Concise report

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Treatment of severe, chronic hand eczema: results from a UK-wide survey

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Summary

Treatment of severe hand eczema (HE) that is resistant to topical potent corticosteroid treatment is challenging. In 2013, we surveyed 194 UK dermatologists to obtain information about their usual treatment pathways to inform the choice of the comparator in a trial of alitretinoin in severe HE (ALPHA trial); the results indicated that the treatment approaches favoured by UK dermatologists differ. Psoralen combined with ultraviolet A (PUVA) and alitretinoin were identified as the most frequent first-line treatment options for hyperkeratotic HE, whereas oral corticosteroids were identified as the most frequent first-line treatment for vesicular HE, followed by PUVA and alitretinoin. In terms of potential adverse effects of long-term or repeated use, oral steroids and ciclosporin A were reported to cause most concern. There is uncertainty about which treatment gives the best short and long-term outcomes, because of a lack of definitive randomised controlled trials evaluating the effectiveness of different treatment pathways in severe HE.

Hand eczema (HE) is a common disease, with up to 10% of the population reporting the presence of HE at least once in a single year.[1–3] HE has a mean disease duration of over 10 years. It is estimated that 5–7% of all patients with HE may develop severe, chronic HE[4] (CHE), which is resistant to treatment with potent topical corticosteroids. CHE has a poor prognosis and can cause considerable impairment of the patient's quality of life. The overall socioeconomic impact is also high as a result of prolonged sick leave, job changes and unemployment.[1,4]

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Treatment of severe CHE resistant to topical treatment with potent corticosteroids is challenging, and treatment response is often unsatisfactory. There is a knowledge gap as to what are the most effective short- and long-term treatments for severe CHE, because of a lack of randomized controlled trials (RCTs) directly comparing first-line HE treatments on which therapy recommendations could be based. Previously published studies are difficult to compare because of heterogeneity in the patient populations, HE subgroups, HE severity, duration of treatment and outcomes used.[5]

As data on current treatment pathways for severe CHE in the UK were lacking, we distributed a survey via the UK Dermatology Clinical Trials Network and British Association of Dermatologists to obtain data to inform the choice of the comparator arm in the ALPHA trial, a trial of alitretinoin in severe HE. In total, 194 dermatologists responded to the survey, which consisted of

8 questions (Supplementary Table S1 online) on the treatment of severe hyperkeratotic or vesicular CHE. The treatment options included: psoralen ultraviolet (UV)A (PUVA), alitretinoin (9-*cis*-retinoic acid), narrowband UVB, ciclosporin A, oral steroids, methotrexate, azathioprine, mycophenolate mofetil and acitretin.

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For the treatment of hyperkeratotic CHE, PUVA and alitretinoin were considered as first choices by 40.2% and 30.9%, respectively, of the dermatologists surveyed, while narrowband UVB and mycophenolate mofetil would never be used by 45.4% and 38.1%, respectively (Fig. 1a). For vesicular CHE, 37.6% of those surveyed would consider oral steroids first, with PUVA and alitretinoin considered as first-line treatment by 26.3% and 15.5%, respectively. Narrowband UVB, acitretin and mycophenolate mofetil would never be used for the treatment of vesicular CHE by 43.3%, 37.1% and 35.1%, respectively (Fig. 1b). The survey results also indicated that 58.2% and 41.2% of doctors were very concerned about the potential adverse effects (AEs) of long-term (e.g. $\geq$ 3 months) or repeated use of oral steroids and ciclosporin A, respectively (Table 1).

The surveyed dermatologists had diverse opinions on the most effective treatment for severe HE in terms of long-term outcome (e.g. stable 3–6 months after cessation of therapy), with alitretinoin and PUVA considered to be most effective by 42.3% and 28.9%, respectively (Table 2).

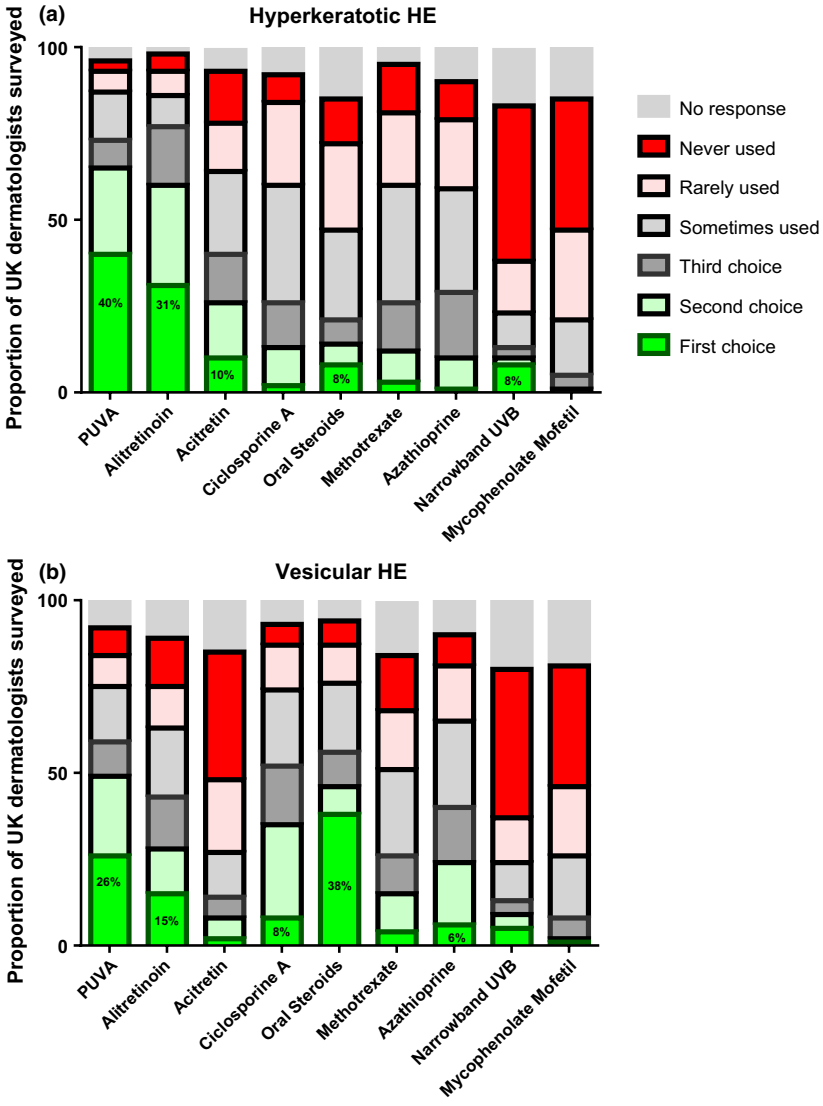

Figure 1 Treatment choice for hyperkeratotic (a) and vesicular (b) HE. The graph depicts the percentage of responses of all dermatologists surveyed for each category given.

The survey results indicated that topical steroids are often recommended for use in conjunction with systemic treatment for the management of severe CHE. The most frequently used topical steroids belong to the 'very potent' and 'potent' classes, including clobetasol propionate 0.05% (Dermovate; GlaxoSmithKline, Uxbridge, Middlesex, UK) (n = 101; 52.3%), mometasone furoate 0.1% (Elocon; Merck, Sharp and Dohme, Hoddesdon, Hertfordshire, UK) (n = 55; 28.4%) and betamethasone valerate BP 0.1% (Betnovate; GlaxoSmithKline) (n = 32; 16.5%). The majority of emollients recommended by those surveyed did not contain urea. It was acknowledged that the patient's preferences are important.

Existing evidence on systemic treatment options with special focus on alitretinoin has been summarized in the Evidence Review Group's report[6] on alitretinoin for the treatment of severe CHE. The report highlighted that although alitretinoin has been demonstrated to be efficacious for the treatment of severe CHE that is unresponsive to potent topical corticosteroids, data are lacking in terms of comparison with other treatment approaches, and longer-term (> 48 weeks) outcomes, including relapse.

The benefits of emollient therapy are widely accepted. The survey indicated that dermatologists recommend the use of emollients and topical steroids in conjunction with systemic treatment and PUVA. However, none of the published RCTs on alitretinoin permitted the use of topical steroids concomitantly or during follow-up, and the results of these trials are therefore not directly applicable to standard practice in the National Health Service.

The combination of 5- or 8-methoxypsoralen followed by broadband UVA exposure is frequently used for conditions affecting the hands and feet, including psoriasis and eczema. Although this survey did not distinguish between systemic and topical (where methoxypsoralen is applied in form of immersion, cream or gel) PUVA, clinical experience in a number

Table 1 Concern about potential adverse effects of long term (e.g. ≥ 3 months) or repeated use of treatment.

	No response, *n* (%)	A little concerned, *n* (%)	Concerned, *n* (%)	Very concerned, *n* (%)	Total, *n* (%)
PUVA	12 (6.2)	86 (44.3)	76 (39.2)	20 (10.3)	194 (100.0)
Alitretinoin	19 (9.8)	116 (59.8)	55 (28.4)	4 (2.1)	194 (100.0)
Acitretin	28 (14.4)	130 (67.0)	32 (16.5)	4 (2.1)	194 (100.0)
Ciclosporin A	6 (3.1)	18 (9.3)	90 (46.4)	80 (41.2)	194 (100.0)
Oral steroids	9 (4.6)	10 (5.2)	62 (32.0)	113 (58.2)	194 (100.0)
Methotrexate	15 (7.7)	96 (49.5)	76 (39.2)	7 (3.6)	194 (100.0)
Azathioprine	13 (6.7)	67 (34.5)	97 (50.0)	17 (8.8)	194 (100.0)
Narrowband UVB	34 (17.5)	118 (60.8)	39 (20.1)	3 (1.5)	194 (100.0)
Mycophenolate mofetil	28 (14.4)	59 (30.4)	93 (47.9)	14 (7.2)	194 (100.0)

UVB, ultraviolet B; PUVA, psoralen ultraviolet A. The table shows the number and percentage of responses received for each treatment option.

Table 2 Long-term treatment outcome and concomitant topical corticosteroids.

	Most effective treatment in terms of long-term outcome, *n* (%)*	If the patient is using topical steroids, do you recommend continuation?			
		Yes, *n* (%)	No, *n* (%)	Not applicable, *n* (%)	Not answered, *n* (%)
PUVA	56 (28.9)	165 (85.1)	10 (5.2)	9 (4.6)	10 (5.2)
Alitretinoin	82 (42.3)	156 (80.4)	18 (9.3)	6 (3.1)	14 (7.2)
Acitretin	27 (13.9)	138 (71.1)	17 (8.8)	16 (8.2)	23 (11.9)
Ciclosporin A	27 (13.9)	160 (82.5)	13 (6.7)	10 (5.2)	11 (5.7)
Oral steroids	8 (4.1)	118 (60.8)	44 (22.7)	15 (7.7)	17 (8.8)
Methotrexate	34 (17.5)	159 (82.0)	10 (5.2)	13 (6.7)	12 (6.2)
Azathioprine	34 (17.5)	157 (80.9)	12 (6.2)	11 (5.7)	14 (7.2)
Narrowband UVB	9 (4.6)	103 (53.1)	8 (4.1)	62 (32.0)	21 (10.8)
Mycophenolate mofetil	3 (1.5)	118 (60.8)	10 (5.2)	38 (19.6)	28 (14.4)
Don't know	39 (20.1)	–	–	–	–
Not answered	4 (2.1)	–	–	–	–

UVB, ultraviolet B; PUVA, psoralen ultraviolet A. The table gives number and percentage of responses received for each treatment option. *For example, stable 3–6 months after cessation of therapy.

of UK centres suggests that systemic PUVA is effective, but it can have systemic AEs, and has been replaced in many dermatology centres in Europe and the UK by topical PUVA treatment as a well-tolerated alternative.[1,7] The effectiveness of topical PUVA has not been compared with that of other treatment approaches for severe CHE, and the available studies on PUVA treatment in CHE are all based on small numbers of patients. Furthermore, these studies used different HE severity subgroups and outcome measures compared with the alitretinoin studies, thus preventing a comparison of both treatments across studies.

In summary, when patient education,[8] allergen/irritant avoidance and topical treatment are insufficient to control severe HE, UV therapy or systemic immune-modifying drugs are used.[1,9,10] Despite alitretinoin being the only licensed systemic agent for severe CHE to potent topical corticosteroids, our survey results indicate that treatment approaches of UK dermatologists for severe CHE differ. Some comments provided were that: 'Alitretinoin is new and expensive so limited use in practice so far', 'UVB very helpful but logistically very difficult to persuade patients into thrice-weekly visits for 2–3 months'. The survey results demonstrated uncertainty about which treatment gives the best long-term outcomes, and additional comments provided indicated that this is due to limited evidence comparing treatment pathways in severe CHE, indicating a need for RCTs. The survey identified alitretinoin and PUVA as popular first-line treatment choices for both severe and vesicular CHE. These results were used to inform the design of the ALPHA trial which is currently recruiting and randomising patients with severe CHE unresponsive to treatment with potent topical corticosteroids to either alitretinoin or immersion PUVA as used in standard practice. The trial will evaluate outcomes at short- (12 weeks) and longer-term (up to 52 weeks) timepoints, using various outcomes for comparability with other studies, and will describe second-line treatments in patients with a poor response to first-line therapy.

Learning points

- Currently, treatment pathways for severe hand eczema in the UK are diverse.
- PUVA and alitretinoin are both widely used as first choice treatment for severe hand eczema.
- The majority of UK dermatologists are very concerned with the potential AEs of long term or repeated use of ciclosporin A.
- Further studies reflecting standard practice are needed to guide treatment pathways.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:
Table S1. Survey questions.

