Scoping systematic review of treatments for eczema

Helen Nankervis, Kim S Thomas, Finola M Delamere, Sébastien Barbarot, Natasha K Rogers and Hywel C Williams*

Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK

*Corresponding author

Declared competing interests of authors: Sébastien Barbarot reports grants from Le Collège des Enseignants en Dermatologie de France (CEDEF) during the conduct of the study and grants from Astellas, personal fees from GlaxoSmithKline, personal fees from Sinclair Pharma, personal fees from Astellas, grants from the Foundation for Atopic Dermatitis, Pierre Fabre Laboratory, and grants from Pierre Fabre Laboratory as an investigator outside the submitted work. Hywel Williams is Deputy Director of the National Institute for Health Research Programme, chairperson of the HTA Commissioning Board, and Programme Director for the Health Technology Assessment programme.

Published May 2016
DOI: 10.3310/pgfar04070

Scientific summary

Scoping systematic review of treatments for eczema

Programme Grants for Applied Research 2016; Vol. 4: No. 7
DOI: 10.3310/pgfar04070

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Eczema, also known as 'atopic eczema' or 'atopic dermatitis', is a chronic, itchy, inflammatory skin condition. Eczema affects around 20% of UK children and 5% of adults, and its prevalence is increasing. Eczema is a complex disease caused by a combination of genetic and environmental influences.

Objectives

This review aimed to scope and summarise current randomised controlled trials (RCTs) of eczema to inform evidence-based clinical practice and to identify possible research gaps for the future. The review is an update of a previous similar review published in 2000 by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme. The new information in this update places current treatment options in the context of best-quality evidence. This review was conducted as part of a NIHR Programme Grant for Applied Research award (RP-PG-0407-10177), details of which are found in a companion report.

Methods

Only RCTs of treatments for eczema were included, as other forms of evidence are associated with higher risks of bias. Inclusion criteria for studies included availability of data relevant to the therapeutic management of eczema; mention of randomisation; comparison of two or more treatments; and prospective data collection. Participants of all ages were included. Eczema diagnosis was determined by a clinician or according to published diagnostic criteria. The risk of bias was assessed using the Cochrane Collaboration risk-of-bias tool. We used a standardised approach to summarising the data and the assessment of risk of bias and we made a clear distinction between what the studies found and our own interpretation of study findings.

Outcomes

The main outcomes for this review were change in patient-rated symptoms; global severity as rated by patients or physicians; change in composite rating scales (both named and un-named); quality of life; and adverse events.

The following electronic databases were searched from the end of 2000 to 31 August 2013: MEDLINE; EMBASE; the Cochrane Central Register of Controlled Trials and the Cochrane Skin Group Specialised Trials Register; the Latin American and Caribbean Health Sciences (LILACS) database; the Allied and Complementary Medicine Database (AMED); and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). Disease terms for atopic eczema [as a text word and medical subject heading (MeSH) term if possible] were combined with a search for RCTs. A manual filtering process was undertaken to assess whether a reference fitted the review's inclusion criteria. Full papers were scrutinised in cases of doubt. Excluded studies were identified by one reviewer and checked by a second reviewer in cases of uncertainty. All papers were catalogued on an EndNote X6 database (Thompson Reuters, CA, USA).

There were no language restrictions; non-English-language papers were screened for eligibility by international colleagues and data were fully abstracted if eligible.

Results

Main findings

This review included 287 new trials covering 92 different treatments including topical, systemic, non-pharmacological, behavioural, complementary and alternative treatments. As with the earlier review, which included 254 eczema treatment trials, trial reporting was generally poor (randomisation method: 2% high, 36% low and 62% unclear risk of bias; allocation concealment: 3% high, 15% low and 82% unclear risk of bias; blinding of the intervention: 15% high, 28% low, 57% unclear risk of bias). Only 22 (8%) trials were considered to be at low risk of bias for all three quality criteria.

There was reasonable evidence of benefit to support the following treatment comparisons: superiority of topical corticosteroids compared with vehicle; superiority of 0.03% and 0.1% topical tacrolimus compared with mild-potency topical corticosteroids, mainly in children with moderate to severe eczema; superiority of 0.1% tacrolimus over moderate topical corticosteroids for adults with moderate to severe facial eczema; superiority of topical pimecrolimus over vehicle, mainly in children with mild to moderate eczema; superiority of topical tacrolimus compared with pimecrolimus for adults and children with eczema of all severities; superiority of Atopiclair™ (Graceway Pharmaceuticals) emollient compared with vehicle in children and adults with mild to moderate eczema; superiority of topical corticosteroids 2 days a week compared with vehicle for preventing flares, mainly in adults and children with moderate to severe eczema; superiority of tacrolimus 2 or 3 days a week over vehicle for preventing flares in children and adults with mild to severe eczema; superiority of pimecrolimus over vehicle for preventing flares, mainly in children with mild to severe eczema; superiority of narrowband ultraviolet B (UVB) light therapy compared with placebo (visible light) for adults with moderate to severe eczema; superiority of ciclosporin over placebo, mainly in adults with severe eczema; superiority of azathioprine over placebo in adults with moderate to severe eczema; and superiority of educational intervention compared with no educational intervention, mainly in children with moderate to severe eczema.

There was evidence of no clinically useful benefit for the following: twice daily compared with once daily topical corticosteroids; topical corticosteroids containing antibiotics for non-infected eczema; protease inhibitor SRD441 (Serentis Ltd) compared with vehicle in adults with mild to moderate eczema; emollient with furfuryl palmitate in children with unspecified eczema severity; cipamfylline cream in adults with eczema on the arms of unspecified severity; *Mycobacterium vaccae* vaccine in children with moderate to severe eczema; probiotics for treating established eczema in children whose disease severity was not clearly described; ion-exchange water softening devices in children with moderate to severe eczema; and dietary supplements rich in linoleic acid such as evening primrose oil and borage oil in children and adults with eczema of unspecified severity.

The trial evidence was not clear enough to make recommendations with regard to using emollients to reduce the severity of eczema and prevent flares or to reduce the need for other eczema treatments; topical corticosteroids in combination with antibiotics for infected eczema; wet wraps in addition to topical corticosteroids; antiseptic bath additives; topical antifungals; other topical treatments such as WBI-1001 cream (Welichem Biotech Inc.), topical coal tar, topical vitamin B_{12} or *Vitreoscilla filiformis* lysate cream; oral treatments including antihistamines, prednisolone, methotrexate, montelukast, mycophenolate mofetil, pimecrolimus and naltrexone; immunotherapy (desensitisation); omalizumab; mepolizumab; autologous blood therapy; tandospirone citrate; full-spectrum light therapy; excimer laser; intravenous immunoglobulin; specialised clothing (silk or synthetic fibres with or without antibiotics); environmental interventions such as house dust mite reduction; staying in a different climate; different approaches to the organisation of care such as additional visits to the doctor or nurse-led clinics; support groups; e-health management; dietary interventions such as prebiotics, dietary restrictions and synbiotics; complementary therapies such as Chinese herbal treatment; hypnotherapy; massage therapy; aromatherapy; acupuncture; acupressure; other herbal treatments; psychological therapies such as stress reduction techniques and biofeedback; and balneotherapy (salt baths).

There was a complete absence of RCT evidence for dilution of topical corticosteroids, impregnated bandages (zinc paste bandages), soap avoidance, frequency of bathing and the role of routine patch testing.

Changes in the evidence base since the previous review in 2000

Topical calcineurin inhibitors, educational interventions, oral azathioprine and Atopiclair have entered the category of 'reasonable evidence of benefit' since the previous review in 2000.

Some interventions have now been tested sufficiently to suggest that they are not clinically useful. These include topical corticosteroids containing antibiotics for eczema that is not overtly infected, probiotics, ion-exchange water softeners and supplements rich in linoleic acid (e.g. evening primrose oil).

Many dietary, non-pharmacological, complementary and other topical or systemic interventions have been investigated in small and generally poorly reported trials resulting in inconclusive findings.

Clinical relevance of the new evidence

Patients and setting

Eczema participants included in the published trials are generally skewed towards moderate or severe disease as most trials recruited participants through secondary care. For some interventions, such as systemic treatments and light therapy, this may be appropriate. However, for the more commonly used topical interventions such as emollients, topical corticosteroids and bath products, it is important to evaluate the interventions in a primary care setting where most patients are cared for.

Trial duration and comparators

There has been some improvement in the length of RCTs, with many trials of topical corticosteroids and calcineurin inhibitors lasting from 6 months to 1 year. There is still a tendency for pharmaceutical companies to undertake placebo-controlled studies, which do not give information on how new treatments compare with existing treatments. For example, topical tacrolimus and pimecrolimus have now been tested in a total of 30 placebo-controlled studies, the ethics of which is questionable. Encouragingly, some trials are now using 'standard care' as a comparator, making it easier to assess the clinical relevance of the evidence.

Outcomes

There has been a modest improvement in the number of trials that include participant-reported outcome measures, although the results were often poorly reported. The move towards using the same core outcome sets as encouraged by the Harmonising Outcome Measures for Eczema (HOME) initiative [see www.homeforeczema.org (accessed 11 October 2015)] can only be beneficial for future clinical interpretation and evidence syntheses.

Limitations of this review

Despite searching the main bibliographic databases (MEDLINE and EMBASE) and several smaller, specialist databases (CINAHL, AMED and LILACS), it is still possible that we might have missed some RCTs. Masking the identity of the trial authors from the review team was not practically possible, which may have introduced bias when summarising qualitative aspects of the results. Given the very wide scope of this review and heterogeneous nature of participants, interventions and outcomes, it has not been possible to undertake detailed meta-analysis for single interventions. These will hopefully be conducted within much narrower intervention-specific Cochrane systematic reviews. As with all systematic reviews, the evidence presented will become out of date quite rapidly for some topics, and readers are directed to our Global Resource of EczemA Trials (GREAT) database [see www.greatdatabase.org.uk (accessed 11 October 2015)] for newly published eczema RCTs.

Many of the treatments that are lacking in RCT evidence have been studied using uncontrolled designs. Rare treatment adverse effects reported outside RCTs could also have been missed.

Our classification of treatment options into categories such as 'evidence of benefit to support' is not tantamount to a positive recommendation for widespread use or otherwise, as that is the remit of guideline developers and depends on factors such as magnitude of benefit, adverse effects and how the treatment compares with existing active treatments, as well as factors such as availability and cost.

Conclusions

Implications for research

Primary research

Although not unique to eczema, perhaps the biggest priority for future research is to better understand why researchers across the world continue to conduct small, poorly planned, unregistered and poorly reported trials. In addition, there is a lack of clinical trials conducted in a primary care setting where most patients are seen. The research questions being investigated often fail to reflect the most pressing questions for clinicians and patients.

Our recent James Lind Alliance Priority Setting Partnership, reported in the companion report to this review, used consensus methodology to identify the most important treatment uncertainties as judged by patients and clinicians. It is salutary that three treatment areas with no RCT evidence at all are included on the list of priority topics as identified by patients and health-care professionals.

Of the topics identified, the following areas seem to be most pressing when set in the context of the updated evidence base from this review:

1. role of allergy testing in the management of eczema
2. use of emollients in the management of eczema
3. washing and bathing – no trials to date have examined frequency of bathing or the role of different wash products in the management of eczema
4. optimum use of topical corticosteroids – the significant anxiety from parents and some health-care providers over potential adverse effects, such as skin thinning and systemic absorption, need to be addressed by observational studies, and head-to-head trials of pimecrolimus or tacrolimus compared with topical corticosteroids for the prevention of flares are needed
5. systemic therapies for severe eczema in children
6. education for health-care providers (including doctors, nurses and pharmacists) and cost-effective education programmes for patients and their families.

Some important topics have already been picked up by NIHR funding bodies and large pragmatic trials are currently under way in the UK evaluating the role of topical and oral antibiotics for the treatment of infected eczema [ChildRen with Eczema, Antibiotic Management (CREAM) study; UK Clinical Research Network (UKCRN) ID 11233, silk clothing for the management of moderate to severe eczema (UKCRN ID 15132) and the role of bath emollients in the management of eczema Bath Additives in the Treatment of cHildhood Eczema (BATHE); HTA reference number 11/153].

Secondary research

Several Cochrane reviews of eczema, which will provide a more in-depth analysis of specific interventions, either have been completed or are in progress. Overviews of existing systematic reviews are also needed, as is the application of mixed-treatment comparisons for understanding more about treatments that have yet to be compared in head-to-head trials.

Methodological research

The greatest methodological challenge is in the field of outcome measures. Despite significant progress from international consensus in identifying the four core outcome domains of symptoms, clinical signs, quality of life and long-term control outlined in our companion report, there is still work to be done in identifying and developing appropriate instruments for these domains and for establishing suitable tools for routine clinical practice.

Implications for health care

The evidence base of RCTs for eczema has accelerated since the last HTA programme systematic review and many commissioners, guideline developers, health-care professionals and patients can now refer to this report for a rapid summary of relevant evidence to support everyday decisions in the treatment of eczema. In addition to the established approach for treating eczema flares with topical corticosteroids, perhaps the single largest advance in eczema treatment since the last review has been the strong evidence supporting the value of a proactive approach for maintaining eczema remission through the use of twice weekly topical corticosteroids, topical tacrolimus or topical pimecrolimus. Educational approaches have also emerged as a promising intervention that should be tailored to the treatment setting.

Equally important is the understanding that some interventions now have sufficient evidence to suggest little or no benefit for eczema patients. These include the use of topical corticosteroids containing antibiotics when used for the management of non-infected eczema, probiotics, ion-exchange water softeners and supplements rich in linoleic acid (borage oil, evening primrose oil).

Funding

Funding for this study was provided by the Programme Grants for Applied Research programme of the National Institute for Health Research.

Programme Grants for Applied Research

ISSN 2050-4322 (Print)

ISSN 2050-4330 (Online)

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

The full PGfAR archive is freely available to view online at www.journalslibrary.nihr.ac.uk/pgfar. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Programme Grants for Applied Research* journal
Reports are published in *Programme Grants for Applied Research* (PGfAR) if (1) they have resulted from work for the PGfAR programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Programme Grants for Applied Research programme

The Programme Grants for Applied Research (PGfAR) programme, part of the National Institute for Health Research (NIHR), was set up in 2006 to produce independent research findings that will have practical application for the benefit of patients and the NHS in the relatively near future. The Programme is managed by the NIHR Central Commissioning Facility (CCF) with strategic input from the Programme Director.

The programme is a national response mode funding scheme that aims to provide evidence to improve health outcomes in England through promotion of health, prevention of ill health, and optimal disease management (including safety and quality), with particular emphasis on conditions causing significant disease burden.

For more information about the PGfAR programme please visit the website: http://www.nihr.ac.uk/funding/programme-grants-for-applied-research.htm

This report

The research reported in this issue of the journal was funded by PGfAR as project number RP-PG-0407-10177. The contractual start date was in September 2008. The final report began editorial review in April 2014 and was accepted for publication in May 2015. As the funder, the PGfAR programme agreed the research questions and study designs in advance with the investigators. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The PGfAR editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, CCF, NETSCC, PGfAR or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the PGfAR programme or the Department of Health.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).