Clinical Medicine Insights: Dermatology

REVIEW

Alitretinoin for the Treatment of Chronic Eczema of the Hand

J. English
Consultant Dermatologist, Queen's Medical Centre, University Hospital, Nottingham, NG7 2UH, UK.
Corresponding author email: john.english@nuh.nhs.uk

Abstract: Chronic hand eczema (CHE) is a very common and distressing dermatological condition which follows a remitting and relapsing course over time. Traditional treatment strategies are limited and unsatisfactory, particularly for patients who are unresponsive to potent topical corticosteroids. Studies have demonstrated that alitretinoin is effective and well tolerated in the treatment of severe CHE. In a large-scale clinical trial, a 30 mg dose of alitretinoin produced ‘clear’ or ‘almost clear’ hands in nearly half of patients treated, with a 75% median reduction in signs and symptoms by 24 weeks, and with 4 out of 5 patients showing an improvement. Furthermore, the small percentage of patients who relapsed 6 months after responding to initial treatment with alitretinoin were successfully re-treated with a second course of the drug. Treatment with alitretinoin is generally well tolerated, with manageable side effects consistent with other retinoid therapies. Alitretinoin is the first and only evidence-based therapy specifically licensed for the treatment of severe CHE unresponsive to topical corticosteroids. Clinical experience of alitretinoin post license indicates similar efficacy and tolerability to the clinical trial environment, supporting its place as a first line treatment option in CHE guidelines published to date.1-4

Keywords: chronic hand eczema, unresponsive, anti-inflammatory
Introduction

Hand eczema is the most common skin disorder affecting the hands, with a point prevalence of 1 to 5% among adults in the general population, and a 1 year prevalence of up to 10%, depending whether the disease definition includes more pronounced or mild cases.5–7 Hand eczema frequently develops into a chronic condition, with disease remaining active even after avoidance of allergens and/or irritants thought to be causative.8 It is estimated that 5% to 7% of hand eczema patients have severe chronic hand eczema (CHE), and 2% to 4% are unresponsive to standard treatment.9

In addition to the direct medical consequences of the disease, CHE is a significant burden to patients and society. Being localised to such a highly visible area of the body, CHE can cause major psychosocial problems such as anxiety, low self-esteem and social phobia,10 and has a considerable impact on patients’ quality of life.9,11 CHE has been shown to be a major cause of lost earnings, with symptoms such as itching, blisters and painful fissures limiting patients’ abilities to carry out some occupations.

Hand eczema is a heterogeneous disease of varying aetiology, morphology and severity. Some studies have shown a higher incidence of HE in female patients which is most likely due to environmental factors.9 It has been estimated that 70%–80% of childhood eczema is due to an inherited allergic susceptibility, and amongst those with childhood eczema, there is a threefold increase in the risk of hand eczema.12 It is known that environmental exposure to skin allergens or irritants, and presence of endogenous factors such as atopy plays an interrelated role in the aetiology of hand eczema.6,12 but it is frequently not possible to completely identify or eliminate the full range of causative factors.9,13,14

In a substantial number of hand eczema patients, the disease develops into a chronic condition even when an initial causative agent is avoided.9 Particularly in the case of occupational dermatitis, allergic and irritant contact dermatitis usually appears to precede the development of a more chronic condition. It is possible that inflammatory changes in the skin increase the likelihood of acquiring a secondary allergy—the second stage in a long series of events which usually also includes the direct entry of allergens through a compromised skin barrier. Sensitisation may be reduced by preventative measures early in the evolution of irritant contact dermatitis. Clinical signs and symptoms of CHE comprise classic features of eczema localised to the hands, including erythema, oedema, hyperkeratosis, scaling, lichenification, vesiculation/blistering, fissures, pruritus and pain.15–18

CHE is usually managed in escalating steps.13 Initial therapy consists of identification and avoidance of allergens and reduced exposure to irritants, and the use of emollient creams to moisturise and protect the skin.13 Topical corticosteroids are invariably added as the next step, although long-term use is limited by rebound flare-ups, tachyphylaxis and poor efficacy in severe CHE. Long-term administration of high potency topical corticosteroids can further weaken the skin barrier and cause skin atrophy. Phototherapy may be used as a further topical option despite weak evidence of efficacy in hand eczema and inconvenience to patients.13

Limited treatment options have been available for CHE patients beyond topical corticosteroids. Oral corticosteroids may be useful in controlling acute flare ups but are not a suitable long term option. Off-label immunosuppressants, such as azathioprine, cyclosporine or methotrexate have been used to improve the most troublesome features of CHE but may be associated with significant toxicity or rapid relapse on stopping, making them unsuitable for long-term use.13

Recent studies have suggested a favourable risk-benefit ratio for the use of the endogenous retinoid alitretinoin in the intermittent treatment of severe CHE unresponsive to potent topical corticosteroids. In contrast to the synthetic retinoid acitretin sometimes used on a semi-continuous basis in hyperkeratotic hand dermatoses, alitretinoin has been shown capable of clearing long standing hand eczema and producing durable remission with mostly only typical short term retinoid side effects.

There are two structurally distinct families of nuclear receptors associated with the retinoids—retinoic acid receptors (RARs) and retinoid X receptors (RXRs). Each of these families in turn contains three distinct receptors—alpha, beta, and gamma—with more isoforms belonging to each subtype.19 The existence of numerous retinoid receptor isoforms may explain the complexity and pleiotropic activity of retinoids.20 RARs bind both all-trans- and 9-cis-retinoic acid,
but only 9-cis-retinoic acid binds to RXRs, hence alitretinoin has been described as a panagonist of retinoid receptors. Binding to and activation of the various retinoid receptors might be responsible for certain biological effects of alitretinoin, however, no precise link has been shown between patterns of receptor binding and therapeutic activity in CHE hence the precise mechanism of action of alitretinoin remains unknown.

**Alitretinoin Mechanism of Action: The Anti-Inflammatory Effect**

CHE has been shown to be caused by exposure to either irritant or allergic/atopic trigger factors. Although the clinical features of CHE are well defined, the underlying pathophysiological mechanisms are still not fully understood. Induction of allergic responses activates both the epidermal compartment and also the immune system by inducing antigen-specific effector and memory T cells and causing chemokine receptor regulated leukocyte migration to sites of inflammation.\(^2\)\(^1\)

During contact irritancy, skin structural cells as well as immune cells are activated, and pro-inflammatory cytokines such as TNF-\(\alpha\) and IL-1 family members are induced, in turn mediating further recruitment of immune cells to produce an inflammatory reaction.\(^2\)\(^1\)

During an allergic reaction, haptens and allergens also activate antigen-presenting cells which migrate to local lymph nodes to activate specific T-cells which differentiate into memory T-cells, re-circulate, and may subsequently extravasate to make contact with antigen-presenting cells during further contact with the allergen. In CHE there is a predominance of Type 1 effector cytokine production, as represented by interferon-\(\gamma\). An excess of IL-4 production is also found in CHE lesions (Fig. 1).\(^2\)\(^1\)

Chemokines, a family of small, cytokine-like proteins play a crucial role in bi-directional communication pathways between structural cells of the skin and the immune system, and control the migration of leukocyte subsets to the skin. Chemokines expressed on endothelial cell membranes mediate the adhesion of leukocytes and are the stimulus for extravasation into perivascular tissues. Subsequently, matrix-bound chemokine gradients will further direct leukocyte subsets to epidermal or sub-epidermal locations.

Alitretinoin is thought to interfere with different stages of the inflammatory process seen in chronic contact eczema.\(^2\)\(^1\) Recent data have shown that within structural cells, alitretinoin markedly suppresses the expression of chemokines thought to be pathogenically relevant (e.g., CXCL9 and CXCL10), thereby impairing the recruitment of inflammatory leukocytes. Via this mechanism, alitretinoin may interfere with initiation as well as maintenance of contact eczema lesions. In contrast to isotretinoin, alitretinoin also markedly impairs mixed leukocyte reactions and has been shown to suppress leukocyte activation in a dose-dependent manner. Detailed flow cytometric analyses have shown significant dose-dependent suppression of activation-associated molecules on the surface of activated T cells by alitretinoin.

Interaction with antigen presenting cells is crucial for the differentiation and activation of memory T cells because without co-stimulation, the lymphocyte becomes tolerant and will not be activated. Alitretinoin has been shown to significantly suppress the expression of co-stimulatory molecules on the surface of antigen-presenting cells.

In summary, alitretinoin may exert an anti-inflammatory effect in chronic hand eczema by (Fig. 2): Interfering, in the early phase, with cytokine-induced chemokine production in structural cells of the skin and interfering with the recruitment of pathogenic leukocyte subsets to the skin.

Modulating leukocyte activation processes to interfere with co-stimulatory molecule function which in turn reduces effective antigen presentation to impair leukocyte activation, proliferation and expansion.\(^2\)\(^1\)
The pharmacokinetic profile of alitretinoin in patients and healthy volunteers demonstrates delayed absorption—a class effect for the highly lipophilic retinoids, with moderate to high inter-and intra-subject variability of exposure (>30%). Variability in exposure is not reduced when dose is adjusted post-hoc for body weight. When alitretinoin is taken with food, exposure is enhanced by a factor of 4 and variability is markedly decreased. Alitretinoin should therefore always be taken with a meal. In studies, single or repeat dose administration of alitretinoin resulted in exposure to alitretinoin and its 4-oxo-metabolite that was dose proportional in the 5 to 30 mg dose range. Importantly, a study carried out in patients with moderate or severe CHE, and a study carried out in healthy volunteers showed no time effect of exposure after chronic administration for up to 24 weeks. In summary, drug exposure appears to be dose proportional and constant throughout a dosing period of up to 6 months when alitretinoin is given at 10 or 30 mg per day and no evidence of drug accumulation has been observed. Results of a mass balance study demonstrate that oral alitretinoin is absorbed, extensively metabolized, and eliminated by 11 days post-administration. Excretion was mainly in urine (63%) with a smaller amount in faeces (30%). Mean total excretion was 93.5% of the administered dose. Excretion products comprised the glucuronide of 4-oxo-alitretinoin (6%) and numerous small molecular entities, most of which were present in amounts too low to identify.

Contraception and Pregnancy
Retinoids are known teratogens and effective contraception is therefore mandatory in women of childbearing potential during and after alitretinoin therapy. A study in healthy females showed that no drug-drug interactions were observed between oral alitretinoin and the commonly prescribed combined oral contraceptive (COC) ethinyl estradiol/norgestimate thus oral contraceptives are considered suitable as the primary contraception method during alitretinoin treatment. A 30-day post-treatment contraception period is appropriate because the levels of alitretinoin and its main metabolite return to endogenous levels within 24 h to 3 days. In contrast, the requirement for contraception after treatment with acitretin (t½ 39–96 hours] extends to 3-years post treatment.

Drug Interactions
When co-administered with ketoconazole, a strong inhibitor of CYP 3A4, alitretinoin AUC increased by 40% and Cmax by 60% but there was no effect on ketoconazole PK. Alitretinoin did not affect

Metabolism
The main metabolite of alitretinoin in plasma is 4-oxo-alitretinoin increasing in proportion to the alitretinoin dose administered. The extent of metabolism is variable but independent of dose and subject gender.
the pharmacokinetics of ciclosporin A nor did co-administration affect the pharmacokinetics of alitretinoin. A slight reduction of simvastatin plasma levels (AUC decreased by 16% and Cmax by 23%) was observed when co-administered with alitretinoin.

Use in CHE Patients
A 24-week, repeat dose pharmacokinetic study in patients with CHE confirmed that alitretinoin exposure in patients is similar to that obtained in normal healthy volunteers in short-term studies, with plasma concentrations returning to endogenous levels within days of discontinuing therapy. A subgroup analysis confirmed that there was no statistically significant difference in exposure to both alitretinoin and its main metabolite for body weight (> or <80 kg), suggesting no rationale for weight based dosing (as practiced for other retinoids). Similarly there was no significant difference in exposure between patients with creatinine clearance (> or <100 mL/min) or age (> or <50 years).

Therapeutic Efficacy
Early clinical studies
An open label, proof-of-concept study demonstrated the efficacy of alitretinoin in 38 difficult to treat CHE patients who had failed to respond adequately to topical corticosteroids. Thirty-four patients (89%) were assessed to have a ‘very good’ or ‘good’ response in terms of reduction of total lesions and symptoms.28

All patients enrolled in the subsequent, larger scale trials of alitretinoin were unresponsive to treatment with potent topical corticosteroids, making such agents unsuitable as a study comparator. All randomised studies were controlled against a placebo arm because none of the potential comparators (eg, phototherapy, off label systemic agents) were sufficiently characterised to serve as a reference treatment for CHE.

The phase II study of alitretinoin was a double-blind, randomised, placebo-controlled, dose-ranging study of 312 patients with moderate or severe CHE unresponsive to potent topical corticosteroids. Alitretinoin (10, 20 and 40 mg) was found to significantly improve disease status in a dose dependent manner, as determined by a Physician’s Global Assessment (PGA) rating of ‘clear’ or ‘almost clear’ in up to 54% of patients.

Dose-dependent improvements in secondary efficacy parameters of Total Lesion Symptom Score (TLSS) and Patient’s Global Assessment (PaGA) were also seen.18

The BACH Study
Findings from these early trials informed the design of the phase III trial, the largest clinical trial conducted in CHE to date; the Benefit of Alitretinoin in Chronic Hand eczema (BACH) study.29 Only patients with severe CHE unresponsive to topical corticosteroids were eligible for inclusion in this prospective, randomised, double-blind, placebo-controlled, parallel-group study. The study enrolled 1,032 patients, with average disease duration of approximately nine years. Patients were randomised to receive alitretinoin 30 mg (n = 409), alitretinoin 10 mg (n = 418) or placebo (n = 205) once daily for up to 24 weeks. The phase II study18 had indicated that alitretinoin improved signs and symptoms of CHE over the entire 12-week treatment period with no plateau in the decline of TLSS at the end of the study, thus BACH investigated treatment of up to 24 weeks. The primary efficacy parameter, PGA, was evaluated at baseline and subsequently at four-weekly intervals throughout the study, with response (primary endpoint) defined as a PGA rating of ‘clear’ or ‘almost clear’ hands. Secondary efficacy parameters included modified Total Lesion Symptom Score (mTLSS), a composite measure of individual severity scores for erythema, vesiculation, hyperkeratosis, pruritus/pain, oedema, desquamation and fissures, in addition to a Patients Global Assessment (PaGA), time to response and extent of disease.

Both doses of alitretinoin showed significantly greater efficacy compared with placebo at end of treatment. The number of patients in the 30 and 10 mg groups achieving the primary endpoint were n = 195 (48%; P < 0.001) and n = 115 (28%; P = 0.004), respectively, compared with 34 patients (17%) in the placebo group (Fig. 3). After 24 weeks, the median reduction in mTLSS in the 30 and 10 mg groups was 75% and 56%, respectively, compared with 39% for placebo (Fig. 4). Moreover, the 30 mg dose of alitretinoin had reduced mTLSS by 58% after just 12 weeks. Improvements were seen in all seven of the individual signs and symptoms that make up the mTLSS and none were seen to plateau at the end of the study, suggesting that treatment beyond 24 weeks
studies used fixed dosing without the possibility of dose modification to manage toxicity, as per normal clinical practice with oral retinoids. The open-label study enrolled 249 adult patients with severe CHE, who were unresponsive to treatment with topical corticosteroids, who initially received alitretinoin 30 mg but allowing flexible dosing to manage adverse events. Efficacy results were comparable with the findings in the blinded studies.\textsuperscript{18,29} PGA ratings of ‘clear’ or ‘almost clear’ hands were achieved in 116 patients (46.6%), and 159 patients (63.9%) were classified as partial responders with ratings of ‘clear’, ‘almost clear’, or ‘mild disease’. PaGA results were again consistent with PGA with 115 (46.2%) patients rating their disease as ‘clear’ or ‘almost clear’ at end of treatment. All other secondary efficacy parameters showed improvements consistent with those observed in the BACH study for the 30 mg dose.

Re-treatment of Relapsed Patients

Patients responding in the BACH study with ‘clear’ or ‘almost clear’ hands and who had experienced a relapse within the 24-week follow-up period were eligible to participate in an additional study to assess the efficacy of a second course of alitretinoin.\textsuperscript{21} A total of 117 patients were randomised to receive either the treatment they received in the BACH study (30 mg or 10 mg) or placebo in a 2:1 fashion for 12–24 weeks. As in BACH, response was defined as a PGA rating of ‘clear’ or ‘almost clear’ hands. Both doses of alitretinoin produced higher response rates compared with their respective placebo control, with 80% of patients retreated with 30 mg achieving a PGA response (versus 8% for placebo \( P < 0.001 \)). Median time to response was 12.1 weeks, comparable with the initial course.

Open-label Treatment

Although the double-blind, phase II and III studies had shown alitretinoin to be well tolerated, these might lead to additional PGA responses. The median time to response (‘clear’ or ‘almost clear’ hands) for alitretinoin 30 mg was 12.9 weeks.

A high degree of correlation was seen between physician’s (PGA) and patient’s (PaGA) assessment of efficacy (correlation coefficient 0.82; Kendall’s tau). This is noteworthy given that other studies have shown that physicians tend to assign higher disease improvement ratings than their patients. The median reduction in extent of disease (defined as the percentage of hand area affected by disease) was significantly reduced by alitretinoin 30 mg treatment compared with placebo (75% versus 33%; \( P < 0.001 \)). Patients who had achieved ‘clear’ or ‘almost clear’ hands during the BACH study were followed up for relapse during an active-treatment free, 24-week observation period, with relapse defined as return to an mTLSS score \( \geq 75\% \) of its baseline value in the BACH study. The median time to relapse was 5.5–6.2 months with approximately two-thirds of responders still in remission at 24-weeks follow-up.

Continuation of Alitretinoin Therapy for Patients not Showing a PGA Response after 24 weeks

In an open-label extension of the BACH study, 243 patients who had not responded to their initial regimen with ‘clear’ or ‘almost clear’ hands (whether on 10 mg, 30 mg or placebo) received open label alitretinoin 30 mg once daily for an additional 12–24 weeks.\textsuperscript{30} Of most clinical relevance was the finding of a PGA response rate of 39.1% in patients in whom the 30 mg dose had not been fully effective during BACH but

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Patients with ‘clear’ or ‘almost clear’ hands at the end of treatment. \textbf{Note:} Response defined as PGA rating of ‘clear’ or ‘almost clear’ hands at end of treatment.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Improvement in signs and symptoms over time: median% reduction in mTLSS (ITT population). \textbf{Note:} *\( P < 0.001 \) vs. placebo.}
\end{figure}
who had been randomised to continue to receive this dose for a further 12–24 weeks. This suggests that a proportion of patients who fail to achieve clear or almost clear hands after a single course of alitretinoin may do so with prolongation of treatment (Fig. 6).

**Safety Findings**

Alitretinoin has been shown to be well tolerated in the treatment of patients with severe CHE unresponsive to treatment with topical corticosteroids, with no findings noted in special safety assessments conducted during the clinical studies to detect potential effects shared with other retinoids. No differences were seen in psychiatric questionnaires (Centre for Epidemiological Studies Depression Scale, General Health Questionnaire) or in the incidence or severity of psychiatric adverse events observed between the treatment and placebo groups. Similarly, bone density assessments or skeletal radiographs did not reveal any effect of dosing on bone mineralisation or extra-osseous calcifications. Beside dry eyes, no other treatment-related effects were observed in ophthalmological assessments. In addition, electroretinograms were performed in a pharmacology study involving 32 patients exposed for 24 weeks. No effect on retinal function was observed. Overall, two fatalities were seen, both in patients receiving the 10 mg dose. Both events (myocardial infarction and acute cardiac failure) were assessed as unrelated to alitretinoin.

Adverse events reported from the trials were generally dose-dependent, manageable and consistent with other compounds in the retinoid class. Headache was the most commonly occurring AE in patients treated with alitretinoin 30 mg, and the most common reason for study withdrawal (Table 1). Headaches usually occurred within the first three to ten days of treatment and were typically managed using a standard analgesic such as ibuprofen or paracetamol and temporary dose interruption or dose reduction if required. Mucocutaneous reactions were reported in 10% of patients in the BACH study receiving the 30 mg dose, which is lower than those reported for other retinoids. The adverse event profile of the second 12–24-week courses of alitretinoin was comparable with that observed during the first course of treatment in the BACH study and there were no late-arising safety signals.

**Laboratory Abnormalities**

Observed laboratory abnormalities in the BACH study were typical effects of retinoids. Increases in serum cholesterol and triglyceride levels were the most commonly reported abnormalities (Table 2). These changes either resolved or improved markedly within 4 weeks after the end of therapy. Three cases of marked hypercholesterolemia were either present at baseline or were non-fasting values. Reduced thyroid-stimulating hormone (TSH) levels were reported in the alitretinoin 30 mg group but were not always accompanied by corresponding reductions in T4. No clinical hypothyroidism was observed and no patient required any clinical intervention during the study (such as dose interruption, supplementation with thyroid hormones, etc.). Unlike other retinoids, there was little or no apparent effect on hepatic enzyme or bilirubin levels.

Laboratory abnormalities in the open label and retreatment studies were comparable with those in the BACH trial. Approximately half of the patients with marked abnormal increases in serum cholesterol or triglyceride levels in the retreatment study had similar abnormalities during the initial BACH trial.
Table 1. Common AEs reported in at least 3% of patients in any treatment group.

<table>
<thead>
<tr>
<th>Treatment emergent AEs ≥3% in any group</th>
<th>BACH Study</th>
<th>Open-label Study</th>
<th>Re-treatment Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 203)</td>
<td>Alitretinoin 10 mg (n = 418)</td>
<td>Alitretinoin 30 mg (n = 410)</td>
</tr>
<tr>
<td>Patients with any AEs (%)</td>
<td>49.8</td>
<td>51.7</td>
<td>59.5</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6.9</td>
<td>5.3</td>
<td>5.9</td>
</tr>
<tr>
<td>Upper RTI</td>
<td>2.0</td>
<td>1.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Erythema</td>
<td>1.5</td>
<td>1.7</td>
<td>7.3</td>
</tr>
<tr>
<td>Eczema</td>
<td>4.9</td>
<td>3.8</td>
<td>3.2</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>2.5</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2.0</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Headache</td>
<td>6.4</td>
<td>10.8</td>
<td>19.8</td>
</tr>
<tr>
<td>Dry lips</td>
<td>2.0</td>
<td>2.2</td>
<td>3.7</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.5</td>
<td>2.4</td>
<td>3.4</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1.0</td>
<td>1.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Flushing</td>
<td>1.0</td>
<td>1.2</td>
<td>4.4</td>
</tr>
<tr>
<td>Blood CPK elevated</td>
<td>2.0</td>
<td>1.9</td>
<td>3.2</td>
</tr>
<tr>
<td>Blood triglyceride elevated</td>
<td>0</td>
<td>0.7</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Retreatment with alitretinoin resulted in no significant late-arising toxicities (255 patients received alitretinoin treatment for a maximum period of 48 weeks).

The Use of Alitretinoin in Clinical Practice

The TOCCATA study

A recent study (TOCCATA) was designed to compare the results from the BACH study with routine clinical practice. TOCCATA was a non-interventional study in 680 patients with severe CHE, who were treated with alitretinoin as per label for 12–24 weeks. The primary efficacy parameter was the PGA, with response being defined as ‘clear’ or ‘almost clear’ hands according to PGA at the end of treatment. Overall treatment response was highly comparable with that in the BACH study with 56.7% of patients achieving the primary endpoint. A high response rate was observed in all of the morpho-

Table 2. Marked laboratory abnormalities in the BACH study.

<table>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>Placebo</th>
<th>Alitretinoin 10 mg</th>
<th>Alitretinoin 30 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH high</td>
<td>0</td>
<td>0</td>
<td>1/50 (2.0%)</td>
</tr>
<tr>
<td>&gt;7.4 mU L⁻¹ (age ≤ 20 years)</td>
<td>0</td>
<td>0</td>
<td>1/50 (2.0%)</td>
</tr>
<tr>
<td>&gt;6.3 mU L⁻¹ (age &gt; 20 years)</td>
<td>0</td>
<td>0</td>
<td>4/50 (8.0%)</td>
</tr>
<tr>
<td>TSH low</td>
<td>0</td>
<td>0</td>
<td>4/50 (8.0%)</td>
</tr>
<tr>
<td>&lt;0.6 mU L⁻¹ (age ≤ 20 years)</td>
<td>0</td>
<td>0</td>
<td>4/50 (8.0%)</td>
</tr>
<tr>
<td>&lt;0.3 mU L⁻¹ (age &gt; 20 years)</td>
<td>0</td>
<td>0</td>
<td>4/50 (8.0%)</td>
</tr>
<tr>
<td>Thyroxine low</td>
<td>0</td>
<td>0</td>
<td>2/50 (4.0%)</td>
</tr>
<tr>
<td>&lt;8.3 pmol L⁻¹ (age ≤ 65 years)</td>
<td>0</td>
<td>0</td>
<td>8/38 (21.1%)</td>
</tr>
<tr>
<td>&lt;8.0 pmol L⁻¹ (age &gt; 65 years)</td>
<td>0</td>
<td>0</td>
<td>5/38 (13.2%)</td>
</tr>
<tr>
<td>Cholesterol high (&gt;7.77 mmol L⁻¹)</td>
<td>1/33 (3.0%)</td>
<td>2/17 (11.8%)</td>
<td>8/38 (21.1%)</td>
</tr>
<tr>
<td>Triglycerides high (&gt;5.66 mmol L⁻¹)</td>
<td>1/33 (3.0%)</td>
<td>1/17 (5.9%)</td>
<td>5/38 (13.2%)</td>
</tr>
<tr>
<td>AST high</td>
<td>0</td>
<td>0</td>
<td>2/50 (4.0%)</td>
</tr>
<tr>
<td>&gt;90 U L⁻¹ (male)</td>
<td>0</td>
<td>0</td>
<td>1/50 (2.0%)</td>
</tr>
<tr>
<td>&gt;72 U L⁻¹ (female)</td>
<td>0</td>
<td>0</td>
<td>1/50 (2.0%)</td>
</tr>
<tr>
<td>Bilirubin high (&gt;37 μmol L⁻¹)</td>
<td>0</td>
<td>0</td>
<td>1/50 (2.0%)</td>
</tr>
</tbody>
</table>
logical forms; dyshidrosiform (47.9%), hyperkeratotic-rhagadiform (59.2%) and fingertip (52.2%), and patients with a short disease duration were shown to require a shorter duration of treatment with alitretinoin.

**International Treatment Guidelines**

Given the limited options available to patients unresponsive to topical corticosteroids, treatment guidelines are now evolving to include alitretinoin. In the UK, the National Institute of Health and Clinical Excellence (NICE) has recommended alitretinoin as a first-line treatment option for patients who fail to respond to topical corticosteroids. The German Dermatology Association (DDG) has also recently published guidelines for the treatment of CHE and these recommend the use of alitretinoin for persistent or chronic relapsing hand eczema when Class 2–4 topical glucocorticoids and/or UV therapy have failed. Soon to be published Canadian guidelines propose the use of alitretinoin for patients unresponsive to potent topical corticosteroids or for those who have relapsed following steroid treatment or for those who respond to a first course of alitretinoin and subsequently relapse whilst a consortium of French CHE experts concluded that if CHE becomes persistent, alitretinoin should be the treatment of choice. A recent Italian advisory paper suggested using alitretinoin for severe disease and forms of CHE that do not respond adequately to local treatments or phototherapy.

**Alitretinoin in clinical practice**

It is recommended that alitretinoin treatment is started at a dose of 30 mg in most patients, with dose reduction to 10 mg as needed for the management of adverse reactions. Up-titration is an option for patients whose dose was reduced or who were started on a lower dose, eg, for pre-existing cardiovascular conditions.

As in the case of other retinoids, serum cholesterol and triglycerides should be monitored. The laboratory test interval may be adapted to the response of the patient’s laboratory values to the medication. For patients with diabetes, obesity, cardiovascular risk factors, or a lipid metabolism disorder, a recommended starting dose is 10 mg and can be titrated up as necessary to a maximum daily dose of 30 mg.

As mentioned previously, mucocutaneous reactions occur in around 10% of patients which is lower than those reported for other retinoids. Since alitretinoin has not been associated with significant changes in hepatic enzymes or bilirubin levels (unlike other retinoids), liver function tests are not required. Whereas inflammatory bowel disease and diabetes mellitus have been observed following treatment with other retinoids, these have not been seen in clinical trials with alitretinoin.

Like all retinoids, alitretinoin is a potent teratogen and strict pregnancy prevention measures must be observed before, during and after treatment. Alitretinoin has a shorter half-life (mean t½ 2–10 hours) than acitretin (mean t½ 39–96 hours). This is particularly relevant for females of childbearing potential as contraception is required for 1-month post treatment with alitretinoin compared with 3 years for acitretin. No other laboratory monitoring is required by the alitretinoin SPC with the exception of regular pregnancy testing for women of childbearing potential. There is no need for weight-based dosing of alitretinoin as no correlation has been shown between body weight and drug exposure or clinical response.

**Summary**

Alitretinoin is the first and only evidence-based therapy specifically licensed for the treatment of severe CHE unresponsive to topical corticosteroids. Possibly because it is a panagonist of retinoid receptors, alitretinoin appears to have a spectrum of anti-inflammatory activity that is distinct from that of other retinoids used in dermatology. Clinical trials have demonstrated that alitretinoin is effective and well tolerated in the treatment of severe CHE. Additional post-license clinical experience has shown that data collected under strict trial conditions can be reproduced during routine clinical practice.

In conclusion, alitretinoin is a proven systemic therapy for the treatment of severe CHE, with an ability to clear or substantially improve chronic hand eczema that has not previously been described for other treatment modalities. These findings support alitretinoin’s place as a first line treatment option in CHE guidelines published to date.

**Disclosure**

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author has received honoraria for speaking on the management of chronic hand eczema by Basilea. The peer reviewers of this paper report no
conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.

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