Alitretinoin versus phototherapy as the first-line treatment in adults with severe chronic hand eczema: the ALPHA RCT

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Scientific summary

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Scientific summary

Background

Hand eczema (HE) is common and an important cause of morbidity and occupational disability. One-year prevalence of HE is up to 10% in the general population, with 5–7% developing chronic hand eczema (CHE).

Current evidence is not compelling enough to guide clinical practice. When patient education, irritant/contact allergen avoidance, moisturisation and topical corticosteroids are insufficient to control CHE, ultraviolet therapy (PUVA) or systemic immune-modifying drugs are used. There is no treatment pathway generally accepted among UK dermatologists. Most UK dermatology centres use phototherapy (mostly Immersion PUVA) or alitretinoin as first-line treatment for uncontrolled CHE.

ALPHA is the first trial comparing alitretinoin with Immersion PUVA as a first-line therapy for patients with uncontrolled severe CHE.

Objectives

Primary objective

Compare alitretinoin and Immersion PUVA as first-line therapy in terms of disease activity at 12 weeks post planned start of treatment.

Secondary objectives

- Compare alitretinoin and Immersion PUVA in terms of disease activity over time (focusing on 24 and 52 weeks post planned start of treatment).
- Compare alitretinoin and Immersion PUVA in terms of time to relapse.
- Compare alitretinoin and Immersion PUVA in terms of quality of life (QoL) and patient benefit over 52 weeks post planned start of treatment.
- Determine cost-effectiveness of alitretinoin compared with Immersion PUVA over the short and longer term.
- Determine the educational need for patients.
- Compare alitretinoin and Immersion PUVA in terms of safety.

Exploratory objectives included subgroup analyses to assess whether treatment response is affected by pre-specified baseline characteristics.

Methods

Design

Prospective, multicentre, open-label, two-arm parallel group, adaptive randomised controlled trial with one planned interim analysis and an economic evaluation.

Participants

Patients with severe CHE unresponsive to at least 4 weeks of treatment with potent topical corticosteroids.

Primary end point

Natural logarithm of the Hand Eczema Severity Index (HECSI) + 1 at 12 weeks post planned start of treatment.

Secondary end points

- Disease activity, measured by HECSI, modified Total Lesion Scoring System (mTLSS) and Physician's Global Assessment (PGA) at 12, 24, 52 weeks post planned start of treatment.
- Time to relapse, defined as time between achieving clear/almost clear overall on the blinded assessor PGA and scoring 75% of their baseline HECSI, with sensitivity assessed by redefining relapse as 50% of their baseline HECSI.
- Dermatology Life Quality Index (DLQI) and Patient Benefit Index for Hand Eczema (PBI-HE) at 12, 24 and 52 weeks post planned start of treatment.
- Person-Centred Dermatology Self-Care Index (PeDeSi) at 12 and 52 (or 24) weeks post planned start of treatment.
- Reported adverse events (AEs) and serious adverse events (SAEs) over 52 weeks post planned start of treatment.
- Cost-effectiveness of alitretinoin compared with Immersion PUVA at week 12, 52 (short term) and over 10 years (long term).

Randomisation

Participants were randomised using minimisation 1 : 1 to alitretinoin 30 mg/day or Immersion PUVA for 12 weeks to 24 weeks. Randomisation factors were: randomising site, disease duration, clinical phenotype, atopy status, DLQI and skin type.

Analysis

Linear mixed models accounting for the longitudinal data structure were fitted to primary (HECSI) and secondary end points (mTLSS, DLQI) on the intention-to-treat (ITT) population, with adjustment for: smoking history, body mass index (BMI), foot involvement, baseline score, time since planned start of treatment and treatment group. Participant and participant–time interaction were fitted as random effects. An ordinal logistic mixed model was fitted to the PGA, and an ordinal logistic model without random effects was fitted to the PeDeSI at 12 weeks.

Exploratory analyses explored differential treatment effects in pre-planned subgroups, correlation of scoring systems and second-line therapies, and safety data were summarised.

Total cost and quality-adjusted life-years (QALYs) were estimated at weeks 12, 52, and 10 years after treatment initiation. The latter were combined to estimate short- and long-term cost-effectiveness. Short-term cost-effectiveness was estimated via a within-trial analysis at weeks 12 and 52 and via Markov model to estimate 10-year cost-effectiveness of both interventions. A resource use questionnaire was used to estimate short- and long-term cost of interventions and standard care, while EuroQol-5 Dimensions, three-level version (EQ-5D-3L) responses were used to estimate utility values and generate QALYs. This analysis followed the NHS and personal and social perspective (PSS). Cost-effectiveness was determined using National Institute for Health and Care Excellence (NICE) guidelines. Secondary analysis included societal perspective and QALYs determined by the DLQI.

Data collection

Data were collected at baseline, 4-weekly to week 36 and 8-weekly to week 52.

Sample size

A minimum of 500 and maximum of 780 participants were required to detect a relative difference, or fold change, of 1.3 in HECSI score between treatment arms at 12 weeks post planned start of treatment (80% power; two-sided 5% significance level) assuming a coefficient of variation (CV) between 1.175

and 1.7 and 20% attrition. Note that a fold change of 1.3 is equivalent to a fold change of 0.77 if there was a benefit in the opposite direction. A sample size review was planned after 364 participants reached 12 weeks post planned start of treatment but was conducted early in August 2017. Following Data Monitoring and Ethics Committee (DMEC) review, a sample size of 514 participants was recommended based on a CV of 1.2.

Results

Screening and recruitment

Thirty-one NHS hospitals in England, Scotland and Wales assessed 1557 patients for eligibility, registered 582 (37.4%) and randomised 441 (75.8%) participants between October 2015 and June 2021.

Of 1557 patients screened, 642 (41.2%) were ineligible, with 347 (54.0%) not having a severe CHE diagnosis. Of 915 eligible patients, 582 (63.6%) were consented and registered. Of 333 patients who did not consent, 74 (22.2%) thought the Immersion PUVA schedule or travel was inconvenient, and 28 (8.4%) did not want alitretinoin. Of 141 patients not randomised, the main reasons were not meeting the eligibility criteria [*n* = 69 (48.9%)] or patient choice [*n* = 29 (20.6%)].

Of patients randomised, 220 (49.9%) were allocated to alitretinoin and 221 (50.1%) to Immersion PUVA. Of those allocated to alitretinoin, 201 (91.4%) started treatment within 7 days post randomisation compared with 165 (74.7%) of those allocated to Immersion PUVA. In total, 132 (29.9%) participants withdrew from, or were lost to, follow-up. The ITT population included 441 (100.0%) participants.

Primary outcome

Hand eczema severity index at 12 weeks

In terms of relative change, the median [interquartile range (IQR)] score at 12 weeks was equal to 30% (10–70%) of that at baseline for the alitretinoin group compared with 50% (20–100%) in the Immersion PUVA group. There was a statistically significant benefit of alitretinoin compared with Immersion PUVA at 12 weeks, with an estimated fold change of 0.66 (0.52, 0.82), $p = 0.0003$ at 12 weeks.

Secondary end points

Hand eczema severity index over 52 weeks

There was no evidence of a difference between alitretinoin and Immersion PUVA at 24 weeks or 52 weeks, with the estimated fold change [95% confidence interval (CI)] equal to 0.92 (0.798 to 1.08) and 1.27 (0.97 to 1.67), respectively.

Modified total lesion symptom score over 52 weeks

There was no evidence of a difference between treatment groups over 52 weeks, with the estimated difference (95% CI) equal to −0.37 (−1.23 to 0.48) at 12 weeks, −0.14 (−0.84 to 0.56) at 24 weeks and 0.41 (−0.59 to 1.40) at 52 weeks.

Physician's Global Assessment over 52 weeks

At 12 weeks, the proportion of participants with available data achieving clear or almost clear (via blinded assessment) was 27.6% (47/170) for alitretinoin and 23.6% (35/148) for Immersion PUVA. Over 52 weeks, 59.4% (123/207) of alitretinoin participants with available data achieved at least one clear/almost clear assessment compared with 61.5% (118/192) of Immersion PUVA participants.

There was no evidence of a difference between treatment groups over 52 weeks, with the estimated odds ratios (alitretinoin vs. Immersion PUVA) for achieving lower PGA scores and 95% CI equal to 1.22 (0.90 to 1.64) at 12 weeks, 1.18 (0.89 to 1.56) at 24 weeks and 1.10 (0.64 to 1.89) at 52 weeks.

Dermatology quality of life index over 52 weeks

There was a statistically significant benefit of alitretinoin compared with Immersion PUVA, with mean scores (95% CI) estimated to be 0.95 (0.09 to 1.82) lower at 12 weeks for the alitretinoin group compared with Immersion PUVA. There was no statistically significant treatment effect at 24 weeks [estimated difference in mean scores = −0.18 (−0.92 to 0.56)], but at 52 weeks, there was a statistically significant treatment effect with increased scores in the alitretinoin group compared with the Immersion PUVA group [estimated difference in mean scores = −1.62 (−2.62 to −0.62)]. The differences observed in the DLQI were not clinically significant.

Person-Centred Dermatology Self-Care Index at 12 weeks

At baseline, 16.1% (*n* = 71) were assessed as having sufficient knowledge, ability and confidence to self-manage their condition, with a similar distribution of education needs across treatment groups. At 12 weeks, the proportion of participants with available data who had sufficient knowledge and education was 26.2% (117/324), 28.0% (49/175) in the alitretinoin group and 24.2% (36/149) in the Immersion PUVA group. There was no evidence of a difference in terms of educational need between treatment groups, with an estimated odds ratio (alitretinoin vs. Immersion PUVA) of 0.65 (0.39 to 1.08).

Patient Benefit Index – hand eczema over 52 weeks

At 12 weeks, the median (IQR) score was equal to 2.3 (1.4–3.2) in the alitretinoin group and 1.9 (0.9–2.8) in the Immersion PUVA group. At 24 weeks, the median (IQR) score was unchanged at 2.3 (1.2–3.5) in the alitretinoin group but had increased to 2.8 (1.4–3.5) in the Immersion PUVA group. At 52 weeks, the median (IQR) score was 2.6 (1.6–3.3) in the alitretinoin group and 3.0 (1.7–3.6) in the Immersion PUVA group.

Time to relapse

At treatment phase completion, 34.1% (*N* = 75) of participants allocated to alitretinoin achieved a clear or almost clear response, compared with 25.8% (*N* = 57) allocated to Immersion PUVA. When relapse was defined as 75% of the baseline HECSI score, 20% (*n* = 15) of alitretinoin responders relapsed compared with 15.8% (*n* = 9) of Immersion PUVA responders. When relapse was defined as 50% of the baseline HECSI score, 37.3% (*n* = 28) of alitretinoin responders and 36.8% (*n* = 21) of Immersion PUVA responders relapsed.

Health economic analysis

Within-trial estimated costs indicate that Immersion PUVA is more costly than alitretinoin at weeks 12 and 52 (week 12: £3236 vs. £1904; week 52: £4424 vs. £3336, respectively). Treatment costs are the main drivers of Immersion PUVA costs (including therapy cost, medication and follow-up). Out-of-pocket expenditures are also higher for patients assigned to Immersion PUVA. These increase the cost difference at weeks 12 and 52 (from £1333 to £1650 at week 12 and from £1081 to £1841 at week 52). Immersion PUVA's QALYs are higher at both time points (week 12: 0.165 vs. 0.159 and week 52: 0.798 vs. 0.761). When using DLQI, the estimated QALYs were slightly higher for alitretinoin compared with Immersion PUVA (week 12: 0.158 vs. 0.154; week 52: 0.784 vs. 0.782, respectively).

When combined, the incremental cost-effectiveness ratios (ICERs) indicate alitretinoin is cost-effective at weeks 12 and 52 in all scenarios (primary analysis, societal perspective, and QALYs derived from DLQI). These results are robust, as the probability of cost-effectiveness is between 96% and 100%.

Long-term cost-effectiveness

The 10-year cost estimates indicate that patients allocated to alitretinoin are slightly more costly than Immersion PUVA (£5432 vs. £5361, respectively). In terms of QALYs, Immersion PUVA is slightly more effective (6.535 vs. 6.530, respectively). The latter suggests Immersion PUVA is the cost-effective strategy; however, results are uncertain, as only 50% of the probabilistic analysis iterations indicate this is the case.

Safety data

Seventy-nine participants had 135 reportable AEs, 25.0% (*n* = 55) participants allocated to alitretinoin and 10.9% (*n* = 24) participants allocated to Immersion PUVA. There were four serious AEs (SAEs; two alitretinoin, two Immersion PUVA); one suspected/expected to be related to treatment, and three related to underlying CHE. There were four pregnancies (three alitretinoin, one Immersion PUVA), including one alitretinoin patient in active treatment, who stopped treatment immediately.

Treatment compliance

In total, 212 (96.4%) participants randomised to alitretinoin and 196 (88.7%) randomised to Immersion PUVA received treatment. Full 'trial' compliance (≥ 80% received and no treatment breaks > 7 days during the first 12 weeks) was observed in 65.9% (*N* = 145) participants allocated to alitretinoin and 24.0% (*N* = 53) allocated to Immersion PUVA.

Subgroup analysis

No differential treatment effects were observed within subgroups defined by disease duration, clinical phenotype, disease severity, presence of atopy, filaggrin loss of function mutation, smoking history, BMI, foot involvement or biomarkers identified through tape stripping.

Conclusion

Alitretinoin and Immersion PUVA both led to reductions in symptoms. As a first-line therapy, alitretinoin showed a more rapid improvement and was superior to Immersion PUVA in terms of primary end point at 12 weeks. This difference was not observed at later time points. Alitretinoin was more cost-effective over the short term (12 and 52 weeks) with robust results. Long-term analysis indicates that Immersion PUVA is cost-effective in the long term; these results, however, are uncertain.

These findings will inform clinical management of patients with severe CHE. Alitretinoin may be considered as the recommended first-line therapy; however, Immersion PUVA may also be considered for longer-term outcomes, particularly in patients where alitretinoin is not an appropriate treatment.

Recruitment was difficult, with perceived treatment pathway challenges. The trial implemented a self-referral service, through which 13.8% of randomised participants were recruited. The Immersion PUVA schedule was problematic, with more than 20% of participants declining participation citing this as their main reason. Immersion PUVA treatment compliance was poor, and regular twice-weekly treatment was not achieved by most patients.

Hand eczema severity index (HECSI) was the chosen primary outcome measure because it incorporated more details about the condition compared with PGA, which had been used previously. Furthermore, HECSI is continuous rather than discrete, which meant a smaller sample size was required for a desired level of power. The results from ALPHA will help inform future CHE trial designs.

Most participants had some educational need for how to manage their condition, and overall, there remains a need for better therapeutic approaches for severe CHE. Just 59% and 61% of patients allocated to alitretinoin and Immersion PUVA, respectively, were known to achieve a clear/almost clear assessment at any time point during the trial period. Further work includes deeper analysis of substudies and pilot data to inform future research, which is needed to understand the long-term effects of treatments.

Trial registration

This trial is registered as ISRCTN80206075.

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