FINAL DRAFT PROTOCOL: THE EFFECTIVENESS AND COST-EFFECTIVENESS OF PIMECROLIMUS AND TACROLIMUS FOR ATOPIC ECZEMA

A. Details of the research team

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B. Full title of research question

What is the effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema relative to current standard treatments.

C. Clarification of research question and scope

Atopic dermatitis (or eczema) is a skin condition characterised by inflammatory lesions of very varied manifestations including redness, dryness, itching, thickening of the skin and scaling. Lesions may be limited to small isolated patches resolving within a short time or can evolve into widespread persistent disease or recurrent flares, sometimes complicated by bacterial or viral skin infections. Objective measurement of eczema severity is difficult. Standard measurement scales exist (such as the Atopic Dermatitis Severity Index, ADSI, and many others)[1] encompassing the extent of areas affected and the intensity or spectrum of symptoms, including erythema (redness), pruritus (itching), exudation (weeping), excoriation (peeling) and lichenification (skin thickening).

Although a chronic, non-fatal condition, eczema causes considerable distress and costs to patients and carers, including itching and sleep disturbances, the need for special clothing, frequent use of messy ointments and emollients, and often restriction of sports activities and social interaction with consequent risk of stigma and isolation.[2]

Atopic eczema is likely to be determined at least in part by genetic susceptibility, triggered by a range of environmental factors such as irritants, temperature, infections, stress, clothing and allergies to house dust mite,, some foods and pollen. Its prevalence has increased considerably over the last 30 years, for reasons that are unclear, and currently effects about 6.5% of the population each year.[3] Eczema affects 5-15% of children in school age,[2] with 60% of cases starting within the first year of life and 85% within five years.[4] Most children present a mild form, with spontaneous remission within childhood in 40-60% of the cases.[4] Adults account for a third of the cases[5] and generally present with more severe disease.

Eczema management mostly occurs in primary care, and includes a combination of preventative measures with topical treatment. Patients are advised to avoid contacts with allergens, such as detergents, wool, lanolin, select clothing and to reduce house

dust mite, often in association with food restrictions or supplementation and prolongation of breast-feeding in infants.[5,6]

Topical treatment frequently relieves symptoms and may facilitate remission or clearance of eczema. Many patients are recommended abundant use of skin moisturisers or emollients. Standard treatment also includes corticosteroids[6-8] of mild potency for maintenance therapy or high potency to treat flares. Despite the introduction of newer, safer corticosteroids,[8] concerns around potential local and systemic side effects of corticosteroids (such as skin atrophy, disfiguring striae (lines on the skin) or telangiectasia (redness), adrenal suppression and growth retardation[7]) still remain in many patients and parents, especially regarding long-term use.[9] Such concerns may hamper adherence to treatment, especially in paediatric or mild cases, whilst the balance between potential benefits and discomfort and risk to the patient is yet little studied. Corticosteroids should also be use with great caution in certain delicate areas of skin such as the eyelids.

The recent introduction of advanced immunosuppressive therapy (calcineurin inhibitors) is thought to offer potential enhanced effectiveness and tolerability.[10]

- Tacrolimus (FK506) is a macrolide compound derived from Streptomyces Tsukubaensis.[11]
- Pimecrolimus is a macrolactam and the parent compound to a class of semi-synthetic derivatives for topical use, including SDZ ASM 981.[8,12]

Their relevance for eczema is similar and resides in the potential to inhibit T-cell activation interrupting the process between T-cell ligation, binding to macrophilin-12 and forming a complex which blocks the inhibition cytokine gene transcription. A second mechanism seems to reduce symptomatic pruritus, by inhibiting the release of histamine and inflammatory mediators and blocking activation of IL-3 and IL-5 cytokine genes. Thirdly, the stimulation of autologous lymphocytes regulated by Langerhans cells is inhibited.[8]

Compared to corticosteroids, pimecrolimus and tacrolimus may offer a better side-effect profile, with marked reduction of skin atrophy,[11] yet proof of higher efficacy in controlling pruritus in children and adults has not been clarified.

Limited knowledge has been collated on the effect of available treatments on disease progression and on sustainability of response. It is believed that pimecrolimus and tacrolimus might be effective in decreasing relapse and occurrence of flares in the long term. Tacrolimus may also offer a more acceptable therapy, with faster efficacy and better tolerability compared to other immunosuppressants, such as azathioprine, cyclosporine, methotrexate, phosphodiesterase inhibitors or interferon Gamma.[13]

There is limited pre-existing work on the effectiveness of pimecrolimus and tacrolimus. A previous HTA review[5] on treatment for eczema includes a brief overview on pimecrolimus and tacrolimus treatments; at that time evidence was limited to two small trials of effectiveness and one pre-clinical trial.

Pimecrolimus cream (Elidel, 1%, Novartis) was first licensed in 2000 by the FDA and in Japan, and was introduced in the UK in 2003 for acute treatment of mild to moderate atopic eczema, including flares in adults and children over the age of two. The recommended dose is twice daily until symptoms clear.

Tacrolimus cream (Protopic, 0.03%, Fujisawa) was registered in the EC in February 2002 for topical use and licensed in the UK in March/April 2002 for adults and

children (over the age of two) with moderate to severe atopic eczema where other treatments have failed. 0.1% tacrolimus is only licensed for use in adults. The recommended dose is twice daily application until symptoms clear and for a further week afterwards. Currently it is advised that treatment with tacrolimus be initiated by a specialist.

For both treatments, exposure to excessive UV light should be avoided.

Scope

This technology assessment aims to ascertain clinical and cost effectiveness of pimecrolimus in the treatment of mild and moderate atopic eczema, and tacrolimus in the treatment of moderate to severe atopic eczema. For both drugs, adult and child (over the age of two) populations will be assessed. All randomised trials of pimecrolimus versus any emollient or topical corticosteroids will be included. All randomised trials of tacrolimus versus topical corticosteroids, short courses of systemic steroids, other immunosuppressives or phototherapy will be included.

A cost-utility analysis will be carried out if sufficient data are available from the literature, or other sources. If a well designed cost-utility analysis is already available and required data is available, this will form the basis for the assessment of cost-effectiveness.

Intervention

Pimecrolimus cream (1%) (Elidel®, Novartis) for mild to moderate atopic eczema.

Tacrolimus ointment (0.03% and 0.1%) (Protopic®, Fujisawa) for moderate to severe atopic dermatitis unresponsive or intolerant of standard treatment.

Comparator

Current standard treatment - regular emollient used in conjunction with topical corticosteroids in mild to moderate atopic eczema and topical corticosteroids, short courses of systemic steroids, other immunosuppressives or phototherapy in moderate to severe atopic eczema.

Populations of interest

Children (over the age of two) and adult patients recruited in primary care clinics or specialised dermatology clinics. Patients with mild to moderate eczema and patients with moderate to severe eczema.

- Inclusion criteria

Participants with a primary diagnosis of atopic eczema as made by a physician or using defined criteria such as those described by the UK working party.[14]

- Exclusion criteria

Studies will be excluded if patients with the following characteristics are not reported separately:
Eczema secondary to other inherited or acquired disorders of immunodeficiency
Seborroic dermatitis
Allergic or contact eczema
Nummular (discoid) dermatitis
Fungal or parasitic skin infections
Cutaneous T-cell lymphoma

Outcomes

The review will focussed on patient centred outcomes.

- Effectiveness: Immediate response rates (using standardised measures of improvement, symptoms and/or severity scales), sustained response rates, avoidance of flares.
- Duration of treatment, changes in therapy
- Adverse effects (including deterioration of symptoms, skin atrophy, systemic toxicity, treatment withdrawal, incidence of local skin infections)
- Quality of life: Patients and parents' perceived quality of life.
- Cost effectiveness (cost-effectiveness analyses only)

Patient preferences

Where available, information on the treatment preferences of patients and caregivers will be extracted from included trials.

Time perspective

Follow up of at least three weeks.

D. Review and report methods

Search strategy

A preliminary search has established that no systematic reviews on this topic have yet been completed. A search strategy will be developed for the electronic databases shown below. For the question of effectiveness, publications that describe trials comparing pimecrolimus to emollients and topical corticosteroids, and those comparing tacrolimus to topical corticosteroids, short courses of systemic steroids, other immunosuppressives or phototherapy will be sought. Only studies with an experimental design and a comparison group will be considered for inclusion.

The search will be performed in:

- Electronic databases, including Medline PubMed, Embase, The Cochrane Library (including Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, Cochrane Skin Group Specialised Registrar), Science Citation Index, Web of Science Proceedings, DARE, NHS EED, HTA databases;
- Trial registers in the UK (National Research Register), Current Controlled Trials, US (Clinical Trials.gov) Canada;
- Bibliographies
- Contacting research groups and industry
- Websites of patients' self-help groups (for example The National Eczema Society)

Two researchers will independently assess relevance of the abstracts retrieved and full texts of these papers will be obtained. Two researchers will then independently assess whether these trials fulfil the inclusion criteria.

Inclusion

RCTs or systematic reviews of pimecrolimus or tacrolimus compared to corticosteroids, emollients or both for treatment of mild to severe eczema;

Non randomised evidence may be considered if it gives the best estimates of a required parameter (for example adverse effects or patient preferences) or where RCT data is scanty or uninformative.

Cost-effectiveness, cost-utility and cost-benefit studies of pimecrolimus compared to corticosteroids, vehicle or both for treatment of mild to moderate atopic eczema, and of tacrolimus compared to topical corticosteroids, short courses of systemic steroids, other immunosuppressives or phototherapy for treatment of moderate to severe atopic eczema will be included.

Exclusion

Non-randomised studies, case-control studies, case series, case reports
Studies only available as abstracts
Animal models
Pre-clinical and biological experimentation in vitro or on humans;
Studies not reporting patient relevant outcomes;
Studies on patients with secondary eczema or on non-eligible patients
Studies not published in English

Data extraction

Data will be extracted by one researcher and checked by a second researcher, with differences resolved by consensus.

Quality assessment

The methodological quality of included RCTs and systematic reviews will be assessed using the criteria reported in the NHS CRD Report No. 4. Cost-effectiveness or cost-utility studies will be assessed following the methodology reported in Drummond (BMJ).

Methods of analysis/synthesis

Meta-analysis will be performed if sufficient randomised evidence is located of reliable homogeneity. Otherwise, a tabulated description of the available evidence will be presented and discussed.

The meta-analysis will use a fixed effects method if there is sufficient homegenity. Analyses will be based on intenet to treat data. Sources of heterogeneity will be identified and their impact explored. Sub-group analysis will be specified prior to meta-analysis, and be based on further examination of the papers to be included.

Estimation of effectiveness, quality of life, costs and cost-effectiveness or cost-utility

Cost data will be extracted from published work, NHS costs and industry submission as appropriate. If insufficient data are retrieved from published sources, costs will be derived from individual Trusts or groups of Trusts. Costs will be discounted at 6% and benefits at 1.5%. Both costs and discount will be tested for sensitivity.

If possible, an independent cost-utility model will be developed to determine cost-effectiveness and cost-utility of treatment with pimecrolimus and tacrolimus compared to emollients and corticosteroids. Ideally, the model will consider treatment, relapse, for a sufficiently long period (1 year) and if sufficient data are available, longer-term outcomes and costs (clearance of symptoms or eradication of eczema). However, if insufficiently robust data are available, an alternative short-term model may be constructed encompassing intermediate outcomes.

E. Handling industry submission

Information provided by the industry will be included in the report when meeting our inclusion criteria (RCTs) and for information on costs.

A critique of any industry models submitted will be undertaken. The extent of the detail in this critique will depend on the number and size of the industry submissions.

Any "commercial in confidence" data taken from the industry submissions will be underlined and the source identified in the assessment report.

F. Project management

Timetable

Initial draft protocol: 15th July 2003
Final draft protocol: 5th August 2003
Progress report: 31st October 2003
Initial draft report to peer review: 15th December 2003 (tbc)
Final draft report/ Final report to NICE: 26th January 2004

Competing interests

None

External reviewers

A panel of reviewers is currently being formed. The panel will act as expert resource to guide the review process. At least two independent reviewers will be identified as peer reviewers of the initial draft report.

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