

Alitretinoin (Toctino): new oral retinoid for chronic hand eczema

John English MRCP

KEY POINTS

- alitretinoin is a vitamin A derivative licensed for the treatment of severe chronic hand eczema in adults that is unresponsive to potent topical corticosteroids
- available as 10mg and 30mg capsules (30, £411.43 – both strengths)
- dosage initially 30mg once daily with food, reducing to 10mg daily in case of unacceptable adverse reactions; continue for 12-24 weeks depending on response; should only be prescribed by dermatologists, or physicians with experience in the use of systemic retinoids
- in clinical trials, severe chronic hand eczema unresponsive to potent topical steroids was significantly improved with alitretinoin, with 48 per cent of patients taking 30mg daily showing clear or almost clear disease
- common side-effects include headache; dyslipidaemia, raised creatine kinases; anaemia, increased iron-binding capacity and thrombocytes, decreased monocytes; TSH and free T4 decreased; conjunctivitis, dry eye, eye irritation; flushing; dry skin, dry lips, cheilitis, erythema, alopecia
- contraindicated in women of childbearing age (see SPC for Pregnancy Prevention Programme), breastfeeding and certain conditions (see SPC)
- drug interactions include tetracyclines, ketoconazole, simvastatin, other retinoids
- a valuable alternative treatment for severe hand eczema when avoidance, emollients and topical steroids have failed to control symptoms



Alitretinoin (Toctino) is a new oral retinoid to treat severe chronic hand eczema that has failed to respond to topical steroids. In this New products review Dr John English discusses the clinical trial evidence for its efficacy and describes its place in treatment.

Hand eczema is an umbrella term for dermatoses of different clinical subtypes involving the hands. It varies in severity from mild changes affecting a few fingers to a severe blistering, itchy eruption involving the entire hand.¹ Hand eczema has a major impact on earnings and quality of life, often resulting in repeated consultations, unemployment, time off work and interference with leisure activities.^{2,3}

It is estimated that the prevalence of hand eczema of all severities is approximately 10 per cent but only around half of people affected seek

medical help.¹ Chronic severe hand eczema, which may account for 5-7 per cent of all cases, is associated with skin thickening, causing painful cracks and fissures.¹ In one study of 868 people with hand eczema, 44 per cent reported symptoms in the previous year and 12 per cent reported continuous symptoms.³

Aetiology

Chronic hand eczema probably develops from allergic or irritant contact dermatitis, although there may be no single identifiable cause.¹ Irritant contact allergy is more com-

mon, but allergic contact dermatitis has a worse prognosis if the allergen is not identified and avoided.⁴ The aetiology of hand eczema can be difficult to identify, or may no longer be important in the clinical manifestation of the condition.¹

Atopy is an important risk factor, reportedly present in 16-50 per cent of cases depending on definitions and the population studied. Some occupations carry a high risk of contact dermatitis.

Irritants include food, gloves, soaps, detergents and oils; water can also be a contact irritant or worsen

symptoms. Allergens include fragrances, adhesive resins (*eg* in shoes), chromium, nickel, biocides and chemicals associated with rubber.^{1,5}

Management

There is a lack of high-quality evidence on which to base management.⁶ The three main principles for the management of irritant contact eczema are avoidance, or at least exposure reduction, of the irritant, protection against exposure (*eg* wearing appropriate gloves) and substitution of a non-irritant alternative (*eg* in occupational exposure). Similarly, detection and avoidance of allergens is the first step in managing allergic contact dermatitis.⁴

Barrier creams may not protect against exposure to irritants and may promote complacency in the workplace. By contrast, there is good evidence that soap substitutes and after-work creams reduce the incidence and prevalence of contact dermatitis.⁴

Most patients with hand eczema are treated with skin protection and topical agents.¹ Treatment typically comprises a topical steroid, soap substitutes and emollients. There is some evidence that systemic treatments are effective for steroid-resistant hand eczema.⁴ However, the current alternatives are unsatisfactory for long-term use as they require either attending the hospital regularly for phototherapy, or taking immunosuppressive drugs such as azathioprine or ciclosporin (Neoral).¹

Alitretinoin

The retinoids are a group of vitamin A derivatives with a wide range of pharmacological properties and therapeutic applications in dermatology. They have been shown to affect cell proliferation and differentiation, apoptosis, angiogenesis, keratinisation and sebum secretion, and to have immunomodulatory properties.⁷

This diversity partly reflects differences in their binding with two

subtypes of nuclear receptors, retinoic acid receptors (RARs) and retinoic X receptors (RXRs). The natural ligand for RARs is tretinoin (all-trans retinoic acid); ligand binding to RARs is modulated by RXRs, for which the natural ligand is alitretinoin (9-cis-retinoic acid). RXRs also modulate ligand binding with other hormone receptors, notably thyroid hormones.⁸

Retinoids have established roles as topical or systemic treatments for severe acne, psoriasis and certain cancers, but little has been published on their use in the treatment of eczema.

Alitretinoin (Toctino) is a new oral retinoid licensed for use in adults who have severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids. The recommended dose is initially 30mg per day, reducing to 10mg if adverse effects are unacceptable. A course of treatment is usually 12-24 weeks.

In a small pilot study in patients with eczema, oral alitretinoin was associated with a good or very good response in 89 per cent of patients after one to five months' treatment.⁷ All forms of eczema responded and adverse effects were reportedly mild. These encouraging findings lead to further trials of alitretinoin in the treatment of hand eczema.

Efficacy

To date, two randomised, double-blind, placebo-controlled trials have been published. Both defined the primary end-point as the proportion of patients rated clear/almost clear by physician global assessment (PGA) of dermatitis severity (clear/almost clear/mild/moderate/severe); total lesion symptom score (TLSS) and patient global assessments (PaGA) were secondary end-points. Other systemic treatments were not allowed.

The first trial was a dose-ranging study in which 319 patients with

End-point	Placebo	Alitretinoin dose/day				
		10mg (%)	20mg (%)	30mg (%)	40mg (%)	
<i>Primary end-point</i>						
PGA	n=319 ⁸ n=1032 ⁹	27 17	39 28	41 -	- 48	53 -
<i>Secondary end-points</i>						
PaGA	n=319 ⁸ n=1032 ⁹	12 15	29 24	34 -	- 40	43 -
TLSS	n=319 ⁸ n=1032 ⁹	-25 -39	-59 -56	-52 -	- -75	-71 -
PGA: physician global assessment of clear (no residual visible dermatitis) or almost clear (minimal erythema and/or scaling) PaGA: patient global assessment of clearing or almost clearing (90% clearing of signs and symptoms compared with placebo) TLSS: median per cent change in total lesion symptom score (sum of scores on scale of 0-3 for erythema, oedema, vesicles, desquamation, hyperkeratosis, fissures, pruritus/pain) compared with baseline						

Table 1. Primary and secondary efficacy end-points in two randomised, placebo-controlled trials of alitretinoin^{9,10}

moderate (majority enrolled) or severe chronic hand eczema were randomised to placebo or treatment with alitretinoin 10, 20 or 40mg per day for 12 weeks; all also used an emollient.⁹ Most had hyperkeratotic eczema (82 per cent), fingertip eczema (28 per cent) and/or pompholyx (23 per cent). The aetiology of eczema was unknown in 45 per cent of patients; the remainder were equally divided between allergic and irritant causes.

The median duration of disease was 2.8-3.9 years. Previous treatment, which included a topical steroid unless intolerant, achieved a transient response in 80 per cent and no response in the remainder. Twenty-four per cent of patients did not complete the trial due in equal measures to lack of efficacy, adverse effects or loss to follow-up.

Alitretinoin was associated with a dose-dependent increase in the proportion of patients meeting the primary end-point (see Table 1). This was statistically significant for the trend, but significance was not reported for individual doses compared with placebo.

All doses of alitretinoin were significantly superior to placebo for PaGA and TLSS reduction. In this dose-ranging study TLSS was still falling in the treatment groups at 12 weeks, with no plateau seen; this was the rationale for extending treatment duration in the phase III trial. The response to alitretinoin was independent of the type or severity of eczema and the response (none or transient) to previous treatment.

The second study compared alitretinoin 10 or 30mg per day

with placebo in 1032 patients with severe hand eczema refractory to topical steroids (about half of the patients had a transient response), standard skin care and avoidance of known allergens or irritants; all patients used an emollient.¹⁰

Treatment was stopped in those with a PGA rating of clear/almost clear after 12 weeks, while the others continued treatment for 24 weeks (results were not reported separately). Again, most patients had hyperkeratotic-type eczema (85 per cent), pompholyx (27 per cent) or fingertip eczema (46 per cent), but aetiology was not reported. Median disease duration was 4.4-5.2 years.

Seventy-four per cent of patients completed the trial; withdrawals were mainly due to adverse events (31 per cent of withdrawals from alitretinoin versus 16 per cent with placebo) or inadequate response (33 versus 62 per cent).

PGA response rates and secondary end-points were significantly higher with both doses of alitretinoin compared with placebo (see Table 1), but the two doses were not significantly different from one another. Hyperkeratotic and fingertip eczema responded slightly better compared to pompholyx-type eczema (49, 44 and 33 per cent, respectively, at 30mg per day versus 12, 18 and 16 per cent with placebo). Statistical significance was not reported.

In a repeat of the study, the 117 patients who responded to alitretinoin 10 or 30mg per day but relapsed within 24 weeks repeated their assigned treatment for a further 12 or 24 weeks.¹¹ Compared

with those taking alitretinoin, placebo recipients were more likely to have other types of eczema and less likely to have hyperkeratotic eczema. Primary and secondary end-points were similar to those of the main trial, although statistical significance was not reported.

Safety and tolerability

Dose-related adverse effects associated with alitretinoin include headache (21 per cent at 30mg per day and 11 per cent at 10mg per day *vs* 6-9 per cent with placebo in the large clinical trial¹⁰) and flushing (6 and 1.6 per cent at 30 and 10mg per day, respectively).

Headache accounted for most withdrawals due to adverse events in clinical trials and was severe in 5-6 per cent of patients taking 30 or 40mg per day. Other common adverse events included conjunctivitis, dry lips, alopecia and erythema.

Alitretinoin has rarely been associated with psychiatric changes, including depression. In the smaller trial,⁹ patients were specifically asked about mood changes; depression was not reported in either study.

Alitretinoin was associated with dose-dependent increases in serum levels of total cholesterol, triglycerides and creatine kinases, and reductions in thyroid-stimulating hormones and haemoglobin. No clinical consequences during the trial were reported, but frequent monitoring of lipids should be considered in patients with diabetes, obesity, other cardiovascular risk factors or lipid disorders.

Alitretinoin undergoes hepatic metabolism by CYP3A4 enzymes.



Forum

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Its metabolism is reduced by strong inhibitors of this system, such as ketoconazole (Nizoral), but not weaker inhibitors, such as simvastatin and ciclosporin A. Levels of simvastatin are reduced slightly by alitretinoin and dose adjustment may be necessary.¹² Benign intracranial hypertension (pseudotumour cerebri) has been reported after concomitant use of retinoids and tetracyclines; this combination must therefore be avoided.

As with other retinoids, alitretinoin is teratogenic and is contraindicated during pregnancy. Women of childbearing age must be enrolled in a pregnancy prevention programme.

Place in therapy

Hand eczema is a common problem and, for some, one that is chronic and refractory to topical treatments. Alitretinoin has the potential to provide a valuable alternative when avoidance, emollients and topical steroids are unsuccessful. At doses of 30mg per day, about half of patients can expect substantial or complete clearance of their symptoms.

However, there will be a few patients who will not be able to tolerate the side-effects, such as head-

aches. In the main trial, dose reduction to 10mg was not permitted in the event of headache, but a reduction in dose should be considered before deciding whether to discontinue treatment.

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Dr English is consultant dermatologist at Queen's Medical Centre, Nottingham University Hospitals NHS Trust