A programme of research to set priorities and reduce uncertainties for the prevention and treatment of skin disease

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Scientific summary

The prevention and treatment of skin disease

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Scientific summary

Background

Skin diseases are very common and are one of the most frequent reasons for visiting a general practitioner (GP) in the UK. This report focused on five topic areas.

1. Eczema prevention: a common disease for which little is known about effective prevention strategies.
2. Eczema treatment: a much researched area, but navigating and appraising this evidence is difficult.
3. Vitiligo: a disease of skin pigmentation loss, which can be traumatic for people with dark skin types. Relatively little UK-based research has been conducted.
4. Squamous cell skin cancer (SCC): one of the most common forms of skin cancer in older people and a national priority area.
5. Pyoderma gangrenosum (PG): a rare, painful and debilitating disease that is lacking in high-quality trial evidence to guide clinical decision-making.

Objectives

Our aim was to set research priorities, reduce uncertainties surrounding skin disease prevention and treatment and to disseminate the results.

Specific objectives were to:

- systematically review existing evidence for preventing eczema and treating vitiligo, eczema and SCC
- identify research gaps and prioritise these as important research questions for patients and clinicians
- undertake pilot and feasibility studies to develop identified research priorities into trial proposals for submission to National Institute for Health Research (NIHR) partners
- establish the best outcome measures for future trials and, if possible, establish international consensus over core outcome sets (added post award)
- complete a multicentre, randomised controlled trial (RCT) of PG treatments
- summarise and disseminate research findings into web-based patient information resources and encourage the adoption of new evidence into clinical guidelines
- boost dermatology research capacity in the NHS.

Methods

A variety of methods following the research cycle were employed: eight systematic reviews, three prioritisation exercises, two pilot RCTs, three feasibility studies, two core outcome initiatives, four funding proposals for national RCTs and a completed national RCT. Reporting guidelines were followed [Cochrane; Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA); Grading of Recommendations Assessment, Development and Evaluation; Consolidated Standards of Reporting Trials (CONSORT); Strengthening the Reporting of observational studies in Epidemiology; James Lind Alliance guidelines; Core Outcome Measures in Effectiveness Trials (COMET); and COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN)] as appropriate. Specific research questions and methods included the following.

Eczema prevention

1. What is the current evidence base for eczema prevention? Overarching review of seven systematic reviews including 39 RCTs.
2. How should a new case of eczema be defined in prevention trials? Systematic review of definitions used in eczema prevention studies.
3. How feasible is it to conduct a national RCT of skin barrier enhancement using emollients from birth for the prevention of eczema? Pilot RCT including 124 families in five centres.
4. What is an appropriate design for a national definitive trial on skin barrier enhancement for the prevention of eczema? Detailed funding proposal ready for submission to funders.

Eczema treatment

1. What is the current evidence base for eczema treatment? Overarching review of eczema RCTs and systematic reviews published since the NIHR Health Technology Assessment (HTA) review published in 2000.
2. How can research evidence about eczema treatment be synthesised into an easily accessible format that prevents duplication of effort in searching for trial evidence? Development of an online database containing summaries for all published RCTs and systematic reviews on eczema treatment [Global Resource of EczemA Trials (GREAT) database].
3. Is there evidence of outcome reporting bias in published eczema RCTs? Systematic review of outcomes in trial reports compared with trial registry outcomes.
4. What core outcomes should be included in future eczema trials? International initiative using consensus methodologies and systematic reviews of psychometrics and measurement properties of existing outcomes.
5. What are the most pressing treatment uncertainties for eczema? Ascertained by James Lind Alliance priority setting partnership (PSP).
6. What is an appropriate design for a national trial on silk therapeutic clothing for eczema management? Detailed funding proposal ready for submission to funders.

Vitiligo

1. What is the current evidence base for the treatment of vitiligo? Update of Cochrane systematic review.
2. What outcomes are most important to patients and how might they be assessed? Systematic review of outcomes used in vitiligo trials, international electronic Delphi (e-Delphi) study to define core outcome domains, and online surveys and discussion groups to establish the validity of a patient-reported outcome measure.
3. What are the most pressing treatment uncertainties for vitiligo? James Lind Alliance PSP.
4. Is a national RCT of handheld narrowband ultraviolet light B (NB-UVB) light therapy for the treatment of vitiligo feasible? Pilot RCT performed 29 patients recruited in two UK centres.
5. What is an appropriate design for a national trial of the most commonly used vitiligo treatments? Detailed funding proposal ready for submission to funders.

Squamous cell skin cancer

1. What is the current evidence base for SCC management? A Cochrane systematic review of RCTs and a systematic review of observational studies for SCC management.
2. What are recurrence rates following treatment of SCC? Clinical audit of histology data from a secondary care hospital in Nottingham.
3. What are the most pressing treatment uncertainties for SCC? Priority setting consensus among health-care professionals (HCPs) responsible for the management of SCC patients.
4. How feasible is it to conduct a national RCT to define excision margins for surgery and the role of adjuvant radiotherapy (ART) for people with high-risk SCC? Patient questionnaire with 24 respondents and focus group discussion with seven participants.

5. What is an appropriate design for a national definitive trial on the role of excision margins and adjuvant therapy, in determining treatment success in SCC patients? Detailed funding proposal ready for submission to funders.

Pyoderma gangrenosum

1. How clinically effective and cost-effective is ciclosporin compared with prednisolone for PG treatment? Multicentre, pragmatic RCT comparing ciclosporin (4 mg/kg/day) with prednisolone (0.75 mg/kg/day) in 121 patients with PG.
2. How effective is topical therapy [clobetasol propionate (Dermovate®, GlaxoSmithKline) or tacrolimus (Protopic®, Astellas Pharma)] for PG treatment in patients for whom systemic therapy is contraindicated? Observational cohort study of patients ineligible, or unwilling, to take part in the RCT of systemic therapies.

Results

Eczema prevention

Our overview of seven systematic reviews included 39 RCTs covering 14 different prevention strategies found no clear evidence of benefit from any of the interventions reviewed. Those that may require further investigation include hydrolysed formula milks, probiotics, prebiotics and barrier enhancement with emollients.

Our review of new eczema case definitions showed that many rely on the presence of symptoms for a prolonged duration. A modified UK Working Party Criteria definition was proposed, for which the time frame for the presence of an itchy skin condition is reduced from 1 year to 4 weeks.

The pilot RCT of skin Barrier Enhancement for Eczema Prevention (BEEP) included 124 families and demonstrated recruitment and retention was feasible and that contamination of the control group was minimal. Patient preference and biophysical testing established Doublebase® gel (Dermal Laboratories) and Diprobase® cream (Schering-Plough) as suitable interventions. Clinical results provided the first signal from a RCT that daily full-body emollient application for 6 months from birth can prevent eczema [risk ratio 0.50, 95% confidence interval (CI) 0.28 to 0.90; $p = 0.017$]. This may simply reflect the use of emollients up until the assessment period, so larger studies are required to assess eczema incidence at 1 and 2 years of age.

Eczema treatment

The updated scoping systematic review of eczema treatments included 287 new RCTs and 40 systematic reviews and is available as a separate report. The GREAT database contains > 500 trials in a user-friendly searchable format. The database provides a rich resource for methodological projects, including our systematic review of outcome reporting bias in eczema RCTs, which highlighted the need for clearer trial reporting and more detailed information in trial registries.

The Harmonising Outcome Measures for Eczema (HOME) initiative identified four core outcome domains for inclusion in future trials: clinical signs (assessed by Eczema Assessment Severity Index scale), patient-reported symptoms, quality of life (QoL) and long-term control.

The research PSP identified four top priorities that were shared by both patients and HCPs: the best and safest ways of using topical corticosteroids, long-term safety of topical corticosteroids, the role of allergy tests in eczema management and the most effective emollients. A further 10 research priorities were identified; five were prioritised by patients and five by HCPs.

A RCT trial proposal of silk therapeutic clothing for the eczema management was developed and funded by the NIHR HTA funding stream.

Vitiligo

A Cochrane systematic review in 2010 included 38 additional trials, covering eight treatment categories. Methodological quality of these trials was generally poor and trial heterogeneity prevented meta-analysis. In general, combination therapies (usually including light therapy) seemed most effective.

The systematic review of outcome measures demonstrated 96.2% of published trials included percentage repigmentation; however, this was measured using 48 different scales. Surveys and online discussion groups found percentage repigmentation was not always relevant to the patient and outcomes should include the notion of how noticeable lesions are after treatment. An international e-Delphi consensus study identified seven core outcome domains for inclusion in future studies: repigmentation, safety, maintenance of repigmentation, cosmetic acceptability of repigmentation, cessation of spread, burden of intervention and QoL.

Ten priority topics were identified through the PSP; two have since been incorporated in a NIHR HTA commissioned call. The pilot trial conducted within this programme was essential for informing the design of our successful trial proposal for this call. Issues addressed included willingness of participants to be randomised, suitability and safety of handheld NB-UVB devices for home use, how to measure and report outcomes, and a training manual was developed (paper and digital versatile disc) to standardise training in the proposed national trial.

Cutaneous squamous cell skin cancer

The Cochrane systematic review found just one RCT on the treatment of SCC so the scope was expanded to include a review of observational studies, which identified 118 studies in seven treatment categories, providing critical information for guiding the design of future RCTs. Two topics were prioritised through consensus:

1. What is the best excision margin for preventing SCC recurrence?
2. How effective is ART following excision for high-risk SCC?

A trial proposal has been developed in collaboration with the National Cancer Research Institute to address these questions, and qualitative work with patients was used to inform the trial design relating to acceptability of recruitment methods and information needs of patients prior to participation. An audit of histology and clinical findings for SCCs removed over a 1-year period was used to inform recruitment rates, eligibility criteria and likely recurrence rates at 5 years.

Pyoderma gangrenosum

Our national trial of two commonly used systemic therapies for PG (ciclosporin and prednisolone) found no difference between the treatments in velocity of healing at 6 weeks (adjusted mean difference 0.00 cm^2/day, 95% CI –0.20 to 0.21 cm^2/day; $p = 0.975$) or for any secondary outcomes. Only half of participants had healed for their target lesion by 6 months. Side effects occurred in two-thirds of participants and for those who healed, 30% had a subsequent recurrence, which suggests that this is a chronic condition that may require maintenance therapy.

A parallel observational study including participants who were ineligible, or unwilling, to take part in the RCT of systemic therapies found that topical therapy was effective in about half of cases (44%). However, participants generally had milder disease and smaller lesions. One-third of participants required subsequent systemic therapy and 13 entered the RCT.

Capacity building

Research infrastructure in the dermatology community has been enhanced through the establishment of a dermatology patient panel, training three researchers to doctor of philosophy (PhD) level and 15 trainees having taken part in the UK Dermatology Clinical Trials Network's (UKDCTN's) fellowship programme.

Conclusion

The programme has summarised, mapped and prioritised research in three skin diseases and developed four national trial proposals, addressing areas of importance to patients and the NHS. A national trial has been completed on a rare and painful skin condition that was lacking in RCT evidence to guide clinical practice.

As for many areas of skin research, fewer – but better-quality – trials are needed so that clearer clinical conclusions can be reached. This can be achieved through wider collaboration, trial protocol registration, complete reporting and international consensus over core outcome sets.

Implications for health care

As yet, there is no clear evidence that previously tested strategies prevent eczema development in children. Nevertheless, findings from our pilot study involving emollient application from birth provide preliminary evidence of benefit. A larger, national, trial is under way to confirm this.

Our overarching systematic review of eczema treatments has identified treatments that work, those that do not and those for which evidence is unclear. These results can be used to inform updates of clinical guidelines and patient information resources. The GREAT database provides an international resource to reduce duplication of research effort and provide easy access to summary information on all eczema RCTs.

Vitiligo and SCC have been highlighted as areas with limited RCT evidence to guide practice. Although many vitiligo trials exist, the sheer number of interventions tested and the variability in trial methodologies makes it impossible to collate this evidence in a meaningful way. For SCC, the opposite is true and there has been just one previous RCT on the topic.

In relation to rarer skin diseases such as PG, this programme has demonstrated that networks of clinicians working together to address important questions can be effective in delivering RCTs. For the first time, the most commonly used systemic therapies for PG treatment have been compared. This trial has countered the generally held perception that ciclosporin is more effective than prednisolone and treatment decisions may now be based around the side effect profile of the two drugs for individual patients.

Recommendations for research

Many of the urgent priority areas for research identified within this programme have been picked up as commissioned calls by the NIHR HTA programme. In addition, the NIHR Efficacy and Mechanism Evaluation programme issued a themed call on skin disease following the eczema PSP and the NIHR priority area of chronic conditions in childhood fits well with eczema and vitiligo research.

A full list of research recommendations for each work programme is in the body of this report. The most important recommendation for future research is to discourage research wastage caused by the continual production of small, poorly designed and reported studies. Instead, we would recommend following the basic premises of the research cycle: identifying uncertainties from systematic reviews, prioritising topics with stakeholders, reducing the risks associated with a full-scale trial through feasibility work, and then conducting large collaborative pragmatic studies that best inform everyday practice in the NHS and other health-care systems.

Trial registration

This trial is registered as BEEP (ISRCTN84854178 and NCT01142999), Study of Treatments fOr Pyoderma GAngrenosum Patients (STOP GAP) (ISRCTN35898459) and Hand Held NB-UVB for Early or Focal Vitiligo at Home (HI-Light Pilot Trial) (NCT01478945).

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