Home-based narrowband UVB, topical corticosteroid or combination for children and adults with vitiligo: HI-Light Vitiligo three-arm RCT

Jonathan M Batchelor,[1†] Kim S Thomas,[1*†] Perways Akram,[2] Jaskiran Azad,[3] Anthony Bewley,[4] Joanne R Chalmers,[1] Seau Tak Cheung,[5] Lelia Duley,[6] Viktoria Eleftheriadou,[7] Robert Ellis,[8,9] Adam Ferguson,[10] Jonathan MR Goulding,[11] Rachel H Haines,[6] Hamdi Hamad,[12] John R Ingram,[13] Bisola Laguda,[14] Paul Leighton,[1] Nick Levell,[15] Areti Makrygeorgou,[16] Garry D Meakin,[6] *et al.*‡

[1]Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK
[2]Department of Medical Physics and Clinical Engineering, Nottingham University Hospitals NHS Trust, Nottingham, UK
[3]The James Cook University Hospital, South Tees Hospitals NHS Foundation Trust, Middlesbrough, UK
[4]Whipps Cross Hospital and The Royal London Hospital, Barts Health NHS Trust, London, UK
[5]Blackheath Hospital, Winchester House, London, UK
[6]Nottingham Clinical Trials Unit, Nottingham, UK
[7]Leicester Royal Infirmary, Leicester, UK
[8]York Hospital, York Teaching Hospital NHS Foundation Trust, York, UK
[9]Medical School, Newcastle University, Newcastle upon Tyne, UK
[10]Royal Derby Hospital and the London Road Community Hospital, University Hospitals of Derby and Burton NHS Foundation Trust, Derby, UK
[11]Solihull Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[12]Cannock Chase Hospital and New Cross Hospital, The Royal Wolverhampton NHS Trust, Wolverhampton, UK
[13]Division of Infection and Immunity, Cardiff University, Cardiff, UK
[14]Chelsea and Westminster Hospital, Chelsea and Westminster Hospital NHS Foundation Trust, London, UK
[15]Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK
[16]West Glasgow Ambulatory Care Hospital, NHS Greater Glasgow and Clyde, Glasgow, UK

*Corresponding author Kim.Thomas@Nottingham.ac.uk
†Joint first authors
‡The full author list can be found in *Appendix 1*.

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Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

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Scientific summary

HI-Light Vitiligo three-arm RCT

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Scientific summary

Background

Vitiligo is a skin condition that results in complete loss of pigment. It affects around 0.5–2% of the world's population and can develop at any age. Vitiligo can be distressing for patients, especially when it occurs on exposed areas, such as the face and hands.

Current clinical guidelines for the management of vitiligo recommend topical corticosteroids, narrowband ultraviolet B light, topical tacrolimus and combination treatments, but the evidence base for all treatment approaches is limited.

The Home Interventions and Light therapy for the treatment of vitiligo (HI-Light Vitiligo) trial addresses two priority topics from a James Lind Alliance Priority Setting Partnership that were highlighted as being important to people with vitiligo and health-care professionals:

1. Which treatment is more effective for vitiligo – steroid creams/ointments or light therapy?
2. How effective is ultraviolet B light therapy when combined with creams or ointments in treating vitiligo?

Objectives

1. To evaluate the comparative effectiveness and safety of home-based interventions for the management of active, limited vitiligo in adults and children. Comparing:
    - hand-held narrowband ultraviolet B light with potent topical corticosteroids [mometasone furoate 0.1% ointment (Elocon®, Merck Sharp & Dohme Corp., Merck & Co., Inc., Whitehouse Station, NJ, USA)]
    - combination of hand-held narrowband ultraviolet B light plus potent topical corticosteroids with potent topical corticosteroids alone.
2. To assess whether or not treatment response (if any) is maintained once the interventions are stopped.
3. To compare the cost-effectiveness of the interventions from an NHS and, separately, a family perspective.
4. To understand the barriers to and facilitators of adoption of these interventions in the UK NHS.

Methods

Study design

A multicentre, three-arm, parallel-group, pragmatic, placebo-controlled randomised controlled trial, with nested health economic analysis and process evaluation.

Recruitment and follow-up

Participants were recruited from 16 UK hospitals, with recruitment from primary care, secondary care and community advertising, and were trained to deliver the treatments in their homes.

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Treatment was for 9 months with a further 12-month follow-up; participants attended hospital clinics on 2 consecutive days at baseline for recruitment and training, and then at 3, 6 and 9 months to assess outcomes. Follow-up to 21 months was carried out using 3-monthly questionnaires.

Eligibility criteria

Participants were aged ≥ 5 years, with a diagnosis of non-segmental vitiligo, limited to approximately ≤ 10% of body surface area, and at least one vitiligo patch that had been active in the last 12 months (self-reported). Participants had to be willing to stop other vitiligo therapies, able to follow the treatment instructions and comply with safety precautions at home, and willing and able to give informed (or parental/carer) consent.

Participants were excluded if they:

- had segmental or universal vitiligo
- had vitiligo limited solely to areas contraindicated for treatment with potent topical corticosteroids
- had a history of skin cancer, radiotherapy use or photosensitivity (based on minimum erythemal dose test)
- had an allergy or contraindication to mometasone furoate
- were pregnant, breastfeeding or likely to become pregnant during the trial
- were on immunosuppressive drugs
- were involved in another clinical trial.

Participants could also be excluded if an investigator thought that they were unable to use the treatments safely.

Interventions

Participants received a hand-held narrowband ultraviolet B light unit (active or dummy) and either topical corticosteroids (mometasone furoate 0.1% ointment) or placebo ointment (vehicle). Treatments were used for up to 9 months. Participants received face-to-face training, online training and a written handbook of instructions.

At baseline, participants selected a target patch that had been active in the last 12 months and in which they most wanted to see improvement. Participants could select up to two further study patches for treatment, with a maximum of one on each of three anatomical regions (head and neck, hands and feet, and rest of the body). Participants could treat additional patches if they wished, but these were not assessed in the study.

Hand-held narrowband ultraviolet B light (Dermfix 1000 MX, Dermfix Limited, Chalfont St Giles, UK) was used on alternate days. The treatment schedule had a starting dose of 0.05 J/cm^2 and increased incrementally. Participants recorded treatment times and side effects in a participant diary.

Topical corticosteroids or placebo ointment was applied once daily on alternate weeks (i.e. 1 week on, 1 week off).

Outcomes

Primary outcome

Treatment success at the target patch of vitiligo after 9 months of treatment was measured using the participant-reported Vitiligo Noticeability Scale. Treatment success was defined as vitiligo being ‘a lot less noticeable’ or ‘no longer noticeable’ compared with before treatment.

Secondary outcomes

- Blinded assessment of treatment success (using Vitiligo Noticeability Scale) at the target patch by a panel of three blinded assessors with vitiligo using digital images at baseline and 9 months.
- Participant-reported treatment success for each of the three body regions using the Vitiligo Noticeability Scale, assessed at 9 months (all assessed patches).
- Onset of treatment response at the target patch: assessed by investigators using the question 'Compared with the start of the study, has there been a change in the vitiligo patch?'. Onset of treatment response was defined as 'stayed the same (i.e. not worsened)' or 'improved' as all target patches were active patches at baseline.
- Percentage repigmentation: for the target patch at 9 months, using digital images assessed by a clinician unaware of treatment allocation (treatment success $\geq$ 75% repigmentation), plus blinded assessment by investigators at 3, 6 and 9 months.
- Vitiligo-specific and generic quality of life: assessed at end of treatment (9 months) and end of follow-up (21 months).
- Maintenance of treatment response: assessed by participants for the target patch of vitiligo at 12, 15, 18 and 21 months post randomisation, using the question 'Compared to since you stopped using the study treatments, has there been a change in the vitiligo patch?'. Loss of treatment response was defined as a response of 'worse' at any time point.
- Burden of treatment: time per session for active light treatment and participant-reported treatment burden for topical corticosteroids and light treatments at 3, 6 or 9 months.

Safety outcomes

Adverse reactions during the treatment phase were recorded. Events of interest were predefined as grade 3 or 4 erythema and skin thinning. All serious adverse events were also recorded.

Sample size

The target sample size was 440 participants (assuming 15% of participants allocated to topical corticosteroids alone would achieve treatment success, and to detect a clinically significant absolute difference between groups of 20%, with 2.5% two-sided alpha, 90% power and 15% loss to follow-up). A planned sample size review by the Data Monitoring Committee after 18 months of recruitment recommended extending recruitment to 516 participants.

Randomisation and blinding

Participants were randomised to active topical corticosteroids plus dummy narrowband ultraviolet B light (topical corticosteroids-only group); active narrowband ultraviolet B light plus placebo ointment (narrowband ultraviolet B light-only group); or active topical corticosteroids ointment plus active narrowband ultraviolet B light (combination group). Randomisation was minimised by recruiting centre, body region of target patch (head and neck, hands and feet, or rest of the body) and age (5–15 years or $\geq$ 16 years). Randomisation was via a secure web server created and maintained by the Nottingham Clinical Trials Unit to ensure allocation concealment. A central pharmacy distributed the interventions directly to participants' homes.

Participants, research nurses, principal investigators, members of trial management group and data analysts were blinded to treatment allocation. Owing to the unblinding risk from skin erythema after narrowband ultraviolet B light treatment, additional outcome assessments were performed by a panel

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of three patient assessors (for the primary analysis) and a blinded clinician for the secondary outcome of percentage repigmentation, using digital images taken at baseline and at 9 months.

Statistical methods

For all analyses, two prespecified between-group comparisons were made: narrowband ultraviolet B light versus topical corticosteroids, and narrowband ultraviolet B light plus topical corticosteroids versus topical corticosteroids.

Primary analysis was by intention to treat and with multiple imputation of missing data. The number and percentage of participants achieving 'treatment success' was reported. Randomised groups were compared using a mixed-effects model for binary outcomes, adjusted by recruitment centre, body region of target patch and age at randomisation. The primary estimate of effect was the difference in the percentage of participants achieving treatment success at 9 months, with 95% confidence intervals and *p*-values. We also reported relative differences using risk ratios. Sensitivity analyses were conducted to (1) adjust for any variables with imbalance at baseline, (2) repeat primary analysis based on participants with primary outcome data and (3) investigate the impact that treatment adherence had on the results. Planned subgroup analyses were (1) children versus adults; (2) body region of the target vitiligo patch; (3) hypomelanotic patch (an indicator of disease activity), definitely or maybe versus no; and (4) ≥ 4 years duration of vitiligo versus < 4 years. It is thought that patches that are hypomelanotic, with poorly defined borders, are more likely to be active patches, and therefore more responsive to treatment. Patches were assessed at the point of randomisation using a Wood's lamp, and designated as hypomelanotic with poorly defined borders (or 'hypomelanotic' for short) or amelanotic with sharply defined borders. These analyses were conducted by inclusion of appropriate interaction terms in the regression model and were considered as exploratory. An additional post hoc subgroup analysis explored the impact of skin type (types I–III vs. types IV–VI).

Secondary outcomes were analysed by a similar approach, using appropriate regression modelling depending on outcome type.

Health economics

A nested health economic analysis explored cost-effectiveness of the interventions from an NHS perspective (primary) and a family perspective (secondary). These were assessed using participant self-report of health-care appointments (number, which professional and relevance to vitiligo), prescriptions for vitiligo treatments and personal expenses. The base-case analysis estimates an incremental cost per additional successful treatment with incremental cost per quality-adjusted life-year presented in the secondary analyses.

Process evaluation

A mixed-methods process evaluation study was conducted to inform the interpretation of trial results and to explore barriers to and facilitators of adoption of the interventions in the UK NHS.

A total of 25 trial participants (adults, young people or parents) and 10 commissioners were interviewed (nine interviews), 24 recruiting site staff completed an online survey and 13 site staff participated in study-review focus groups.

Interviews and focus group data were analysed thematically using an inductive approach; descriptive statistics were generated for online survey responses. Interview prompts and analysis were informed

by an initial programme theory, which proposed how combination treatment might ideally work in the NHS. Data were organised to address three key questions:

1. Is home-based treatment manageable for people with vitiligo?
2. Should combination treatment be made more widely available?
3. Could combination treatment be made more widely available in the NHS?

Results

Between May 2016 and September 2017, 517 participants were randomised (adults, $n = 398$; children, $n = 119$). Primary outcome data were available for 370 (72%) participants. Baseline characteristics were well balanced.

The median percentage of narrowband ultraviolet B light treatment-days was 81% for topical corticosteroids, 77% for narrowband ultraviolet B light and 74% for combination groups, and for ointment 79% for topical corticosteroids, 83% for narrowband ultraviolet B light and 77% for combination. Just under half of the participants used the treatments for > 75% of the expected duration.

Investigators thought that they had become unblinded for 21%, 28% and 27% of the participants in the topical corticosteroids, narrowband ultraviolet B light and combination groups, respectively. The percentages of participants who thought that they had become unblinded were 39%, 55% and 44%, respectively. Unblinding guesses for narrowband ultraviolet B light were correct approximately 80% of the time, but for topical corticosteroids the guesses were correct less than half of the time.

For the primary outcome, treatment success using the Vitiligo Noticeability Scale at 9 months was reported by 20 out of 119 (17%) of those allocated topical corticosteroids, 27 out of 123 (22%) of those allocated narrowband ultraviolet B light and 34 out of 128 (27%) of those allocated combination treatment. The adjusted risk difference between combination treatment and topical corticosteroids was 10.9% (95% confidence interval 1.0% to 20.9%; $p = 0.03$) and for narrowband ultraviolet B light compared with topical corticosteroids was 5.2% (95% confidence interval −4.4% to 14.9%; $p = 0.29$). Corresponding adjusted risk ratios were 1.93 (95% confidence interval 1.02 to 3.68) for combination treatment compared with topical corticosteroids and 1.44 (95% confidence interval 0.77 to 2.70) for narrowband ultraviolet B light compared with topical corticosteroids.

Participants who adhered to ≥ 75% of expected treatments were more likely to achieve treatment success in the combination group compared with topical corticosteroids (adjusted odds ratio 2.73, 95% confidence interval 1.24 to 6.02), but not for ultraviolet B light compared with topical corticosteroids (adjusted odds ratio 1.52, 95% confidence interval 0.56 to 4.11).

Secondary outcomes supported the primary analysis. Treatment success (Vitiligo Noticeability Scale) based on assessment of digital images by patient reviewers showed similar results but were more likely to suggest benefit from narrowband ultraviolet B light, with evidence of differences in treatment success for both the narrowband ultraviolet B light and the combination groups, compared with the topical corticosteroids group.

Percentage repigmentation success rates (≥ 75% repigmentation), using blinded assessment of digital images, confirmed that combination treatment was better than topical corticosteroids: 4 out of 119 (3%) for the topical corticosteroids group, 9 out of 123 (8%) for narrowband ultraviolet B light group and 18 out of 128 (15%) for the combination group.

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Quality of life was high at baseline for all groups and showed no between-group differences at 9 or 21 months post randomisation.

Overall, 94% of participants achieved onset of treatment response by 3 months for all groups (defined as the active target patch having improved or stayed the same, i.e. not worsened): topical corticosteroids (40% improved, 57% stayed the same); narrowband ultraviolet B light (61% improved, 35% stayed the same); or combination (60% improved, 38% stayed the same).

For participants using active light devices the median treatment time was 20 minutes per treatment session. Participants required just over 1 hour (mean 70 minutes) of face-to-face training prior to using the treatment at home.

Burden of treatment was identified as an issue by 42 out of 142 (30%) participants in the topical corticosteroids group, 38 out of 140 (27%) in the narrowband ultraviolet B light group and 36 out of 149 (24%) in the combination group, although interpretation is difficult as all three groups used both treatments throughout (either active or dummy/placebo). In general, narrowband ultraviolet B light treatment was more burdensome than treatment with topical corticosteroids.

Grade 3 or 4 erythema occurred in 62 (12%) participants (three using dummy), and transient skin thinning occurred in 13 (2.5%) participants (two using placebo), with no serious adverse treatment effects.

In line with the clinical results, the primary cost-effectiveness analysis showed that the unadjusted incremental cost per additional successful treatment was £2328.56 (adjusted £1932.35) for combination treatment compared with topical corticosteroids alone and £4801.92 (adjusted £3335.74) for narrowband ultraviolet B light alone compared with topical corticosteroids alone. Whether or not combination treatment is considered to offer value for money to the NHS depends on the maximum willingness to pay of decision-makers to gain an additional treatment success, and there is currently no evidence as to what the level might be.

Process evaluation findings

Process evaluation findings suggest that stakeholders were positive about the role of combination treatment in the management of vitiligo.

Despite being time-consuming and (potentially) complex, both participants and health-care professionals indicated that, with appropriate support, combination treatment could be managed at home. Appropriate training and ongoing monitoring, particularly in the early stages of treatment are essential, especially given the concerns about potential side effects associated with the treatments.

Trial participants and health-care professionals both advocated the broader use of combination treatment in the NHS, with some caveats about which patients might benefit most.

Both health-care professionals and commissioners recognised that the need for a developed infrastructure (i.e. nursing support, medical physics service) might be a barrier to broader NHS provision. Regional clinics might be a possible solution, as may some form of mixed economy approach, where patients purchase light therapy devices alongside NHS support and training.

Conclusions

Implications for health care

Combination treatment with narrowband ultraviolet B light and potent topical corticosteroids is superior to potent topical corticosteroids alone, although the benefits are likely to be modest. Combination treatment was relatively safe, well tolerated and could be considered cost-effective for people with limited vitiligo that had been active within the last 12 months.

Home-based narrowband ultraviolet B light therapy requires quality control of devices, training and support from health-care professionals with experience of delivering phototherapy services and is time intensive for patients. However, home-based narrowband ultraviolet B light therapy appears to be a useful treatment option for people with localised active vitiligo and provides considerable advantages over hospital narrowband ultraviolet B light therapy, which requires hospital visits two or three times per week.

Use of mometasone furoate 0.1% (a potent corticosteroid) as first-line treatment for vitiligo is supported as it achieved treatment success in one in six individuals and was effective in stopping the spread of active vitiligo patches. It was also found to be safe in both adults and children when used daily on alternate weeks for 9 months.

Treatment effects were lost once interventions were stopped, suggesting that intermittent maintenance therapy is likely to be needed.

These findings require a broad dissemination strategy that includes general practice as well as dermatology services.

Implications for research

Research priorities include:

1. development and testing of new vitiligo treatments with a greater response and longer-lasting effects
2. investigation of treatments suitable for people with widespread vitiligo
3. research into different strategies to maintain treatment response once treatments are stopped
4. further development and validation of outcome instruments to be included in the vitiligo core outcome set, to facilitate combining of trial results in meta-analyses.

Trial registration

This trial is registered as ISRCTN17160087.

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