



Other systemic treatment

Alitretinoin

<p>We suggest alitretinoin for AE patients with severe chronic <i>hand eczema</i>, who are candidates for systemic treatment, duly considering its teratogenicity.</p>		<p style="text-align: center;">100%</p> <div style="text-align: center;">  </div> <p style="text-align: center;">(15/15) Expert Consensus</p>
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alitretinoin: in label for adults with severe chronic hand eczema unresponsive to topical corticosteroids;
dosage adults 10 - 30 mg per day

Mechanisms of action and efficacy

Alitretinoin is a retinoid binding both retinoic acid (RAR) and retinoic X (RXR) receptors, thus delivering anti-inflammatory and anti-proliferative effects. It is licensed in some European countries for the treatment of chronic hand eczema irrespectively of its pathogenesis.

There is one large, multicenter randomized, placebo controlled clinical trial involving 1032 patients with chronic hand eczema, about one third of which were probably atopic hand eczema patients.¹ Improvement of eczema was seen in 75% of the patients. The patient group suffering from atopic hand eczema was not analyzed separately, and extrapalmar symptoms have not been assessed in this trial.

Six patients with AE and prominent hand involvement were treated with alitretinoin for twelve weeks in an uncontrolled, open label trial.² Both, palmar and extrapalmar lesions improved during the trial, as shown by the modified Total Lesion Symptom Score (mTLSS) hand eczema score and the SCORAD.

Dosage: acute flare, short term, long term

According to the mode of action, alitretinoin is suitable for long-term treatment. An alitretinoin treatment course should be planned for 3 to 6 months.

The dosage of alitretinoin is 10-30 mg per day.

Safety

As alitretinoin is highly teratogenic, all females of childbearing potential must adhere to a strict birth control programme.

Monitoring

Before and during therapy: liver enzymes (aspartate aminotransferase (ASAT), aspartate aminotransferase (ALAT), gamma-glutamyl transpeptidase (GGT)), cholesterol, triglycerides, basal thyroid stimulating hormone (TSH), free thyroxine (fT4) peripheral blood levels; pregnancy test in women with childbearing potential.

Combination with other treatments

Concomitantly to alitretinoin, topical therapy with corticosteroids, calcineurin inhibitors and emollients can be applied.

Special considerations

A retrospective analysis of children treated with alitretinoin because of hand eczema and other diagnoses including two severe AE patients, revealed that the response to alitretinoin was moderate in one subject, whereas the other patient failed to improve even after extending treatment to up to 11 months.³

H4R-blocking antihistamines

Mechanisms of action and efficacy

Histamine 4 receptor (H4R)-blocking antihistamines have been recently investigated for moderate and severe AE. In a phase 2a RCT, an investigational compound (JNJ-39758979) showed some efficacy but the study was interrupted after 6 weeks because of safety reasons (severe neutropenia).⁴

In a RCT with another investigational compound (ZPL-3893787) reductions in EASI score and SCORAD score were 50% and 41% respectively vs 27% and 26% for placebo, after 8 weeks. Improvement of pruritus was not different from placebo without relevant safety findings.⁵ The clinical development of this substance was stopped after negative results on efficacy after interim analysis of a phase 2b with a high placebo response of 50% (clinicaltrials.gov).

There is limited evidence available to support the general use of H4R antihistamines for the treatment of AE lesions and pruritus.

References

- [1] Ruzicka T, Lynde CW, Jemec GB, Diepgen T, Berth-Jones J, Coenraads PJ, et al. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. *Br J Dermatol.* 2008;158; 808-817.
- [2] Grahovac M, Molin S, Prinz JC, Ruzicka T, Wollenberg A. Treatment of atopic eczema with oral alitretinoin. *Br J Dermatol.* 2010;162; 217-218.
- [3] Luchsinger I, Vogler T, Schwieger-Briel A, Knöpfel N, Wälchli R, Weibel L, et al. Safe and effective use of alitretinoin in children with recalcitrant hand eczema and other dermatoses - a retrospective analysis. *J Eur Acad Dermatol Venereol.* 2020;34; 1037-1042.
- [4] Murata Y, Song M, Kikuchi H, Hisamichi K, Xu XL, Greenspan A, et al. Phase 2a, randomized, double-blind, placebo-controlled, multicenter, parallel-group study of a H4 R-antagonist (JNJ-39758979) in Japanese adults with moderate atopic dermatitis. *J Dermatol.* 2015;42; 129-139.
- [5] Werfel T, Layton G, Yeadon M, Whitlock L, Osterloh I, Jimenez P, et al. Efficacy and safety of the histamine H(4) receptor antagonist ZPL-3893787 in patients with atopic dermatitis. *J Allergy Clin Immunol.* 2019;143; 1830-1837.e1834.