The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation

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Executive summary

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Executive summary

Objective of study

The objective of this study was to consider the effectiveness and cost-effectiveness of pimecrolimus for mild to moderate atopic eczema and tacrolimus for moderate to severe atopic eczema compared with current standard treatment in adults and children.

Epidemiology and background

Atopic eczema (also known as atopic dermatitis) is a common, chronic, relapsing skin disease characterised by intense itching, dry skin, redness, inflammation and exudation. Severity may vary widely. In the majority of cases, symptoms are mild, although in some, severe itching may lead to loss of sleep, and a range of impairments of quality of life.

Cumulative prevalence of 5–20% by the age of 11 years has been estimated, with 60% occurring before the age of 1 year. By adulthood, many will have grown out of the condition although they may remain with a propensity for eczema later in life. Incidence of eczema has been increasing in recent years.

Most atopic eczema is managed in primary care, with only a few severe or resistant cases referred to consultant dermatologists.

Current treatment is varied, with abundant use of emollients and active treatment with topical corticosteroids being the mainstays of treatment. Numerous other approaches to preventing exacerbation of eczema (such as the use of special clothing, dietary restrictions and avoidance of soaps) and to treating dry, itchy skin (wet wrapping, oil of evening primrose, light therapy, etc.) are available, although evidence for many such treatments is lacking. There may be some consumer resistance to topical corticosteroid use, particularly over the long term and in children.

Two new topical immunosuppressants, pimecrolimus and tacrolimus, have recently been introduced for use in atopic eczema and are the subject of this assessment report.

Systematic review

Systematic review: methods

Electronic databases were searched for published research on the clinical effectiveness and cost-effectiveness of topical pimecrolimus and tacrolimus in atopic eczema compared with current standard treatment (emollients and topical corticosteroids). In addition, bibliographies were searched for relevant publications, also experts and the manufacturers of these agents were approached for information.

Systematic review: number and quality of studies, and direction of evidence

The review included eight randomised controlled trials (RCTs) of pimecrolimus (three of which were submitted on an in-confidence basis), three in children (one of which was submitted on an in-confidence basis) and five in adults (two of which were submitted on an in-confidence basis) containing 1602 subjects (2601 including confidential data). The review includes 10 RCTs of tacrolimus, four in children, five in adults and one containing both adults and children containing 4303 subjects. Of the pimecrolimus studies, four (two of which were confidential) were in moderate to severe eczema, which is not the licensed indication. All the tacrolimus trials were in those with moderate to severe eczema (the licensed indication), although one only included those with lichenified eczema.

Effectiveness of pimecrolimus

Three RCTs of pimecrolimus were provided as commercial in confidence by Novartis Pharmaceuticals UK Ltd.

Overall, the trial reports were of varying quality with methods of randomisation and blinding not stated or unclear in four out of eight.

Four RCTs compared pimecrolimus with a placebo treatment consisting of the base cream or ointment without the active ingredient (vehicle cream). One (two including confidential material) compared pimecrolimus with a potent topical corticosteroid in adults with moderate to severe eczema. **[Confidential information removed]** No studies compared pimecrolimus with mild or moderate topical corticosteroids in patients with mild to moderate disease.

►

[Confidential information removed]

Pimecrolimus was found to be more effective than the placebo treatment according to global measures such as the Investigators Global Assessment, patient-based measures such as number of flares and pruritus and alternative treatment use, that is, the amount of additional topical corticosteroids needed to treat problem eczema. Quality of life also improved more with pimecrolimus compared to the placebo treatment. There was very little evidence available about pimecrolimus compared with topical corticosteroids; what there is does not address the licensed population or potency of topical steroids.

Effectiveness of tacrolimus

Ten RCTs were included in the systematic review. The trials were of variable quality.

A range of populations and comparators were studied. Half of the RCTs compared tacrolimus with the placebo treatment, two trials in children used a very mild potency topical corticosteroid and three in adults compared tacrolimus with potent topical corticosteroids.

Compared to the placebo treatment, both 0.03% and 0.1% tacrolimus were more effective on global measures such as the Physician's Global Evaluation (PGE) and patient-based measures such as pruritus score.

Compared with a mild corticosteroid (1% hydrocortisone acetate), 0.03% tacrolimus was found to be more effective in children as measured by a 90% or better improvement in the PGE.

Compared with potent topical corticosteroids (0.1% hydrocortisone butyrate and 0.12% betamethasone valerate), no significant difference in effectiveness was seen with 0.1% tacrolimus as measured by a 75% or better improvement in the PGE.

One large trial found that 0.1% tacrolimus was more effective than a combined regimen of mild corticosteroid on the face and potent on the body at 6 months. However, this trial had a high drop-out and only provided a comparison with the combined regimen.

Minor application site adverse effects were found to be common with tacrolimus. However, this did not lead to increased rates of withdrawal from treatment in trial populations.

Economic evaluation

Methods for economic evaluation

One published economic evaluation (of tacrolimus) was identified through searching electronic databases. This is of limited relevance to the UK.

Industry submissions for pimecrolimus and tacrolimus were reviewed. The evaluation of tacrolimus did not calculate cost–utility. The evaluation of pimecrolimus was restricted to a comparison with the placebo treatment.

We developed a state transition (Markov) model to estimate cost–utility of tacrolimus and pimecrolimus separately, compared with current standard practice with topical corticosteroids, (a) as first-line treatment and (b) as second-line treatment. The model was adaptable to investigate different treatment pathways for adults and children, for facial and non-facial eczema and for mild to moderate and moderate or severe eczema. A total of eight cohorts of 1000 patients each were therefore modelled.

For children, the model ran for 14 years (ages 2–16 years). For adults, the model ran for 1 year. The cycle length in all cases was 4 weeks.

Cost-effectiveness: results

Pimecrolimus appears unlikely to be considered as a cost-effective treatment in mild to moderate eczema in adults or children compared with topical steroids. In all cases it cost more and conferred fewer quality-adjusted life-years (QALYs). However, the absolute differences in QALYs were small and these results subject to uncertainty. Probabilistic analysis confirmed the high degree of uncertainty in the data.

When compared with emollient alone, pimecrolimus was more likely to be considered cost-effective if decision-makers are willing to pay more than £20,000 for an additional QALY. At a willingness to pay of £30,000 per QALY, the probability that pimecrolimus was more cost-effective was estimated to be 0.55.

Deterministic analyses of tacrolimus suggested that it may be considered cost-effective as a first-line option in moderate to severe facial eczema in adults and body eczema in children. However, these results were subject to great uncertainty. Stochastic analysis, which takes account of some of this uncertainty, showed that neither option (topical steroids or tacrolimus as first- or second-line therapy) had a probability of being cost-effective of more than 50%, assuming that decision-makers are willing to spend £30,000 for an additional QALY. ►

The cost-effectiveness results should be interpreted with caution. Cost-effectiveness acceptability curves based on net benefit show that the probability of any of the regimens being the most cost-effective is low, reflecting the considerable uncertainty in available empirical data. No conclusions can be confidently drawn about the cost-effectiveness of pimecrolimus or tacrolimus compared with active topical corticosteroid comparators.

Conclusions

There is limited evidence from a small number of RCTs that pimecrolimus is more effective than the placebo treatment in controlling mild to moderate atopic eczema. Evidence is lacking comparing pimecrolimus with corticosteroid preparations in patients with the relevant severity of eczema. This is likely to be the crucial comparison in clinical practice.

Economic modelling suggests that pimecrolimus is unlikely to be cost-effective compared with topical corticosteroids in the treatment of children or adults. However, levels of uncertainty are high.

Although greater than for pimecrolimus, the evidence base for tacrolimus in moderate to severe atopic eczema is also limited. At both 0.1% and 0.03% potencies, tacrolimus appeared to be more effective than the placebo treatment and mild topical corticosteroids. However, these are not the most clinically relevant comparators. Compared with potent topical corticosteroids, no significant difference was shown.

Economic modelling suggests that tacrolimus may be cost-effective in treating children with moderate to severe atopic eczema of the face or body. However, levels of uncertainty are high and it is not possible to draw conclusions confidently given the available data.

Short-term adverse effects with both immunosuppressants are relatively common, but appear to be mild. Experience of long-term use of the agents is lacking so the risk of rare but serious adverse effects remains unknown.

Research recommendations

Effectiveness and safety

- Good-quality RCTs and further economic analysis of pimecrolimus in adults and children compared with appropriate potencies of topical corticosteroids in mild to moderate eczema are needed.
- Further large, good-quality RCTs of tacrolimus in adults and children compared with appropriate potencies of topical corticosteroids in moderate to severe eczema are needed.
- Data on long-term use of immunosuppressants, particularly the incidence and nature of adverse effects, are required.

Current and best practice

- There is a dearth of information about the normal treatment patterns and consultations for eczema, including health service utilisation, for sufferers in the UK. Observational studies are needed to provide basic information about this patient group.
- RCTs of the effects of different potencies of topical corticosteroids and different treatment regimens are needed.
- RCTs of the effects of wet-wrapping in children are required.
- Studies to establish the cost-effectiveness of education programmes for those with atopic eczema unwilling to take topical corticosteroids should be undertaken.
- The role of clinician and patient education in supporting the appropriate use of topical steroids should be investigated further.

Research tools

- Researchers and clinicians should try to reach a consensus about how to measure treatment success in treatments of atopic eczema, informed by further research into the reliability of methods of measurement.
- Further studies using general population estimates of utility values for the various severities of eczema would be helpful for future cost–utility analyses.
- Given the limitation of the Markov model for such chronic relapsing conditions, further modelling using other techniques (such as discrete event simulation) are required.

Publication

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