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Alitretinoin

In Severe Chronic Hand Eczema

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Contents

Abstract

▲ Alitretinoin is an endogenous retinoid and acts as a pan-agonist at retinoid receptors, binding with high affinity to both retinoic acid receptors and retinoid X receptors (RXR). Oral alitretinoin once daily is approved for use in patients with severe chronic hand eczema unresponsive to treatment with potent topical corticosteroids.

▲ In a large (n = 1032), randomized, double-blind, placebo-controlled, multicentre study (BACH) of up to 24 weeks' duration in adults with severe chronic hand eczema, significantly more patients in the alitretinoin 10 or 30 mg/day groups than in the placebo group responded to treatment with clear/almost clear hands, as assessed by the Physician Global Assessment (PGA) [primary endpoint].

▲ In an extension phase of the BACH study, alitretinoin was effective in patients who relapsed after responding to initial treatment with the drug. Of patients who had responded to initial treatment with alitretinoin 30 mg/day, significantly more alitretinoin 30 mg/day than placebo recipients responded on the PGA with clear/almost clear hands during the extension phase (primary endpoint; 80% vs 8%). Of those who had responded to initial treatment with alitretinoin 10 mg/day, 48% of alitretinoin 10 mg/day and 10% of placebo recipients responded during the extension phase.

▲ Alitretinoin was generally well tolerated in clinical trials excluding pregnant women. The most common treatment-emergent adverse events and abnormal laboratory test results were consistent with those previously observed with other oral retinoids and RXR agonists.

Features and properties of alitretinoin (9-*cis*-retinoic acid; Toctino®)

Indication		
Severe chronic hand eczema unresponsive to potent topical corticosteroids in adult patients		
Mechanism of action		
Unknown in chronic hand eczema; retinoids are known to affect numerous processes at a cellular level, including cell proliferation, differentiation and apoptosis		
Dosage and administration		
Initial dosage	30 mg once daily	
Dosage range	10–30 mg once daily	
Route of administration	Oral	
Duration of treatment	12–24 wk	
Pharmacokinetic profile (after 28 days of oral 10 [n = 16] or 30 [n = 16] mg once daily doses in patients with refractory chronic hand eczema)		
	10 mg	30 mg
Mean area under the plasma concentration-time curve (ng • h/mL)	123.4	362.8
Mean maximum plasma concentration (C_{max}) [ng/mL]	56.7	150.5
Time to C_{max} (h)	≈3–4	≈3–4
Mean half-life (h)	6.5	4.9
Treatment-emergent adverse events and laboratory abnormalities occurring in ≥5% of patients receiving alitretinoin 30 mg/day		
Headache, erythema, nasopharyngitis, high cholesterol levels, high triglyceride levels, low thyroid-stimulating hormone levels		

Hand eczema is a common skin disorder, and is characterized by scaling, fissures, erythema, vesicles, papules, hyperkeratosis, itching and pain.[1] Additionally, it has a remitting and relapsing course, with disease returning even after sporadic remission.[1] The 1-year prevalence of hand eczema is thought to be ≈10%; chronic severe hand eczema patients make up 5–7% of these patients, and those with topical treatment-refractory disease make up 2–4%.[1] An estimate of the annual incidence of hand eczema placed it at 5 per 1000 people per year.[1]

The disease is multifactorial; several predisposing endogenous and exogenous factors can affect the chances of developing hand eczema, including being atopic, certain genetic factors and contact with irritants or contact allergens.[1,2] In many countries, work-related hand eczema is the top-ranked occupational disease with regard to incidence.[1]

Hand eczema is associated with a significant negative impact on quality of life and, as the disease is highly visible, anxiety, low self-esteem, social phobia and other psychosocial problems may occur.[1] Increased severity of hand eczema has been shown to be significantly correlated to decreased quality of life.[3] Additionally, hand eczema has been linked to huge economic loss; it is a major cause of lost earnings, as well as morbidity.[1] A recent study investigating the societal costs of severe, refractory, chronic hand eczema in Germany showed that total annual costs (in the base case scenario) came to €860 million (year of cost not reported).[4]

Most hand eczema can be managed with skin protection measures (non-medical), either with or without topical treatments, such as corticosteroids.[1] However, some (those with chronic, topical treatment-refractory disease) require systemic treatment, as recurrent or prolonged use of potent topical corticosteroids is associated with potential skin atrophy and other cutaneous adverse events.[1,5,6] Various systemic treatments can be used, such as oral immunosuppressants (e.g. ciclosporin [used off label in hand eczema]), short treatment courses of oral corticosteroids and oral alitretinoin (9-*cis*-retinoic acid; Toctino®), the only drug specifically approved for use in severe chronic hand eczema. However, systemic treatments are not without their limitations; ciclosporin has been associated with relapse occurring soon after the end of treatment as well as being a potent immunosuppressant,[5] and oral corticosteroids are associated with long-term adverse events such as osteoporosis, glaucoma, cataracts, hypothalamic-pituitary-adrenal axis suppression, hyperglycaemia, hypertension and immunosuppression.[5]

Oral alitretinoin, administered once daily, is an endogenous retinoid indicated for the treatment of adults with severe chronic hand eczema unresponsive to potent topical corticosteroids.[7] This article provides an overview of the pharmacological properties of alitretinoin and reviews the clinical trial data available on the efficacy and tolerability of the drug in adults with severe refractory chronic hand eczema. Topical alitretinoin for the treatment of Kaposi's sarcoma is also available, which is reviewed elsewhere.[8] Medical literature on the use of alitretinoin in chronic hand eczema was identified using MEDLINE and EMBASE, supplemented by Adis-Base (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

This section includes data from two clinical trials in patients with chronic hand eczema,[9,10] the manufacturer's prescribing information,[7] several *in vitro* studies[11-15] and one study in healthy volunteers,[4] supplemented by data from reviews.[8,16,17]

Mechanism of Action

Although the exact mechanism of action of alitretinoin in severe chronic hand eczema is not yet understood, retinoids are known to affect numerous processes at a cellular level, including cell proliferation, differentiation and apoptosis. The efficacy of these drugs in the treatment of this disease may also be explained by effects on immunomodulation, inflammation, angiogenesis, keratinisation and sebum secretion.[7,16,17] Unlike isotretinoin, alitretinoin has

only a minimal effect on sebum secretion in humans.[7,18]

There are two nuclear receptor families for which retinoids are specific agonists: retinoic acid receptors (RARs) and retinoid X receptors (RXRs), each consisting of three subtypes (α, β and γ).[16,17] These receptors form heterodimers with other receptors; while RARs can only bind to RXRs,[17] RXRs bind to many different nuclear receptors, including both RARs and RXRs.[16] Once dimerized, the receptors function as ligand-inducible transcription factors.[16,17]

- The most common retinoid receptors in human skin are RAR-γ and RXR-α.[8] No link between receptor binding patterns and therapeutic efficacy (section 3) of alitretinoin in chronic hand eczema has been shown,[9] and other retinoids that bind to RAR are not effective in patients with chronic hand eczema.[10]
- Alitretinoin is a pan-agonist, binding to and activating RAR and RXR receptors *in vitro* with high affinity and in a saturable manner, while other retinoids bind to subgroups of either RAR or RXR.[11] Alitretinoin binds with higher affinity to RARs than to RXRs. The dissociation constants (K_d) for RAR-α, -β and -γ were 0.31, 0.20 and 0.78 nmol/L, respectively; the K_d for RXR-α, -β and -γ were 1.62, 2.36 and 2.29 nmol/L, respectively. No binding of all-*trans*-retinoic acid to RXRs was detectable at 100 nmol/L, and all-*trans*-retinoic acid demonstrated similar K_d to alitretinoin for RAR-α, -β and -γ (0.37, 0.37 and 0.22 nmol/L, respectively).
- Alitretinoin was as potent as all-*trans*-retinoic acid and more potent than 11-*cis*-retinoic acid and 13-*cis*-retinoic acid (isotretinoin) as an RAR-α activator in an *in vitro* study.[12]
- Alitretinoin showed high affinity for the RXR receptor and was ≈40-fold more potent at RXR-α activation than all-*trans*-retinoic acid, 11-*cis*-retinoic acid and 13-*cis*-retinoic acid.[12]
- As is well established for RXR ligands,[16] alitretinoin can activate RXR when in homodimers or in heterodimers with certain other receptors (permissive partners;[16] e.g. the liver X receptor), but not when RXR is in heterodimers with another group of receptors (nonpermissive partners[16]), which includes RAR.[13] Thus, an RXR-RAR heterodimer can only be activated via RAR.[13] It has been shown that alitretinoin induces the homodimerization of RXR receptors.[14]

Immunomodulatory and Anti-Inflammatory Effects

- Alitretinoin has shown both immunomodulatory and anti-inflammatory effects.[7,15] In lipopolysaccharide-stimulated mouse microglia, alitretinoin inhibited the production of nitric oxide (NO), tumour necrosis factor (TNF)-α, interleukin (IL)-1β and IL-12 p40, but was associated with an increase in monocyte chemoattractant protein-1 production.[15] In lipopolysaccharide-stimulated mouse astrocytes, alitretinoin was associated with decreased NO and TNFα production.[15] Alitretinoin is also associated with downregulation of chemokine (CXC motif) receptor 3 ligands and chemokine (C-C motif) ligand 20 in cytokine-stimulated keratinocytes and dermal endothelial cells,[7] as well as suppression of the expansion of cytokine-activated leukocyte subsets and antigen-presenting cells.[7]

2. Pharmacokinetic Profile

This section focuses on data from the UK summary of product characteristics,[7] supplemented by data from a randomized, double-blind, multiple-dose (10 or 30 mg/day) study in adult patients (n = 32) with moderate or severe treatment-refractory chronic hand eczema (reported in a poster),[19] as well as other, more specific, studies in healthy volunteers (also available as posters).[20-22] The pharmacokinetics of alitretinoin have not been investigated in patients with hepatic or severe renal insufficiency or in patients aged <18 years.

Absorption and Distribution

- Patients with chronic hand eczema demonstrate dose-proportional absorption of alitretinoin 10–30 mg after oral administration.[7] Alitretinoin absolute bioavailability has not been determined.[7]

• After a single 10 or 30 mg dose in patients with chronic hand eczema, area under the plasma concentration-time curve (AUC) values were 113.3 and 300.9 ng • h/mL and maximum plasma concentration (C_{max}) values were 50.7 and 104.7 ng/mL.[19] Time to C_{max} (t_{max}) [estimated from a graph] was ≈3–4 hours for both doses.[19]

• Following multiple doses of alitretinoin 10 or 30 mg once daily, AUC values were 123.4 and 362.8 ng • h/mL, and C_{max} values were 56.7 and 150.5 ng/mL on day 28;[19] t_{max} values (estimated from a graph) remained at ≈3–4 hours. No accumulation was observed after up to 24 weeks of treatment and there were no time-dependent changes in alitretinoin disposition.[7]

• Systemic exposure to alitretinoin is increased by a factor of 4 and exposure variability is decreased when it is taken with food.[7,21] Thirty healthy volunteers received alitretinoin 40 mg with or without food. Respective mean AUC and C_{max} values were 220.2 versus 55.7 ng • h/mL and 82.8 versus 25.4 ng/mL (both $p < 0.001$). Systemic exposure variability decreased from 72% without food to 40% with food. Alitretinoin should thus be taken with a meal (section 5).[7]

• While the volume of distribution of alitretinoin has not been determined in humans, animal studies have demonstrated that it is likely to be greater than the extracellular volume.[7] Alitretinoin is strongly bound to plasma proteins.[7]

• Low concentrations of alitretinoin in seminal fluid were detected after multiple doses of the drug in 12 healthy men receiving alitretinoin 40 mg once daily for 14 days.[22] Seminal fluid samples taken 4 hours after the second dose revealed a maximum alitretinoin concentration of 7.921 ng/mL. Assuming complete absorption, this would correspond to a calculated increase in the alitretinoin plasma levels in the female partner of 0.016 ng/mL; this increase is negligible when compared with endogenous plasma levels. Related retinoids were also at negligible levels in the semen. Alitretinoin administration in male patients is unlikely to affect alitretinoin levels in female partners via seminal transmission of the drug.[22]

• Alitretinoin is highly lipophilic and, as it is probably distributed in breastmilk, is contraindicated in breast-feeding women.[7]

Metabolism and Elimination

• Alitretinoin undergoes oxidation by cytochrome P450 (CYP) 3A4 in the liver;[7] its major metabolite is 4-oxo-alitretinoin.[7,20] Both alitretinoin and 4-oxo-alitretinoin are isomerized into all-*trans*-retinoic acid and 4-oxo-all-*trans*-retinoic acid.[7] In the plasma, 4-oxo-alitretinoin accounts for 35–80% of the systemic exposure of alitretinoin, it is then glucuronidated and eliminated in the urine.[7] Alitretinoin is also degraded to retinol by cleavage of the carbon side chain.[7]

• Alitretinoin is mainly excreted in the urine, with a smaller fraction eliminated in the faeces.[7,20] The manufacturer's prescribing information states that approximately 94% of a dose of radio-labelled alitretinoin was recovered, making the excretion complete.[7] After administration of a single dose of alitretinoin 40 mg and a single dose of [11-^{14}C]-labelled alitretinoin 0.47 mg in six healthy volunteers, 63.2% of the total radioactivity was excreted in the urine and 30.3% in the faeces.[20] Most radioactively labelled compounds (mean 93.5%) were eliminated within 5 days.[20]

• The most common identifiable radioactive product in the urine was the glucuronidated form of 4-oxo-alitretinoin (6.5% of the total); unchanged alitretinoin and 4-oxo-alitretinoin in the faeces made up 1% and 3% of the total dose.[20] A total of 54% and 14% of the administered dose was excreted as unidentified cleavage products in the urine and faeces, respectively.

• In patients receiving alitretinoin 10 or 30 mg/day for 24 weeks, plasma concentrations of both alitretinoin and its metabolites returned to normal ranges after 2–7 days following treatment discontinuation.[19] The half-lives were 6.5 and 4.9 hours for the 10 and 30 mg/day dosages on day 28. The corresponding 4-oxo-alitretinoin half-lives were 6.6 and 7.4 hours.[19] The manufacturer's prescribing information states that the elimination half-life of alitretinoin is 2–10 hours.[7]

Drug Interactions

- Alitretinoin 30 mg pharmacokinetics were not significantly altered by concomitant simvastatin 40 mg or ciclosporin 300 mg (both CYP3A4 substrates) administration in an open-label study in 54 healthy volunteers (available as a poster presentation).[23] However, ketoconazole 200 mg (a strong CYP3A4 inhibitor) administration was associated with significantly ($p < 0.05$) increased alitretinoin AUC from time zero to infinity (AUC_∞) and C_{max} values after both single and multiple alitretinoin doses, potentially a result of inhibition of CYP3A4-mediated metabolism.[23]
- Ciclosporin and ketoconazole pharmacokinetics were not significantly altered during concomitant alitretinoin administration; however, simvastatin systemic exposure was decreased.[23] A single alitretinoin dose significantly ($p = 0.037$) decreased the simvastatin C_{max} value and multiple doses decreased both C_{max} and AUC_∞ values (both $p < 0.05$).
- No clinically relevant changes in either alitretinoin or ethinyl estradiol/norgestimate pharmacokinetics occurred following coadministration of these drugs in an open-label study (published as a poster), indicating that there are no drug-drug interactions between alitretinoin and oral contraceptives.[24]

3. Therapeutic Efficacy

The efficacy of oral alitretinoin in adult patients with severe chronic hand eczema refractory to conventional therapy has been investigated in a large (n = 1032), randomized, double-blind, placebo-controlled, multicentre study (the Benefit of Alitretinoin in Chronic Hand eczema [BACH] study),[9] a pilot study (n = 38)[10] and a randomized, double-blind, placebo-controlled, dose-finding, multicentre study (n = 319).[25] This section focuses on the largest study.[9] Preliminary data from two re-treatment studies in responders to the original treatment who relapsed (reported in a poster)[26] and non-responders to the original treatment (reported in an oral presentation)[27] are also reviewed.

- In the pilot study,[10] 55% of patients receiving alitretinoin 20 or 40 mg once daily achieved a 'very good' (81–100% reduction of total lesion symptom score) response; however, as most patients received a dosage higher than that currently recommended, these data are not discussed further.[10] Results from the dose-finding study[25] confirmed these findings, showing a significant ($p < 0.001$) dose-dependent effect in the primary endpoint, with 27% of placebo, 39% of alitretinoin 10 mg/day, 41% of alitretinoin 20 mg/day and 53% of alitretinoin 40 mg/day recipients showing a 'clear' or 'almost clear' rating on the Physician Global Assessment (PGA; ratings of 'severe', 'moderate', 'mild', 'almost clear' or 'clear').[25]

The BACH Study

The BACH study included alitretinoin-naive adult patients (aged 18–75 years) with severe chronic hand eczema (any type) refractory to standard therapy, of ≥6 months' duration.[9] Severity was defined using the PGA. To achieve refractory status, patients had demonstrated no or transient response to ≥8 weeks' topical corticosteroid treatment (including 4 weeks' treatment with a potent corticosteroid) in the 6 months before enrolment, received standard skin care, and avoided irritants and allergens. Other potential chronic hand eczema mimicking conditions had been ruled out. Women of child-bearing potential had to be using at least two forms of contraception for ≥1 month before treatment, during treatment and ≥1 month following treatment completion. Monthly pregnancy tests were also required in these patients.

Exclusion criteria included abnormal laboratory test results; a Centre for Epidemiological Studies Depression scale score ≥20; a history of major psychotic disorders; or recent or current treatment with investigational drugs, other eczema therapies (including retinoids) or drugs with the potential for drug-drug interactions.[9]

Patients were randomized to treatment with alitretinoin 10 (n = 418) or 30 (n = 409) mg/day or placebo (n = 205), taken after breakfast, for up to 24 weeks.[9] Patients who responded to treatment

(rating of 'clear' or 'almost clear' on the PGA) after 12 weeks stopped treatment; other patients continued for the full 24 weeks.

The primary endpoint of this study was the response (rating of 'clear' or 'almost clear' on the PGA) rate. Assessments using the PGA were based on the area of skin involved and the severity of signs and symptoms (erythema, scaling, pruritis/pain, oedema, fissures, hyperkeratosis/lichenification, vesiculation).[9] Secondary endpoints included modified Total Lesion Symptom Score (mTLSS; rating of 0–3 for the severity of each of seven chronic hand eczema parameters), partial response rate (rating of 'clear', 'almost clear' or 'mild disease' on the PGA), Patient Global Assessment (PaGA; ratings of 'worsening', 'no change', 'mild improvement', 'moderate improvement', 'marked improvement' or 'clear or almost clear'), time to response and time to relapse.[9] Relapse was defined as an mTLSS score ≥75% of baseline. Evaluations of treatment efficacy were conducted every 4 weeks.

At baseline, all patients had chronic hand eczema rated as 'severe', except for one with 'moderate' disease.[9] Slightly more males (56%) than females (44%) were included and the mean age was 48 years.[9] Some patients had more than one type of chronic hand eczema; types included hyperkeratotic (85% of patients), pompholyx (27%), fingertip (46%) and other (14%). Forty-four percent of patients had shown no response to previous corticosteroid therapy, 53% had shown a transient response and 2% had not tolerated corticosteroids.[9] The mean mTLSS was 15.0 at baseline.[9]

Assessments were based on the intent-to-treat population using last-observation-carried-forward imputation.[9] Baseline characteristics did not significantly differ between groups.

- Alitretinoin 10 and 30 mg/day were significantly more effective than placebo with regard to the primary endpoint of response rate in adults with severe chronic hand eczema refractory to potent topical corticosteroid therapy.[9] A total of 47.7% (195 of 409 patients; $p < 0.001$ vs placebo) of alitretinoin 30 mg/day recipients responded (22.0% had a 'clear' and 25.7% had an 'almost clear' disease area) compared with 16.6% (34 of 205) of placebo recipients (2.9% 'clear' and 13.7% 'almost clear').[9] Alitretinoin 10 mg/day was also significantly ($p = 0.004$) more effective than placebo, with 27.5% (115 of 418) of recipients responding (9.3% 'clear' and 18.2% 'almost clear').[9]
- With regard to secondary endpoints, alitretinoin 30 mg/day recipients had a significantly ($p < 0.001$) shorter time to response than those receiving 10 mg/day (85 vs 114 days; placebo 141 days).[28]
- The proportions of alitretinoin 10 and 30 mg/day recipients who rated their disease as 'clear or almost clear' on the PaGA were significantly higher than that of placebo recipients (24% [101 of 418 patients; $p < 0.02$] and 40% [163 of 409; $p < 0.001$] vs 15% [31 of 205]), as was the median percentage reduction from baseline in mTLSS (56% and 75% vs 39%; both $p < 0.001$).[9]
- Significantly greater proportions of alitretinoin 10 and 30 mg/day than placebo recipients demonstrated a partial PGA-rated response (49.5% [207 of 418 patients] and 62.1% [254 of 409] vs 36.1% [74 of 205]; $p < 0.01$ and $p < 0.001$).[9]
- The median time to relapse (in the absence of anti-eczema medication) did not differ significantly between treatments; relapse occurred at a median of 6.2, 5.5 and 5.4 months in the alitretinoin 10 mg/day, alitretinoin 30 mg/day and placebo groups, respectively.[9] The respective proportions of responding patients who had not relapsed by the end of the 24-week post-treatment follow-up period were 70.4% (81 of 115 patients), 62.6% (122 of 195) and 55.9% (19 of 34).[7]
- Efficacy remained dose dependent for all disease types.[9] Patients with hyperkeratotic disease had response rates of 28% (102 of 362) and 49% (170 of 349) versus 12% (21 of 170 patients) with alitretinoin 10 and 30 mg/day versus placebo treatment, respectively. Corresponding figures for patients with pompholyx and those with fingertip disease were 23% (25 of 111) and 33% (37 of 111) versus 16% (9 of 55), and 29% (53 of 180) and 44% (87 of 196) versus 18% (18 of 101). These disease types were not mutually exclusive. No statistical data were reported for these subgroups.[9]

BACH Extension Studies

Responders to the initial treatment in the BACH study who had relapsed within 24 weeks (no active drug treatment for chronic hand eczema was allowed during this time) were re-randomized to treatment with placebo or the original dosage of alitretinoin (10 or 30 mg/day) for 12 or 24 weeks; responders to placebo received placebo again.[26] A total of 117 patients were randomized (2 : 1). Of previous alitretinoin 10 mg/day responders, 10 received placebo and 21 received alitretinoin 10 mg/day, and of previous alitretinoin 30 mg/day responders, 24 received placebo and 49 received alitretinoin 30 mg/day; 13 responders to previous placebo treatment were included.

The primary endpoint was, as in the main BACH study, PGA response rate.[26] Additional secondary endpoints included the mTLSS and the PaGA.

In an additional extension study, 243 patients from the BACH study who did not respond or had an incomplete response to initial treatment were enrolled in an open-label extension study and treated with 30 mg/day alitretinoin for 12–24 weeks.[27]

- Repeated treatment with alitretinoin was effective in patients who had relapsed following initial treatment with the drug.[7,26] Previous responders to alitretinoin 30 mg/day responded to re-treatment with the same dosage at a significantly higher rate than previous responders receiving placebo (80% vs 8%; $p < 0.001$).[7,26] Of those who had responded to initial treatment with alitretinoin 10 mg/day, 48% of alitretinoin 10 mg/day and 10% of placebo recipients responded during the extension phase ($p = 0.10$).[7,26] Previous placebo responders again had a high response rate (70%).[26]
- The proportions of alitretinoin 10 and 30 mg/day recipients who rated their disease as 'clear or almost clear' on the PaGA (a secondary endpoint) were numerically higher than the proportion of placebo recipients (38.1% and 75.5% vs 21.3%), as was the median percentage reduction from baseline in mTLSS (70.8% and 92.3% vs 42.9%).[26]
- Alitretinoin 30 mg/day may be effective in patients who did not respond or had a partial response to initial alitretinoin treatment.[27] Upon treatment with alitretinoin 30 mg/day, 50% of previous alitretinoin 10 mg/day non/partial responders, 39% of previous alitretinoin 30 mg/day non/partial responders and 51% of previous placebo non/partial responders responded to treatment, with PGA ratings of 'clear' or 'almost clear'.[27]

4. Tolerability

Tolerability data for oral alitretinoin are available from the clinical trials discussed in section 3. This section focuses mainly on data from the BACH study[9] and its extension study in patients who responded to treatment,[26] supplemented by data from the dose-finding study[25] and the manufacturer's prescribing information.[7]

- In the dose-finding study,[25] alitretinoin 10 and 20 mg/day was generally well tolerated, with dose-dependent effects. A total of 35% of both alitretinoin 10 and 20 mg/day recipients reported at least one adverse event, 35% of placebo recipients also had at least one adverse event. The most common adverse event was headache in both groups. No particular adverse event led to more than one patient withdrawing from sthe study in the 10 or 20 mg/day groups.[25]
- In the BACH study, alitretinoin treatment for ≤24 weeks was generally well tolerated in adults with severe chronic hand eczema refractory to standard topical corticosteroid therapy.[9] The most common treatment-emergent adverse events and abnormal laboratory test results (figure 1) appear to be dose dependent and were consistent with those observed with other oral retinoids and RXR agonists (such as headache and mucocutaneous effects). Treatment-related adverse events occurred in 34.5%, 37.1% and 49.5% of placebo ($n = 203$), alitretinoin 10 mg/day ($n = 410$) and alitretinoin 30 mg/day ($n = 418$) groups, respectively.[29]
- The only adverse event that led to withdrawal in two or more patients in any treatment group in the BACH study was headache (1%, 4% and 1% of patients withdrew from the alitretinoin 10 mg/day, 30 mg/day and placebo groups, respectively).[9] One percent of each treatment group reported a treatment-related serious adverse event;[29] all serious

events appeared to reflect common health problems in the target population.[9] No treatment-related deaths occurred in this study.[9]

- Abnormally high cholesterol and triglyceride and low thyroid stimulating hormone levels were evident with alitretinoin treatment in the BACH study (figure 1); however, these abnormalities are typical retinoid or RXR agonists, and medication to treat them was not routinely required.[9] Additionally, these changes as observed in clinical trials are dose dependent and reversible, and may thus be improved by dosage reduction.[7] The UK summary of product characteristics recommends that serum cholesterol and triglyceride levels should be monitored, and alitretinoin should be discontinued if hypertriglyceridaemia can not be controlled.[7]
- On re-treatment, among responders, adverse events were similar to those reported in the BACH study, with headache the most common event among alitretinoin 30 mg/day recipients.[26] No adverse event led to more than one withdrawal and no drug-related deaths occurred. Laboratory abnormalities were also consistent with the BACH study.
- Alitretinoin is an endogenous retinoid, an isomer of isotretinoin and tretinoin; retinoids are teratogenic, and thus pregnancy is an absolute contraindication to alitretinoin therapy.[7] Women of child-bearing potential must meet the conditions of the Pregnancy Prevention Programme before they are permitted to be treated with alitretinoin. If pregnancy occurs during or up to 1 month after treatment with alitretinoin, there is a great risk of severe and serious fetal malformation. Potential fetal malformations (associated with retinoids) include facial dysmorphia, cleft palate, and CNS, external ear, eye, cardiovascular, thymus gland and parathyroid abnormalities. Retinoid therapy has also been associated with spontaneous abortion.[7]
- Other retinoid class effects include the potential for psychiatric disorders, musculoskeletal effects, connective tissue disorders, eye disorders, benign intracranial hypertension (potentially linked with concomitant tetracycline use), enhanced effects of ultraviolet light, hepatobiliary disorders, gastrointestinal disorders, allergic reactions, decreased night vision and diabetes mellitus.[7] Inflammatory bowel disease, diabetes, colour blindness and contact lens intolerance, while observed with other retinoids, have not been observed in alitretinoin clinical trials.[7]

5. Dosage and Administration

The recommended dosage for oral alitretinoin in adult patients with chronic refractory hand eczema is 10–30 mg once daily, with a recommended starting dosage of 30 mg once daily.[7] The drug should always be taken with a meal in order to optimize exposure and reduce variability. Treatment duration should be between 12 and 24 weeks, depending on response. For patients with continuing severe disease after 12 weeks of treatment, discontinuation of therapy should be considered.

The recommended initial dosage for high-risk patients (patients with diabetes, obesity, cardiovascular risk factors or a lipid metabolism disorder) is 10 mg once daily; the dosage may be increased to 30 mg once daily if required.[7]

Women of child-bearing potential should receive treatment for a maximum of 30 days and the conditions of the Pregnancy Prevention Programme must be met, including effective contraception and regular pregnancy testing.[7] Pregnancy is an absolute contraindication to alitretinoin treatment, as the drug is teratogenic; in the event of pregnancy, there would be a great risk of very severe, serious fetal malformation.[7] Other contraindications include hepatic or severe renal insufficiency and breast-feeding.[7]

Concomitant treatment with tetracyclines is not permitted, as there have been reports of benign intracranial hypertension among patients receiving both retinoids and tetracyclines.[7]

Local prescribing information should be consulted for detailed information, including further contraindications, precautions, drug interactions and use in special patient populations.

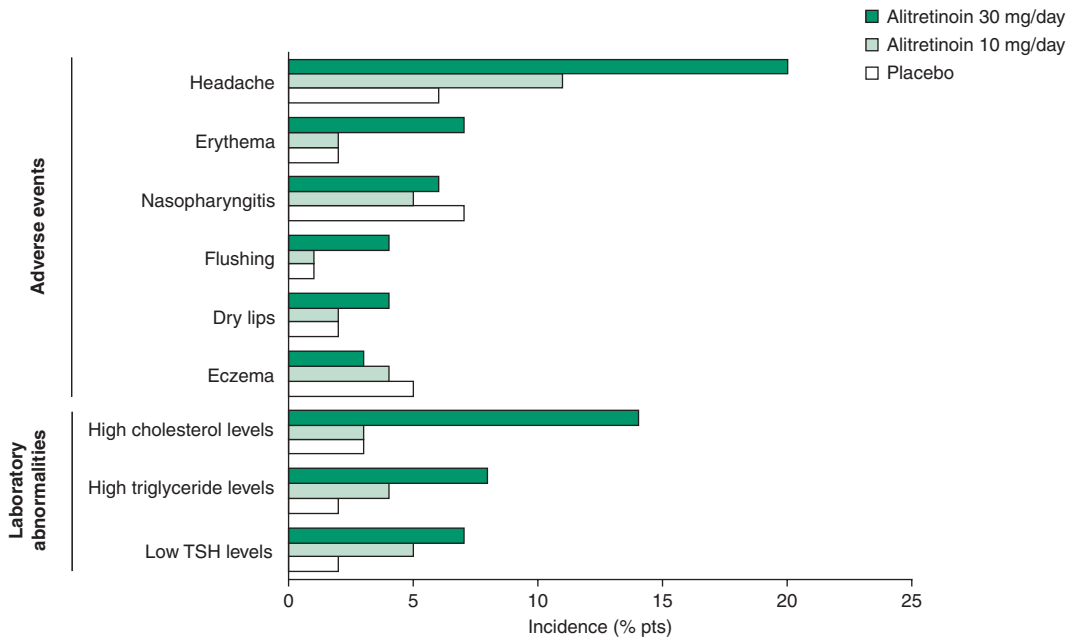

Fig. 1. Comparative tolerability of alitretinoin in patients (pts) with severe chronic refractory hand eczema. Incidence of treatment-emergent adverse events and laboratory abnormalities occurring in ≥4% of pts in a large, randomized, double-blind, placebo-controlled, multicentre study (the Benefit of Alitretinoin in Chronic Hand eczema [BACH] study) in 1032 patients.[9] Pts were randomized to double-blind treatment with alitretinoin 10 (n = 418) or 30 (n = 409) mg or placebo (n = 205) once daily after breakfast, for up to 24 weeks. High cholesterol levels were defined as >7.7 mmol/L, high triglyceride levels as >5.66 mmol/L and low thyroid-stimulating hormone (TSH) levels as <0.6 mU/L (in patients aged ≤20 years) or <0.3 mU/L (in patients aged >20 years).

6. Alitretinoin: Current Status

Oral alitretinoin is approved in several EU countries and is undergoing the approval process in others for use in adult patients with severe chronic hand eczema that is unresponsive to potent topical corticosteroids.

Alitretinoin was effective and generally well tolerated in adult patients with severe chronic hand eczema refractory to topical corticosteroid treatment in a large, well designed trial and extension phases of that trial.

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