CHE treated with potent topical corticosteroids	~48% achieved "clear" or "almost clear" status at week 24 (30 mg dose)	Gradual; maximal response typically requires several months	Systemic adverse events including headache, dyslipidemia, and mucocutaneous dryness; strict teratogenic risk; requires laboratory monitoring	Delayed onset; systemic exposure; contraindications in pregnancy; tolerability may limit long-term use
Phototherapy (PUVA, NB-UVB)	Heterogeneous clinical studies and real-world use	Patients with refractory CHE	Clinically effective in selected patients; variable response rates	Moderate	Risks associated with cumulative UV exposure; potential long-term carcinogenicity	Limited accessibility; logistical burden; lack of standardized protocols; cumulative exposure concerns
Delgocitinib (DELTA 1 & 2 trials)	Phase III, randomized, double-blind, vehicle-controlled trials	Adults with moderate-to-severe CHE inadequately controlled by topical corticosteroids	Significantly higher IGA-CHE success rates vs vehicle at week 16; significant HECSI reduction; improvements in pruritus and DLQI	Relatively rapid; separation from vehicle observed as early as week 4	Favorable safety profile; predominantly mild application-site reactions; minimal systemic exposure; no laboratory monitoring required	Absence of objective barrier function endpoints; limited phenotype-specific analyses
Delgocitinib (real-world evidence)	Observational studies and post-marketing cohorts	Broad, heterogeneous CHE populations, including treatment-refractory patients	Clinically meaningful reductions in HECSI; improvements in pruritus and functional outcomes; consistent effectiveness across phenotypes	Rapid; improvements typically observed within 4–8 weeks	Consistent with clinical trials; good tolerability; high adherence and persistence; no systemic safety signals identified to date	Short follow-up duration; heterogeneity of study design and endpoints; potential selection bias; need for prospective registries

9. Integrative Perspective on Registrative and Real-World Data

Taken together, registrative trials establish efficacy and safety under controlled conditions, whereas real-world data confirm feasibility, adherence, and functional benefit in heterogeneous populations. The convergence of these datasets strengthens confidence in delgocitinib as a meaningful therapeutic advance [30].

However, important questions remain open. Which phenotypes derive the greatest benefit? Does early intervention alter long-term disease trajectory? Can barrier recovery be objectively quantified during JAK inhibition? Addressing these questions will require integration of molecular biomarkers, biophysical measurements, and longitudinal cohort data.

In the broader therapeutic context, delgocitinib represents the first example of precision topical immunomodulation specifically validated in CHE [7]. Its emergence signals a shift from generalized suppression toward targeted pathway modulation. Real-world validation suggests that this conceptual shift translates into tangible clinical improvement.

10. Barrier Repair and Cosmetic Integration

In cosmetic dermatology, barrier repair in chronic hand eczema (CHE) should be viewed as a formulation-focused, mechanism-based intervention rather than just a general emollient effect. While targeted JAK inhibition reduces cytokine signalling, it does not fully restore the altered lipid structure of the stratum corneum (SC). Therefore, optimal management combines biological modulation with structurally appropriate lipid replacement [18].

Formulation Principles: Lipid Stoichiometry and Lamellar Compatibility

The SC acts as a lamellar lipid system where ceramides, cholesterol, and free fatty acids (FFAs) must be supplied in balanced proportions to enable self-assembly into bilayers. Formulations close to physiological ratios (1:1:1) or ceramide-dominant systems (e.g., 3:1:1) are linked with improved lamellar organisation and decreased TEWL.

Key formulation requirements include:

- Ceramide profile: includes long- and ultra–long-chain ceramides (e.g., CER EOS, NP, AP) to promote orthorhombic packing and barrier cohesion [34].
- Cholesterol: modulation of lipid phase behaviour and bilayer stability.
- FFAs (C16–C24): contribution to pH regulation, antimicrobial defence, and enzymatic lipid processing.

Unbalanced formulations (e.g., lacking cholesterol or FFAs) may impede lamellar assembly despite high lipid levels. Therefore, achieving stoichiometric balance and structural compatibility is vital for quality.

Delivery Systems and Adjunctive Components

From a translational formulation perspective, delivery systems are crucial. Multilamellar emulsions (MLE) and lipid-mimetic systems aid in their integration into the SC by mimicking the native lamellar architecture. These systems exemplify a convergence of pharmaceutical and cosmetic design.

Adjunctive components should be selected based on functional roles:

- Humectants (glycerol, urea 2–5%, sodium PCA): support hydration and NMF function.
- pH-modulating systems: restore the acidic mantle and optimise lipid-processing enzymes.
- Mild keratoplastics (urea 5–10%, lactic acid): for hyperkeratotic phenotypes.
- Antioxidants/barrier-supportive actives (e.g., niacinamide): mitigate oxidative stress-induced lipid damage.

Occlusive agents (petrolatum, dimethicone) remain important, especially in fissured CHE, but should be included in lipid-replacement systems rather than used alone.

Translational Assessment of Barrier Function

Integration of instrumental biophysical measurements can enhance clinical evaluation and research design:

- TEWL: functional barrier integrity;
- Corneometry: hydration status;
- Raman spectroscopy/lipidomics: SC lipid composition and organisation.

Such tools facilitate objective monitoring of barrier recovery during combined JAK inhibition and cosmetic therapy, fostering a more quantitative, translational approach.

Practical Implementation for Clinicians

Barrier repair should be prescribed with the same rigour as pharmacological therapy:

- Frequency: ≥2–3 applications/day and systematically post-hand washing;
- Night regimen: occlusion (e.g., cotton gloves) in fissured or severe cases;
- Phenotype-oriented selection:
    - Hyperkeratotic CHE: lipid-replacement + mild keratolytics;
    - Vesicular/inflammatory CHE: high-lipid, low-irritancy emulsions;
    - Fissured CHE: layered approach (barrier cream + occlusive);
- Integration: emollients as baseline therapy, with anti-inflammatory agents applied sequentially or in combination.

Patient adherence is heavily influenced by cosmetic acceptability (texture, absorption, tolerability); therefore, product selection should account for sensory qualities alongside composition. In occupational CHE, barrier repair must be combined with exposure reduction and protective measures.

Integrated Therapeutic Model

The optimal management of CHE can be conceptualised as dual-target therapy:

- Biological axis: targeted immunomodulation (e.g., JAK inhibition).
- Structural axis: formulation-driven restoration of SC lipid architecture.

By reducing IL-4/IL-13 signalling, JAK inhibition may indirectly restore keratinocyte differentiation and filaggrin expression; however, external lipid supplementation remains crucial for rebuilding lamellar structure [35].

This comprehensive, cosmetic science-focused framework aligns with precision dermatology and promotes sustained remission by restoring both inflammatory balance and barrier resilience.

11. Discussion

The emergence of targeted topical JAK inhibition for chronic hand eczema forces a re-evaluation of both disease identity and therapeutic philosophy [7]. CHE has historically been managed through extrapolation—treated as localized atopic dermatitis, as contact dermatitis, or as psoriasis depending on clinical resemblance [6]. This pragmatic approach was understandable in the absence of disease-specific therapies. However, it fostered a conceptual ambiguity that obscured underlying heterogeneity.

Regulatory recognition of delgocitinib consolidates CHE as a legitimate therapeutic indication [30]. Yet this consolidation should not be mistaken for simplification. Rather, it highlights the need to reconcile two realities: CHE is a clinically recognizable entity with shared features of chronicity, localization, and barrier compromise, but it is biologically diverse.

The barrier–immune axis offers a unifying conceptual framework. Regardless of immune polarization, barrier disruption is nearly universal in CHE [36]. Increased transepidermal water loss, altered lipid composition, reduced filaggrin expression, and microfissuring create a permissive environment for inflammatory amplification. Cytokine-driven inflammation further impairs keratinocyte differentiation, perpetuating a self-sustaining loop. Thus, CHE may be understood as a disorder of reciprocal reinforcement between structural fragility and immune activation.

Targeted JAK inhibition intervenes at a critical convergence point. By attenuating multiple cytokine pathways simultaneously, it interrupts inflammatory signaling without broad cytotoxic immunosuppression. Although registrative trials did not directly measure barrier biophysics, clinical improvements in fissuring and scaling imply structural normalization. Indirect evidence from atopic dermatitis suggests that suppression of IL-4 and IL-13 can restore barrier protein expression. Whether similar structural restoration occurs in CHE requires dedicated investigation [37,38].

Real-world data reinforce the clinical relevance of trial findings [30]. Rapid reduction in HECSI scores, high patient adherence, and improved occupational functionality have been observed. Importantly, real-world settings capture phenotypic diversity more accurately than controlled trials, suggesting that efficacy extends beyond narrowly defined subgroups.

For cosmetic dermatology, the implications are profound. The hands are constantly visible and socially expressive. Chronic fissures, hyperkeratosis, and erythema carry psychosocial weight beyond symptom severity. Barrier repair through lipid-replenishing emollients, occupational skin protection programs, and patient education must be integrated with pharmacologic innovation. Anti-inflammatory control without barrier reinforcement risks recurrence [38].

This review has several limitations. It is based on a narrative synthesis rather than a systematic approach, which may introduce selection bias. The heterogeneity of available studies in terms of design, populations, and outcome measures limits comparability. In addition, emerging areas such as biomarker-driven stratification and advanced barrier assessment remain incompletely defined. Finally, real-world data on newer targeted therapies remain limited, particularly regarding long-term outcomes.

Future research should prioritise precision-oriented approaches, including the identification of reliable biomarkers and the development of standardised outcome measures. Clinical studies that integrate targeted therapies with structured barrier-repair skincare are needed to define synergistic effects. Well-designed longitudinal real-world cohorts will also be essential to assess long-term efficacy, adherence, and functional outcomes, while advances in barrier assessment may support more personalised management across CHE phenotypes.

12. Conclusions

Chronic hand eczema is undergoing a conceptual transformation. Historically regarded as a heterogeneous and poorly defined clinical entity, managed by therapeutic extrapolation, CHE is now emerging as a condition with greater diagnostic precision and targeted therapeutic opportunities. The advent of JAK inhibitors—particularly topical delgocitinib—marks a paradigm shift from non-specific immunosuppression to mechanism-based intervention at key inflammatory signalling nodes.

Although challenges remain, particularly the lack of validated biomarkers and the limitations of current classification systems, the trajectory is clear: CHE is transitioning from a descriptive diagnosis to a stratified, treatable disease entity. In this evolving landscape, targeted therapies are not only improving clinical outcomes but also redefining the

principles of management, moving towards precision dermatology, where treatment is increasingly aligned with underlying pathophysiology rather than clinical approximation.

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Abbreviations

CHE	Chronic Hand Eczema
JAK	Janus Kinase
TEWL	Transepidermal Water Loss
HECSI	Hand Eczema Severity Index
TSLP	Thymic Stromal Lymphopoietin

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