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

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CRD summary
This well-conducted review assessed the effectiveness of topical pimecrolimus and tacrolimus for atopic eczema. The authors concluded that there is limited evidence that pimecrolimus and tacrolimus are more effective than placebo and that tacrolimus is more effective than mild corticosteroids, and there are insufficient data on long-term use and safety. The authors' conclusions reflect the limited evidence.

Authors' objectives
To assess the effectiveness and cost-effectiveness of topical pimecrolimus for mild to moderate atopic eczema and the effectiveness of tacrolimus for moderate to severe atopic eczema compared with current standard treatment in adults and children.

Searching
MEDLINE (1966 to 2003), PREMEDLINE (July 2003), EMBASE (1980 to 2003), the Cochrane Library (Issue 2, 2003), DARE (July 2003), the Cochrane Skin Group's Specialised Register, the Science Citation Index (1981 to 2003), Web of Science Proceedings (1990 to 2003), HTA (July 2003), the National Research Register (July 2003), Current Controlled Trials (July 2003), ClinicalTrials.gov (July 2003) and the website of the U.S. Food and Drug Administration were searched; the search terms were reported. The reference lists of selected studies were also checked. Experts in the field and the manufacturers of pimecrolimus and tacrolimus were contacted. The studies had to be available in English.

Study selection
Study designs of evaluations included in the review
Systematic reviews and randomised controlled trials (RCTs) were eligible for inclusion. The studies had to report sufficient information on the baseline characteristics of the participants and methods used to allow an assessment of quality.

Specific interventions included in the review
Studies that compared pimecrolimus and tacrolimus with current standard treatment comprising emollients with or without topical corticosteroids were eligible for inclusion. Studies using systemic treatment as the comparator were excluded.

The review compared pimecrolimus (1% cream) and tacrolimus (0.1% and 0.03% ointment) with placebo and mild and potent topical corticosteroids. The duration of treatment ranged from 2 weeks to 12 months.

Participants included in the review
Studies of adults and children (aged 2 years or older) with mild to moderate atopic eczema in pimecrolimus studies, or moderate to severe atopic eczema in tacrolimus studies, were eligible for inclusion. Studies of people who did not have atopic eczema were excluded. One study evaluating tacrolimus included patients with lichenified eczema. Four studies evaluating pimecrolimus included patients with moderate to severe eczema.

Outcomes assessed in the review
Studies that reported patient-based outcomes were eligible for inclusion. The primary outcome for pimecrolimus was treatment success, which was defined as the proportion of patients with eczema 'clear' or 'almost clear' (score 0 to 1 on the Investigators Global Assessment scale, IGA) compared with those scoring more than 2. The primary outcome for tacrolimus was dichotomous, those scoring 90% or better using the Physician's Global Evaluation (PGE) compared with the rest. The review also assessed the number of flares, disease control, the Eczema Area and Severity Index (EASI), the Atopic Dermatitis Severity Index, body surface area affected, days in remission, concomitant use of topical...
corticosteroids and antihistamines, pruritus, quality of life and adverse effects.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies and resolved any disagreements through discussion.

Assessment of study quality
Internal validity was assessed by considering the following: the adequacy of methods of randomisation; allocation concealment; blinding of the outcome assessment; the number randomised, excluded and lost to follow-up; the use of intention-to-treat analysis; and appropriate power calculations. External validity was assessed on the basis of: the timing, duration and location of the study; the age of the participants; co-morbidity; inclusion and exclusion criteria; concomitant treatment and washout periods; and the duration of follow-up. Studies were classified as having high generalisability if there was a detailed description of the exclusion criteria and participants. The authors did not state who performed the validity assessment.

Data extraction
One reviewer extracted the data and a second reviewer checked them. For each study, the actual numbers of patients with events of interest were extracted, where possible, and the data reanalysed using intention-to-treat analysis with the number randomised as the denominator. If not reported, the statistical significance of differences in proportions between treatments was calculated. Data were extracted from graphs where no actual values were reported.

Methods of synthesis
How were the studies combined?
Studies using similar interventions were combined using a random-effects model. Pooled relative risks (RRs) were calculated for dichotomous data and standardised mean differences for continuous data, both with 95% confidence intervals (CIs). Analyses were stratified by age (adult or child), intervention and duration of treatment. Studies not presenting suitable data for meta-analysis were combined in a narrative.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared statistic (significance level \( P<0.5 \)). Details of the studies were tabulated and differences were also discussed in the text.

Results of the review
Eighteen RCTs (n=6,904) were included in the review. Eight (n=2,601), including three submitted on an in-confidence basis, evaluated pimecrolimus and ten (n=4,303) evaluated tacrolimus.

Pimecrolimus.
The studies were of varying quality. Four studies reported adequate methods of randomisation and five reported blinding of assessors and/or patients. All but one study stated potential conflicts of interest. Most of the studies used intention-to-treat analysis, had high rates of withdrawals, and were rated as having high generalisability. The studies were generally short term (6 weeks); one study in children lasted 12 months.

Children (3 RCTs).
One RCT reported a greater improvement in IGA scores with pimecrolimus compared with placebo, either by at least one point (59.9% versus 33.1%), or in indicating that the skin was clear or almost clear of eczema (26.9 versus 2.9 at 3 weeks, \( P<0.05 \); 27% versus 11.8% at 6 weeks, \( P<0.001 \)). This RCT also reported that a significantly greater proportion of children on pimecrolimus had well or completely controlled eczema (60% versus 39%, \( P<0.05 \)) and a greater median reduction in the EASI score (45% versus 1%, \( P<0.001 \)), and more children had mild or absent pruritis compared with the control group (57% versus 34%).

A second RCT reported that more children treated with pimecrolimus had no flares at 6 and 12 months compared with
those treated with topical corticosteroids (76% versus 52% and 71% versus 43%, respectively). This RCT also reported that a greater proportion of children using pimecrolimus were not using topical corticosteroids (64.7% versus 37.1%, P<0.05) or antihistamines (57.2% versus 92.9%), and used topical corticosteroids for fewer days (4.1 versus 9.1 days) compared with the use of emollients.

The third RCT was confidential.

Adults (5 RCTs).

One RCT reported an improvement in the IGA score of at least one point, indicating that the skin was clear or almost clear of eczema, in a higher proportion of those treated with pimecrolimus compared with placebo (68.6% versus 36.5%, P<0.001). This RCT also reported that more people had no flares at 24 weeks (44.8% versus 18.8%, P<0.001), had a longer time to first flare (144 versus 26 days), avoided the use of topical corticosteroids (14.2 versus 37.2 days usage, P<0.001), and had greater decreases in the quality of life index - atopic dermatitis (QoLIAD) (25.6% versus 7.4%) and Dermatology Life Quality Index (DLQI) scores (22% versus 6.7%) with pimecrolimus compared with placebo.

A second RCT reported that the proportion of patients whose eczema was clear or almost clear at 3 weeks was higher with pimecrolimus than with placebo (11.1% versus 0%, P=0.056), but lower than with topical corticosteroids (11.1% versus 50%, P<0.05). This RCT also reported a greater reduction in EASI scores (pimecrolimus 48.3%; corticosteroids 78%; placebo 0%) and that fewer people had mild to moderate pruritis at 12 months (pimecrolimus 46.7%; corticosteroids 81%; placebo 18.6%) with treatment compared with placebo.

A third RCT reported that topical corticosteroids significantly increased the proportion of patients with moderate or better improvements on the IGA scale compared with pimecrolimus (88.8% versus 52.3%, P<0.001). This RCT also reported a greater reduction in EASI scores (73.9% versus 50.7%, P=0.006) and that more people had mild to moderate pruritis at 12 months (52.4% versus 24.7%, P=0.069) with corticosteroids than with pimecrolimus.

A fourth RCT reported significantly more people had totally or partially cleared eczema (93.8% versus 12.5%, P<0.001) and a greater mean decrease in the Atopic Dermatitis Severity Index score (79.1% versus 10.3%, P<0.01) with pimecrolimus compared with placebo.

The fifth RCT was confidential.

Adverse effects were reported in 4 RCTs. Minor local adverse effects were common: in 3 RCTs, up to 49% of patients reported burning at the application site with pimecrolimus, compared with 3.1 to 35% with placebo and 10% with corticosteroids. The meta-analysis showed no significant difference between pimecrolimus and placebo for rates of bacterial infection or skin burning. Pimecrolimus significantly increased viral infections in comparison with placebo (relative risk 1.97, 95% confidence interval, CI: 1.21, 3.19).

Tacrolimus.

The studies were of varying quality. Five studies reported methods of randomisation. Withdrawal rates were high in groups allocated to placebo. Most of the studies used a modified intention-to-treat analysis. The studies were generally short term (2 to 3 weeks, range: 2 weeks to 6 months). All studies in children and 3 of the 5 studies in adults were rated as having high generalisability.

Children (4 RCTs). Tacrolimus 0.03% was significantly more effective (at least 90% on PGE) than corticosteroids at 3 weeks in children with moderate to severe eczema (RR 2.56, 95% CI: 1.95, 3.36; 2 RCTs). Two further RCTs showed that, compared with placebo, 0.03% and 0.1% tacrolimus ointment significantly increased the proportion of patients cleared or markedly improved on the PGE scale (P<0.007 and P<0.001).

Three RCTs reported statistically significant mean improvements in the EASI score with 0.1% and 0.03% tacrolimus compared with placebo (77%, 72%, 26%, P<0.001; 82%, 75%, 37%, P<0.001; and 76.7%, 66.7%, 47.6%, P<0.001). Two of 3 RCTs reported greater improvements in the pruritus visual analogue scale score with 0.1% and 0.03%
tacrolimus compared with placebo (3.9, 3.2, 1.8, P=0.027; 3.9, 3.9, 0.8; and 3.0%, 2.6%, 3.1%).

Further results for the secondary outcomes were reported.

Adults (7 RCTs).

Six RCTs reported changes in the PGE scale. Three RCTs studied 0.03% tacrolimus and reported improvements in eczema compared with placebo (46.2% versus 13.8%, P<0.01; and 59% versus 10%), but not compared with topical corticosteroids (57.9% versus 70.9%). All 6 RCTs reported results for 0.1% tacrolimus, and reported greater efficacy compared with placebo (100% versus 0%; 57% versus 13.8%, P<0.001; and 81% versus 10%, P<0.001) and topical corticosteroids, but not significantly so (60.7% versus 56.5%; 62.9% versus 40.7%; and 76.9% versus 70.9%). A meta-analysis of 2 RCTs showed that tacrolimus 0.1% was not more effective (at least 75% on the PGE scale) than corticosteroids in adults with moderate to severe eczema (RR 1.08, 95% CI: 0.97, 1.21).

Two RCTs did not report the PGE scale. One reported greater improvements on the EASI scale with topical corticosteroids compared with 0.03% tacrolimus (P<0.05), but not 0.1% tacrolimus. The other reported a greater reduction in the DLQI score with 0.03% and 0.1% tacrolimus compared with placebo (21.1, 27.1 and 5.6, respectively).

Further results for the secondary outcomes were reported.

Withdrawal due to adverse effects occurred in 1.6 to 5.7% of participants on tacrolimus, compared with 4.5 to 12.3% on placebo and 1.6 to 3.3% on topical corticosteroids. The meta-analysis showed no significant difference in overall skin infections between 0.03% or 0.1% tacrolimus and topical corticosteroids. Skin burning was significantly more common with tacrolimus 0.03% (RR 3.49, 95% CI: 2.33, 5.52; 1 RCT) and tacrolimus 0.1% (RR 4.17, 95% CI: 3.36, 5.18; 3 RCTs) in comparison with topical corticosteroids.

### Cost information

Economic modelling suggested that pimecrolimus was unlikely to be cost-effective in comparison with topical corticosteroids in the treatment of children or adults. However, when compared with emollient alone, it was more likely to be considered cost-effective if decision-makers were willing to pay more than £20,000 for an additional quality-adjusted life-year (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.

Economic modelling suggested that tacrolimus may be cost-effective in treating children with moderate to severe atopic eczema of the body, or facial eczema in adults. The stochastic analysis showed neither tacrolimus nor topical corticosteroids had a probability of being cost-effective of more than 50%, assuming a willingness-to-pay of £30,000 for an additional QALY.

The levels of uncertainty in the available empirical data were high, and no conclusions could be drawn about the cost-effectiveness of either pimecrolimus or tacrolimus in comparison with topical corticosteroids.

### Authors' conclusions

There was limited evidence that pimecrolimus was more effective than placebo for mild to moderate atopic eczema, and that tacrolimus 0.1% and 0.03% ointments were more effective than placebo and mild topical corticosteroids. There was insufficient evidence to compare pimecrolimus with corticosteroids, and no difference was found between tacrolimus and potent corticosteroids.

### CRD commentary

The review question was clear in terms of the study design, participants, intervention and outcomes. The extensive search included attempts to locate unpublished studies, thus minimising publication bias. The authors stated that studies not available in English were to be excluded, but one included study was translated from Japanese. There is, however, still the potential for language bias. Two reviewers selected studies and extracted the data, thus reducing the potential for bias and errors. Validity was assessed using specified established criteria, but the methods used were not reported.
Adequate details of each included study were given. The data were appropriately grouped by comparison and outcomes, and only comparable statistically homogeneous studies were combined in a meta-analysis. Overall, this was a well-conducted and clearly presented review. The limitations of the evidence are reflected in the authors' conclusions.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors highlighted the need for good-quality RCTs and further economic analysis of both pimecrolimus and tacrolimus, compared with appropriate potencies of topical corticosteroids, in adults and children with mild to moderate eczema. They further stated that long-term follow-up data on immunosuppressants, including the incidence and nature of adverse effects, are required. Other research recommendations were: observational studies to determine normal treatment and consultation patterns for eczema in the UK; RCTs to compare different potencies and regimens of corticosteroids; RCTs of the effects of wet-wrapping in children; cost-effectiveness studies in people with atopic eczema unwilling to use topical corticosteroids; research into the role of clinician and patient education to support the appropriate use of topical corticosteroids; research into the reliability of methods used to measure treatment success; cost-utility studies using general population estimates of utility values for the various severities of eczema; and research into alternative methods of modelling chronic relapsing conditions.

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