Review

CLINICAL INVESTIGATION

Alitretinoin for the treatment of chronic hand eczema: clinical rationale

Chronic hand eczema (CHE), an inflammatory skin disease, places heavy psychosocial and economic burden on the affected individual and society as a whole. Patch testing is recommended to identify potential causative allergens in each patient. Efficacy of traditional topical treatments render the management of CHE challenging. Oral alitretinoin (9-*cis*-retinoic acid) is a new drug for the treatment of severe, refractory CHE. This review summarizes the advances on oral alitretinoin for the treatment of severe CHE, with emphasis on its particular benefit for hyperkeratotic hand eczema, and discusses pharmacodynamics and pharmacokinetics, clinical trials and knowledge gaps.

Keywords: 9-*cis*-retinoic acid • alitretinoin • chronic hand eczema • hyperkeratotic hand eczema • skin barrier • retinoids

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Background

Diseases of the hands can have detrimental effect on one's earning potential, cause mood disturbance and decrease quality of life [1,2]. Hand eczema, a common skin disorder in the industrialized countries with an estimated annual prevalence of up to 10% in the general population [3], accounts for over 90% of all occupational dermatoses [4,5]. Severe chronic hand eczema (CHE) accounts for 7% of cases of CHE, and 2–4% of these cases are unresponsive to standard therapy [3,6–8]. For patients with severe CHE refractory to potent topical corticosteroids, the estimated overall mean cost is €418.30 (~US$567.00) per patient monthly. This is largely due to the loss in work productivity (43%) [2]. Eighty percent of the patients with hand eczema experiences social or emotional disturbances [1].

CHE is a heterogeneous disease with varying etiology, morphology and severity. Currently there is no agreement on classification of CHE. Widely published phenotypic subtypes are pompholyx (dyshidrotic, vesicular), hyperkeratotic (tylotic) and finger dermatitis. The various etiologies include contact irritant, allergic and atopic processes. Initial diagnostic step involves taking a thorough exposure history and patch testing. The latter identifies potential irritants and allergens to rule in/out allergic contact dermatitis as the contributing cause of CHE, because morphology of skin lesions alone may be misleading.

Historically, the management of CHE poses a special challenge largely owing to its often chronic remitting flaring. A CHE subtype, hyperkeratotic eczema, is regarded difficult to treat and often occurs in middle-aged men between 40 and 60 years old [9–11]. This distinct subtype of CHE presents circumscribed, pruritic, thickened scaling plaques on the palms, and to a lesser extent the soles, with frequent fissuring and cracking. Stigmata of psoriasis such as hyperkeratosis of the elbows, knees and metacarpals are often present. Pruritus and pain secondary to deep fissuring are frequent complaints. This condition may be triggered by contact allergy, irritation and excoriation, but patch tests used to exclude underlying contact allergies generally yield negative results. However, patch testing should be considered to rule out

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allergic contact dermatitis as a primary or secondary factor.

After moisturizers and soap substitutes, the first line of treatment is a topical steroid. Application of topical corticosteroids followed by occlusion using gloves or wet/plastic dressing allows for better drug penetration into the skin [12,13,82]. However, the efficacy of topical medication on CHE may be low, particularly in the case of hyperkeratotic eczema, because the thickened cornified layer renders the penetration of topical medications difficult.

Owing to their immunomodulatory effects, retinoids have long been used to treat inflammatory dermatoses with abnormal keratinocyte proliferation. Use of etretinate, a synthetic systemic retinoid, for eczema keratoticum mannum was first reported in 1982, which led to complete to near-complete skin clearing in within 1–8 months. However the beneficial result was difficult to maintain owing to pronounced side effects of related vitamin A toxicity [14]. In 1999, an exploratory uncontrolled study using oral alitretinoin (9-*cis* retinoic acid) in 38 patients with refractory CHE yielded clinically significant responses in 36 cases (95%) [15]. Although this trial was not placebo-controlled, such a substantial improvement in the majority of patients with refractory history was a remarkable finding, and guided several large randomized control trials. This review compiles recent advances on the use alitretinoin for the treatment of severe, refractory CHE, particularly for the hyperkeratotic subtype. We discuss alitretinoin's pharmacodynamics and pharmacokinetics, followed by reviewing several major clinical trials, and conclude by highlighting current knowledge gaps and future research directions.

Traditional treatments & challenges

Traditional treatment strategies for CHE comprised irritant trigger avoidance, practice of gentle skin care with frequent emollient application, keratolytics and potent topical corticosteroids with occlusion. These therapy options are generally prolonged, and sometimes produce unsatisfactory results. For example, identification and avoidance of potential triggers are not always possible, particularly in the case of occupational dermatitis. Long-term use of potent topical corticosteroids may further weaken the skin barrier, and is restricted by rebound exacerbations, tachyphylaxis and atrophy after systemic absorption. Additionally, topical treatments for dermatologic diseases of the acral areas are cumbersome as medications are easily lost upon physical contact with other surfaces. This creates problems in simple daily activities such as a handshake and typing on a keyboard, which further contributes to social embarrassment and decreased work productivity in those suffering from CHE [1,2]. These impracticalities are probably the main reason for topical medication noncompliance.

Patients refractory to potent topical corticosteroids may benefit from phototherapy such as psoralen and ultraviolet A radiation (PUVA), and systemic immunosuppressants such as methotrexate, cyclosporine or mycophenolate mofetil may occasionally be used for temporary relief. However, potential toxicity prevents long-term use. Furthermore, patients often experience rebound phenomenon with disease exacerbation once the systemic drug is stopped.

Use of oral alitretinoin (Toctino®, Stiefel Laboratories, Middlesex, UK) for the treatment of recalcitrant CHE have shown impressive results with favorable risk–benefit ratio [15–18]. Now available in Europe, Israel, Canada and South Korea, it is the only approved systemic treatment for severe CHE that is unresponsive to potent topical corticosteroids.

Alitretinoin

Alitretinoin (9-*cis*-retinoid acid [RA]), an isomer of isotretinoin (13-*cis*-RA), is a physiologically and endogenously occurring retinoid that is structurally similar to vitamin A. Unlike other retinoids, which are specific agonists of either retinoic acid receptors (RAR) or retinoid X receptors (RXR), alitretinoin is a pan-agonist retinoid, capable of binding to all six retinoid receptors (RAR-α, -β, -γ, and RXR-α, -β, -γ) [19,20]. By binding to specific nuclear receptors, retinoids can decrease cellular proliferation (acting on RAR), promoting apoptosis (acting on RXR) and cell differentiation (acting on RAR) [21]. Exact mechanisms and significance of binding to all six retinoid receptors remains to be established, however, alitretinoin is proven to be efficacious in CHE. Drugs that activate RAR or RXR alone, such as bexarotene gel and oral acitretin, have relatively limited efficacy in CHE [22,23]. Alitretinoin may exert its effect on CHE via synergistic the activation of multiple retinoid receptors.

Mechanism of action

The mechanism of action of alitretinoin in CHE is not fully understood, but likely involves regulating inflammatory responses and keratinocyte proliferation [24–27]. Alitretinoin's anti-inflammatory and immunomodulatory effects on skin have been demonstrated in preclinical studies. It may interfere with cytokine-induced chemokine production by downregulating CXCR3 ligands and CCL20 chemokines (expressed in eczematous skin lesions) in keratinocytes and dermal endothelial cells [26,27]. Reduction of these pathologically relevant mediators by structural cells suggests that alitretinoin may suppress leukocyte migration to

site of skin inflammation, therefore, reducing capacity for immune response.

Alitretinoin modulates activation, proliferation and expansion of T-, B- and antigen-presenting cell populations by interfering with the upregulation of co-stimulatory molecules, such as CD80 on $CD14^+$ monocytes and $CD19^+$ B cells [27]. Alitretinoin can attenuate the inflammatory response of human adherent monocytes to lipopolysaccharides [25]. Additionally, patients with palmoplantar pustular psoriasis treated with alitretinoin have reduced cutaneous neutrophils, macrophages and dendritic cells [24].

Influences on skin barrier function

Topical all-*trans* retinoic acid has a prolonged irritant potential and is associated with an impaired skin barrier. These negative impacts on treated skin were demonstrated by an increased transepidermal water loss, decreased skin hydration and increased skin erythema [28–30]. Although topical retinoids may disrupt the skin barrier, oral alitretinoin does not seem to negatively influence skin barrier function in patients with CHE. In an observational study, treatment with oral alitretinoin at 30 mg daily for 2 months led to no significant increased susceptibility to sodium lauryl sulfate irritation [31]. Additionally, unlike long-term use of corticosteroids [32,33], systemic alitretinoin treatment does not seem to cause skin atrophy or disruption of the stratum corneum lipid profile, including the level of ceramides [31].

In a small study involving six subjects with prominent atopic CHE and moderate atopic eczema, oral alitretinoin at 30 mg daily for 12 weeks in addition to topical therapy led to a clinical improvement of both palmar and extrapalmar atopic eczema [34]. In conclusion, although more research is required to demonstrate the influence of alitretinoin on atopy, alitretinoin should be considered in treatment of refractory atopic hyperkeratotic hand eczema.

Other uses of alitretinoin

Alitretinoin 0.1% gel (Panretin®, Eisai, Inc., NJ, USA) is approved for treatment of cutaneous AIDS-related Kaposi's sarcoma (KS), eliciting durable responses and delayed disease progression [35–37]. In a double-blinded multicenter study, twice daily application for 12 weeks led to a response rate of 37% in alitretinoin gel group versus 7% in placebo group [35]. Treated tumors demonstrate reduced angiogenesis, especially in the upper dermis [36]. Anti-tumor activity may be related to antiviral properties and suppression of IL-6, an autocrine growth factor of KS cells [38,39].

Owing to their ability to induce differentiation of tumor cells into mature cells, systemic retinoids have been widely studied in prevention and treatment of hematologic malignancies. Additionally, all-*trans* retinoic acid and 13-*cis*-RA have been useful in treating blood dyscrasias such as acute promyelocytic leukemia and primary myelodysplastic syndrome [40,41].

Unlike isotretinoin (13-*cis*-RA), which induces sebosuppression [42,43], alitretinoin (9-*cis*-RA) only minimally affects sebum secretion in human, and therefore has little therapeutic activity in acne patients [44].

The use of alitretinoin alone or as an adjunct to tumor necrosis factor antagonist therapy has been reported in successfully treating severe recalcitrant hyperkeratotic and pustular variants of palmoplantar psoriasis [45,46]. A small study involving seven patients with palmoplantar psoriasis treated with oral alitretinoin (30 mg once daily for 12 weeks) reported decreased area and severity of involvement, as well as pain and pruritus intensity. In correlation with clinical improvement, lesional skin biopsies demonstrated significant reduction in innate inflammation, characterized by decreased neutrophil, macrophage and dendritic cell infiltration [24].

Pharmacokinetics & pharmacodynamics

Absorption & distribution

Unlike many drugs that have impaired gastrointestinal absorption with food, absorption of all retinoids is enhanced when administered with food, preferably a high-fat meal containing milk, butter or other fats [47–51]. A high fat meal is defined by the US FDA as 50% caloric intake from fat [52]. Significant increases in mean maximum plasma concentration (C_{max}) has been observed when alitretinoin is taken with food, with four-fold enhancement in systemic drug exposure and reduction in the variability of drug exposures [53]. Alitretinoin should therefore be taken with a meal. Alitretinoin is lipophilic and has similar octanol water partition coefficient (logP = 6.3) [54] to acitretin (logP = 6.4) [55], and is likely to behave similarly to other retinoid classes by strongly binding to plasma lipoprotein [56,57]. C_{max} is typically reached within 3–4 h after dosing in healthy individuals [58].

Metabolism & elimination

Metabolism begins in the gastrointestinal tract, but predominately occurs in the liver by cytochrome P450 3A4 (CYP3A4). Half life ranges between 2 and 10 h, much shorter than either isotretinoin (mean $t_{1/2}$ = 19 h) and acitretin (mean $t_{1/2}$ = 39–96 h) [59]. The main metabolite is 4-oxo-9-*cis*-retinoic acid; 13-*cis*-retinoic acid and all-*trans*-retinoic acid were detected in much smaller plasma concentrations and most likely do not contribute to the therapeutic or toxic effect of alitretinoin [58]. Excretion of alitretinoin is mainly in urine (63%) and feces (30%) [59].

Adverse effects

It has long been known among Eskimos and arctic travelers that ingestion of liver from large mammals causes severe illness from vitamin A toxicity. Gerrit de Veer, a Dutch officer on the Willem Barentsz's third voyage (1596) in search of the Northeast Passage, was the first Westerner to observe hypervitaminosis A caused by consuming polar bear liver [60]. Acute symptoms (2–4 h after ingestion) include drowsiness, irritability, vomiting and severe headache. Late findings (after 24 h) were strikingly widespread skin desquamation and visual disturbances.

Potential systemic retinoid toxicity may affect multiple organ systems and cause various serum laboratory abnormalities [61]. These reported side effects are summarized in Table 1. Similar to all retinoids, alitretinoin is strongly tetratogenic, therefore, strict pregnancy prevention measures must be performed 1 month before, during and after treatment. Since alitretinoin has no clinically relevant pharmacokinetic interaction with ethinyl estradiol and norgestimate, combined oral contraceptives should be used as a primary form of contraception. Trace amount of alitretinoin and its metabolite 4-oxo-alitetinoin has been detected in semen samples in healthy men receiving alitretinoin. When absorption and plasma distribution are considered, increase in plasma levels of alitretinoin is negligible in female partners of males taking alitretinoin [62]. However, there is no evidence that semen exposed to alitretinoin is associated with any birth defects in pregnant female partners.

Alitretinoin is mainly metabolized by the liver, therefore it is contraindicated in patients with liver disease. However, in a recent study where cirrhotic patients received a single oral dose of 30 mg of alitretinoin, their blood and urine analyses showed no significant differences in alitretinoin and its metabolites concentrations following 24-h study period when compared with healthy controls [57]. Current contraindications listed on the manufacturer's website are summarized in Box 1. The most commonly observed side effects of alitretinoin were consistent with retinoid toxicity, and include headache, diarrhea, facial flushing and hypertriglyceridemia, all of which are reversible [61]. Other potential side effects and precautions are outlined in Box 2.

Pharmacokinetic interactions

Co-administration with other CYP3A4 inhibitors can potentially increase plasma level of alitretinoin. Alitretinoin causes a slight reduction (16%) in the plasma level of simvastatin, but has no effect on the pharmacokinetics of ketoconazole and cyclosporine A. Conversely, simvastatin and cyclosporine A have no effect on the pharmacokinetics of alitretinoin, ketoconazole can increase alitretinoin bioavailability and C_{max} [63]. *In vitro* studies have demonstrated no potential interference of alitretinoin on the metabolism of progestins medroxyprogesterone, norgestimate, progesterone and norethindrone. Alitretinoin has no clinically relevant pharmacokinetic interaction ethinyl estradiol/norgestimate (Ortho Tri-Cyclen 28®, Janssen Pharmceuticals, NJ, USA) [64]. Oral combined hormonal contraceptives are therefore appropriate as a primary contraception method.

Major clinical trials on alitretinoin for treatment of recalcitrant CHE

Defining CHE severity & therapeutic response

In clinical trials, hand eczemas of greater than 3 months duration are considered chronic. The

Table 1. Potential systemic retinoid toxicities and physiobiochemical abnormalities.

Organ systems	Toxicities
Mucocutaneous†	Xerosis, photosensitivity, retinoid dermatitis (erythema, pruritus, scaling), cheilitis, dry mucous membrane (nosebleeds), alopecia, nail fragility
Musculoskeletal†	Myalgia, arthralgia, diffuse idiopathic skeletal hyperostosis syndrome
Ophthalmologic	Blepharoconjunctivitis, reduced night vision
Immunologic	Increased susceptibility to staphylococcal infections
Psychological	Suicide and suicide attempt associations
Neurological	Headache, pseudotumor cerebri (especially when combined with tetracycline or minocycline)
Teratogenic	Craniofacial, cardiovascular, thymic, central nervous systemic, retinoid embryopathy
Serum abnormalities‡	Hyperlipidemia§, elevated transaminases, decreased thyroid hormone, leukopenia

†Retinoic acid receptor-selective retinoids cause more mucocutaneous and musculoskeletal symptoms.
‡Retinoid X receptor-selective retinoids cause more physiochemical changes.
§Most common laboratory abnormality; due to increased expression of Apo C-III, leading to decreased lipid uptake from very-low-density lipoprotein into cells.

recalcitrant/refractory status of CHE is defined as no response, or transient response to at least 4 weeks of topical corticosteroids, or intolerance to the regimen [17,18,65,66]. Severity and therapeutic response of CHE can be assessed using the Physician's global assessment (PGA), modified Total Lesion Symptom Score (mTLSS) and Patient's Global Assessment (PaGA) score [17,18,65,66]. The former two measurements were verbal descriptions transcribed from a validated photographic guide used for grading CHE severity [67]. Method of defining CHE severity using PGA is summarized in Table 2.

mTLSS and PaGA are validated measures for therapeutic responses of CHE in clinical trials [18]. The mTLSS is calculated as sum of scores (0 = absent, 1 = mild, 2 = moderate, 3 = severe) assigned by the physician according to seven measures: erythema, edema, vesicles, desquamation, hyperkeratosis, fissures and pruritus/pain. PaGA is a patient-reported assessment of their CHE severity and can be defined as 'clearing or almost clearing' (≥90% clearing of disease signs and symptoms compared with baseline), 'marked improvement' (≥75% clearing), 'moderate improvement"' (≥50% clearing), 'mild improvement' (≥25% clearing), 'no change' or 'worsening'. The Dermatology Life Quality Index (DLQI), a widely utilized instrument used for eczematous skin conditions, can be applied to measure the quality of life in patients with CHE [68,69]. In the UK, alitretinoin is approved by the National Institute for Health and Clinical Excellence (NICE) for treatment of severe CHE unresponsive to potent topical corticosteroids. NICE guidelines define severe CHE as having PGA and DLQI score of 15 or more, and with intolerance, contraindication or inadequate response to second-line treatments, such as cyclosporin, azathioprine or PUVA [70–72].

Benefit of Alitretinoin in Choric Hand Eczema trial

Benefit of Alitretinoin in Chronic Hand Eczema (BACH) study is the largest (n = 1032), randomized, placebo-controlled, multicenter trial assessing the efficacy and safety profile of oral alitretinoin (taken at 10 or 30 mg once daily for up to 24 weeks) in comparison with placebo control, for treatment of severe recalcitrant CHE [18]. Phenotypes of CHE included were hyperkeratotic (83–87%), pompholyx (27% in all three groups), fingertip dermatitis (43–49%) and other (13–15%) [18]. All other concomitant treatments were prohibited, with the exception of an emollient cream.

Efficacy criteria were measured using a mTLSS [15,17]. Treatment led to a significantly higher proportion of patients with clear/almost clear hands (28% in 10 mg group, 48% in 30 mg group) compared with placebo (17%). Dose-dependent efficacy was observed in all types of CHE, with hyperkeratotic and fingertip eczema showing the highest response rate and largest difference (28% in 10-mg group, 49% in 30-mg group) from placebo (12%). Fingertip subtype had the second highest response rate (29% in 10-mg group, 44% in 30-mg group vs 18% in placebo), followed by pompholyx subtype (23% in 10-mg group, 33% in 30-mg group vs 16% in placebo) [18]. Time to response was significantly shorter in the 30-mg group than in the 10 mg ($p < 0.001$). Both dosages achieved durable remission with a median of 5.5 months in the 30-mg group and 6.2 months in the 10-mg group.

Majority of the responders did not relapse by the end of the 24-week observation period following treatment [66]. Disease relapse is defined as a mTLSS score of

Box 1. Alitretinoin contraindications.

Contraindications of alitretinoin

- Pregnancy (absolute contraindication)
- Breastfeeding
- Hepatic insufficiency
- Severe renal insufficiency
- Uncontrolled hypercholesterolemia
- Uncontrolled hypertriglyceridemia
- Uncontrolled hypothyroidism
- Hypervitaminosis A
- Hypersensitivity to other retinoids
- Receiving concomitant treatment with tetracycline
- Rare hereditary fructose intolerance
- Allergies or intolerance excipient ingredients (soya, beeswax, all-rac-α-tocopherol, gelatin, glycerol, sorbitol, iron oxide (red E172, black E172 and yellow E172)

Box 2. Alitretinoin potential side effects and precautions.

- Fetal teratogenicity
- Enhanced UV light sensitivity
- Premature epiphyseal closure, hyperostosis, calcification of tendons and ligaments
- Myalgia, arthralgia, increased serum creatinin phosphokinase
- Dry eyes, decreased night vision, corneal opacities, conjunctivitis
- Benign intracranial hypertension (especially with concomitant use of tetracyclines)
- Increased plasma cholesterol and triglyceride levels
- Change in thyroid function tests (reduction in TSH and T4)
- Transaminitis
- Inflammatory bowel disease
- Hypersensitivity reactions (cutaneous and anaphylactic)
- Potential compromise of male fertility

T4: Thyroxine; TSH: Thyroid-stimulating hormone.
Reported by manufacturer [72].

Table 2. Physician's global assessment for chronic hand eczema.

Severity	Features	Hand surface area involved†
Clear	No residual visible dermatitis	Not detected
Almost Clear	Minimal erythema and/or scaling	<10%
Mild	Clearly visible signs of dermatitis, with no hyperkeratosis, edema, fissures or functional impact	<10%
Moderate	Moderately severe signs of dermatitis, with no edema or fissures, or functional impairment	10–30%
Severe	Marked signs of dermatitis, or edema, fissures or functional impairment	>30%

Use the more affected side (palm or dorsum) of the more affected hand for to estimate the area involved.
†Affected area excludes disease localized to fingertips.

≥75% from baseline within 24 weeks of after treatment cessation. Surprisingly, the 30-mg treatment group had higher relapse rate (38%) than both the 10-mg group (25%) and placebo (35%). The response and relapse rates of the subjects from the BACH trial are summarized in Table 3.

In a follow-up open-label study study, a portion of the initial non-responders from the BACH trial received extended retreatment at 30 mg daily for up to 24 weeks. PGA response rate of a subsequent course of alitretinoin was 50% and 39% in those who previously received 10 or 30 mg daily, respectively, and 51% in those who previously received placebo [73]. Alitretinoin was shown to be well tolerated for overall treatment period of up to 48 weeks.

TOCCATA trial

Toctino® in severe chronic hand eczema – therapy in an observational study (TOCCATA) was a non-interventional observational open study investigating use of oral alitretinoin (10 mg or 30 mg) to treat CHE under daily dermatological practice conditions in Germany [65]. Nearly all of the 680 patients enrolled (99.1%) suffered PGA severe (64.5%) or PGA moderate (34.6). Majority (65%) had the hyperkeratotic-rhagadiform (65%) and vesicular/pompholyx (36%) morphological variant involving both hands (96%). Patients were allowed to continue with concomitant topical treatments. Clinical response was measured by PGA at 4 week intervals.

Table 3. Percentage of responders and relapses from the Benefit of Alitretinoin in Chronic Hand Eczema trial.

	Alitretinoin		
	10 mg (%)	30 mg (%)	Placebo (%)
Responders†	28	48	17
Relapsed‡	25	38	35

†Responders, clear or almost clear.
‡Relapse, an modified Total Lesion Symptom Score score ≥75% from baseline within 24 weeks.

Of 333 patients who completed the study, 57% achieved a PGA rating of 'clear' or 'almost clear'. Best responses were observed in patients with the hyperkeratotic-rhagadiform phenotype (59.2%), followed by fingertip dermatitis (52.2%) and vesicular/pompholyx (47.9%). Not surprisingly, efficacy was most pronounced in patients with 'less' chronic hand eczema (<1-year duration), requiring 20% shorter treatment duration (121 days) than with the mean disease duration of 7 years. Slightly better therapeutic response than that of the BACH trial may be partially explained by the use of concomitant treatments and a lesser percentage of 'severe' patients (64.5% in TOCCATA vs >99% in BACH).

In an observational, open-label study on 15 patients with severe refractory CHE, treatment with oral alitretinoin at 30 mg daily for 3 months led to notable quality of life improvement at both 1- and 3-month points when measured by the DLQI and the visual analog scale (EQD5-VAS) [74].

BACH, TOCCATA and other major clinical trials are summarized in Table 4. Overall, alitretinoin appears to be an effective treatment for severe recalcitrant CHE for up to 24 weeks with a tolerable side effect profile. Higher doses (30–40 mg) provided a more rapid response and higher response rate than lower doses (10–20 mg), with the latter associated with fewer adverse events.

Reported adverse effects of alitretinoin from BACH & TOCCATA trials

Side-effect profile of alitretinoin reported in both BACH and TOCCATA trials are similar to other systemic retinoids. The most common adverse events and abnormal laboratory test results in the BACH trial were similar to those seen in other classes of oral retinoids and RXR agonists, including headache (20%), mucocutaneous events such as erythema, dry lips, eczema, dermatitis and xerosis (14%), and hypertriglyceridemia (3%) [18]. Safety findings in TOCCATA were consis-

Table 4. Alitretinoin major clinical trials for chronic hand eczema treatment.

Trials	Patients	Daily doses	Treatment duration	Response	Ref.
Bollag and Ott (1999)	38 open-label	20 or 40 mg	2.3 months (mean)	89% (TLSS)	[2]
Ruzicka *et al.* (2004)†	319 randomized	10, 20 or 40 mg vs placebo	12 weeks	39% (10 mg) 41% (20 mg) 53% (40 mg) (placebo) (PGA)	[3]
Ruzicka *et al.* (2008) (BACH)	1032 randomized	10 or 30 mg vs placebo	Up to 24 weeks	28% (10 mg) 48% (30 mg) 17% (placebo) (PGA)	[4]
Dirschka *et al.* (2010)	249 open-label	30 mg	Up to 24 weeks	46% (PGA)	[5]
Diepgen *et al.* (2011) (TOCCATA)	680 open-label	10 or 30 ml‡	153 days (median)	57% (PGA)	[6]

†Cohort had moderate or severe chronic hand eczema.
‡>90% received 30 mg.
BACH: Benefit of alitretinoin in chronic hand eczema; PGA: Physician's global assessment; TLSS: Total Lesion Symptom Score; TOCCATA: Toctino® in severe chronic hand eczema – therapy in an observational study.

tent with BACH, with headache as the most frequent adverse reaction (7.5%), followed by hypertriglyceridemeia (4.9%) and hypercholesterolemia (3.8%). Serious adverse drug reactions were documented in only four patients: lymphatic edema, paranoia, recto-sigmoiditis and soft-tissue swelling.

There has been one case of possible sensitization to alitretinoin in CHE [75]. This patient developed paradoxical worsening of CHE after taking oral alitretinoin 30 mg once daily for 15 days. Her disease improved after temporary drug cessation and treatment with systemic and topical corticosteroids. She had a positive oral challenge test when oral alitretinoin was started at a dose of 10 mg once daily. Patch testing confirmed a strong positivity (++) for alitretinoin at 48 and 96 h reading while having negative result to all other allergy tests. Her second flare subsequently resolved after cyclosporine therapy.

Special considerations

Systemic retinoids & pregnancy prevention programs

Owing to its potential teratogenicity, distribution of alitretinoin in Europe to women of childbearing potential is under pregnancy prevention measures supported by the pregnancy prevention program, which provides pregnancy testing and contraceptive guidelines for prescribers, and mandates pregnancy reporting to health authorities and the manufacturers [70]. Unlike the isotretinoin iPLEDGE program enforced by the FDA for pregnancy prevention [76], there is currently no formal government regulated mandatory distribution program for alitretinoin in countries where they are approved.

In a systemic literature review on the compliance of isotretinoin pregnancy prevention programs in Europe, full compliance was seen in only 6–26% of the cases. Despite the fact that a pregnancy prevention program for isotretinoin was in place, 0.02–0.1% of the women using isotretinoin became pregnant [77]. A US survey study reports high non-adherence rate of the iPLEDGE program in women of childbearing potential taking isotretinoin [78]. Women who pledged condoms and oral contraceptive pill use have the highest rate of noncompliance. Those who were previously sexually active are more likely to engage in sexual activity while taking isotretinoin despite pledging abstinence. Approximately 150 women annually become pregnant during isotretinoin treatment. The insufficient compliance to isotretinoin pregnancy prevention program and iPLEDGE raises the need for a more structured and reliable regulation for systemic retinoids. Compliance of alitretinoin pregnancy prevention program and failure rate should be evaluated and closely monitored.

Cost–effectiveness

In a long-term cohort simulation model study, annual cost of alitretinoin for treatment of severe CHE is estimated to be €2212 (~US$300) in the Swiss healthcare system. Compared with supportive therapy (optimized emollients), addition of alitretinoin yielded impressive clinical and cost–effectiveness, with an average gain of 0.230 quality adjusted life years and an incremental cost-effective ratio of €14,816/quality adjusted

life years gained [79]. However, the cost–effectiveness of this model within the healthcare system in other industrialized countries is unknown.

Excipients in alitretinoin

Prescribers of alitretinoin should be aware of the excipient ingredients in alitretinoin capsules [70]. Capsule contains soya-bean oil, beeswax; whereas the capsule shell contains sorbitol, gelatin and iron oxide. Therefore, alitretinoin should not be used in patients allergic to beeswax, soya, iron oxide or with rare hereditary fructose intolerance.

Conclusion & future perspective

Oral alitretinoin demonstrates rapid efficiency and good tolerability in several large clinical trials. All alitretinoin studies were conducted on adult patients. The safety profile and efficacy in patients with renal insufficiency or pediatric patients is unknown and may be an area of further research. Although cirrhotic patients seem to metabolize a single dose of alitretinoin without problem, long-term metabolism and pharmacokinetics of patients with liver diseases are unknown. Additionally, all reports are done using 10, 20, 30 or 40 mg of oral alitretinoin. Efficacy and safety profile of a weight-based dosing is unknown. There has not been any efficacy or tolerability report for treatment durations beyond 48 weeks. Across all major studies, patients with the hyperkeratotic subtypes of CHE have the best improvement with oral alitretinoin. It is possible that achieving the same level of efficacy in other subtypes may require higher dosages and/or longer treatment duration.

Note the moderate relapse risk at 24 weeks post-treatment from BACH trial (25% with 10 mg daily, 38% with 30 mg daily vs 35% with placebo) [66]. These findings highlight the need for better identification of relapse-prone CHE patient population. One area of investigation is to re-evaluate the therapeutic scheme with a possible maintenance regimen for this subset. Concomitant use of traditional treatments (e.g., potent topical corticosteroids with occlusion, topical retinoid receptor agonists and PUVA, among others) in combination with low-dose oral alitretinoin may constitute the potential maintenance protocol with fewer adverse effects. Other areas of potential investigation include pediatric and weight-based dosing, potential for drug sensitization and tachyphylaxis.

Owing to its lipophilic nature, systemic retinoids must be taken with a high-fat, high-calorie meal to ensure optimal and consistent absorption and therapeutic plasma concentration [47–51]. However, daily high-fat diet may be cumbersome and unhealthy, especially when hyperlipidemia is a drug side effect. Isotreintoin-lidose (Epuris™, Cipher Pharmaceuticals Inc., Mississauga, Ontario, Canda) is a novel formulation with enhanced absorption in the absence of dietary fat. The lipid encapsulation technology (Lidose®, Brussels, Belgium) encloses isotretinoin, thereby reaching pharmacokinetic bioequivalence to standard isotretinoin formulation under fed conditions, with significantly greater absorption during fasting [80,81]. Development of a similar alitretinoin formulation can potentially improvement patient outcomes.

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Executive summary

- Oral alitretinoin has therapeutic potential as a nonimmunosuppressive treatment in patients with severe recalcitrant chronic hand ecezma (CHE). It is particularly effective in treating the hyperkeratotic subtype of CHE where the thickened stratum corneum creates a barrier to topical drug delivery.
- Alitretinoin was well tolerated across all studies in both healthy subjects and patients with CHE, with the most frequently reported reversible adverse events being headaches, dry lips/mouth, hyperlipidemia, and decreased TSH.
- Similar to other retinoids, alitretinoin is a strong teratogen. Strict pregnancy protection requirements and counseling are required before, during and 1 month after cessation of treatment for women of childbearing potential.
- While additional relevant studies may be needed to establish alitretinoin's long-term safety and optimal dosing for special patient groups, alitretinoin shows promise in being a efficacious treatment for severe CHE.
- *Textbook of Hand Eczema* (Springer®) by Alikhan, Ali; Lachapelle, Jean-Marie; Maibach, Howard (Eds.) provides additional details on the hand eczema syndrome.

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