Topical calcineurin inhibitors in atopic dermatitis: a systematic review and meta-analysis

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CRD summary
The authors concluded that for atopic dermatitis, topical calcineurin inhibitors were more effective than placebo. Pimecrolimus was as effective as mild but less effective than moderately potent topical corticosteroids. Tacrolimus was more effective than mild and as effective as moderately potent topical corticosteroids. As few data were available and the review had methodological problems, these conclusions appear questionable.

Authors' objectives
To evaluate the effectiveness of topical calcineurin inhibitors for treatment of atopic dermatitis compared with topical corticosteroids and/or placebo.

Searching
MEDLINE was searched from 1997 to 2006. Search terms were reported. The references of articles retrieved were handsearched. The search was limited to articles in English, French and German. Studies available only as abstracts were excluded.

Study selection
Randomised controlled trials (RCTs) that reported the effectiveness of topical pimecrolimus and/or tacrolimus for treating atopic dermatitis in patients of any age were eligible for inclusion, provided the comparator was topical corticosteroids and/or placebo. Studies that reported quality of life were excluded.

About half of the studies in the review included solely children aged less than 17 years; other studies had an age range of up to 81 years. Disease severity was generally mild to very severe in the pimecrolimus studies and moderate to severe in the tacrolimus studies. Some studies included multiple intervention arms with differing doses of calcineurin inhibitor. Topical preparations were in most cases administered twice daily (where reported). A variety of topical corticosteroids of different potency were used as comparators, including hydrocortisone acetate 1% (mild), hydrocortisone butyrate 0.1% (moderate) and betamethasone-17 valerate (potent). Placebo intervention was the topical preparation without the active ingredient. The primary review outcome was treatment effectiveness, defined as an Investigator Global Assessment Score of 0 or 1 for pimecrolimus and as Physician Global Evaluation Score of Clear or Excellent Improvement for tacrolimus. Secondary outcomes were Patient Global Assessment, pruritus scores, frequency of atopic dermatitis flares and steroid sparing. Duration of follow up ranged from three weeks to 12 months. All but two of the studies were sponsored by the same two pharmaceutical companies.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection. [A: A single reviewer performed the study selection.]

Assessment of study quality
The following components of internal validity were considered: randomisation; allocation concealment; double blinding; intention to treat analysis; and power calculation. Components of external validity were also evaluated, including detailed description of study setting, participant characteristics, selection criteria, treatment regimen and duration of follow up. Studies that meet criteria for external validity were designated highly generalisable.

The authors did not state how the assessment was performed. [A: A single reviewer performed the validity assessment twice on each paper.]

Data extraction
Risk ratios (RRs) were calculated from the numbers of events in the control and intervention groups of each study, with 95% confidence intervals (CIs). Data were analysed on an intention-to-treat basis.
The authors stated neither how the data were extracted for the review nor how many reviewers performed the data extraction. [A: Data were extracted by a single reviewer who used a modified template adapted from a Cochrane Collaboration format.]

**Methods of synthesis**
Studies were grouped by intervention and subgrouped by type and/or potency of comparator and by duration of follow up. Data were then combined using a random-effects model to calculate pooled RRs and 95% CIs. The $\chi^2$ test was used to assess for heterogeneity.

**Results of the review**
Nineteen RCTs were included in the review (n=7,378): 10 of pimecrolimus (n=2,959) and nine of tacrolimus (n=4,419). Seven studies were rated as highly generalisable and five were noted to have high internal validity. [A: Eleven RCTs reported adequate methods of randomisation, three reported adequate allocation concealment, all used adequate or double blinding, 16 used intention-to-treat analysis and 10 reported power calculations.]

Pimecrolimus 1% was significantly more effective than placebo at three weeks (RR 2.41, 95% CI 1.31 to 4.43; four RCTs) and six weeks (RR 2.05, 95% CI 1.52 to 2.76; two RCTs). There was significant statistical heterogeneity ($p=0.02$) for the three-week outcome. No statistically significant difference between the groups in effectiveness was found at six or 12 months (one RCT). Findings for secondary outcomes were also significantly superior in the pimecrolimus group.

One RCT found that for moderate to severe atopic dermatitis, pimecrolimus was significantly less effective than a potent topical corticosteroid at three weeks (RR 0.22, 95% CI: 0.09 to 0.54). A second RCT reported that combined potent/mild topical corticosteroid was significantly more effective than pimecrolimus for up to six months (RR 0.89, 95% CI 0.83 to 0.9).

One of three relevant studies reported that in children tacrolimus 0.03% was significantly more effective than placebo at three weeks (RR 2.13, 95% CI: 1.24 to 3.68; one RCT), but tacrolimus 0.1% was not (one RCT). The remaining two RCTs (one in children and one in adults) reported that both 0.03% and 0.1% tacrolimus were significantly more effective than placebo at 12 weeks (RR 4.53, 95% CI 2.93 to 7.00 for 0.03% tacrolimus; RR 5.69, 95% CI 3.72 to 8.72 for 0.1% tacrolimus).

Tacrolimus 0.03% (RR 2.56, 95% CI 1.95 to 3.36; two RCTs) and 0.1% (RR 3.09, 95% CI 2.14 to 4.45; one RCT) were both significantly more effective than a mild topical corticosteroid at three weeks. Single RCTs conducted among adults with moderate to severe atopic dermatitis found that at three weeks tacrolimus 0.03% was significantly less effective than a moderate topical corticosteroid (RR 0.74, 95% CI 0.59 to 0.93), but tacrolimus 0.1% was not significantly different from the moderate topical corticosteroid. At six months tacrolimus 0.1% was significantly more effective than a combined potent/mild topical corticosteroid ($p=0.00001$).

**Authors' conclusions**
For atopic dermatitis, topical calcineurin inhibitors were more effective than placebo. Pimecrolimus was as effective as topical corticosteroids, but less effective than moderately potent topical corticosteroids. Tacrolimus was more effective than mild topical corticosteroids and as effective as moderately potent topical corticosteroids.

**CRD commentary**
The objectives and inclusion criteria of the review were clear, but outcomes were not pre-specified as part of the inclusion criteria. Only one database was searched, so some studies may have been missed. The search was restricted by language and no specific attempts were made to retrieve unpublished studies, so the review was subject to language and publication biases. The reviewers acknowledged the potential for publication bias, but it did not appear that this was formally assessed. Study selection, validity assessment and data extraction were undertaken by a single reviewer without an independent check, which increased the risk of reviewer error and bias.

Relevant criteria were used to assess study validity, which was variable; less than half the studies were rated as highly...
generalisable. As the authors noted, nearly all studies were commercially sponsored. The statistical methods used to pool studies and assess for heterogeneity appeared appropriate in most respects, but where significant heterogeneity was detected it was not formally assessed or explored in the review. Although the authors stated that all age groups and grades of severity showed the same results, the possible impact of clinical heterogeneity between the studies was not formally tested. Most comparisons involved only one or two studies. The authors' statement regarding the equivalent effectiveness of pimecrolimus and mild topical corticosteroids did not appear to be supported by evidence. [A: The authors have sent a correction to the journal for this error in the published paper.]

As few data were available and the review had many methodological problems, the authors' conclusions appear questionable.

Implications of the review for practice and research

Practice: The authors stated that pimecrolimus could be used in milder cases of atopic dermatitis and in long-term maintenance for preventing flare-ups and reducing steroid use. Tacrolimus could be used for moderate to severe cases and as first-line therapy instead of topical corticosteroids.

Research: The authors did not state any implications for further research. [A: The authors stated that there was a need for the following: cost-effectiveness studies of therapies used for atopic dermatitis in Egypt; large good-quality RCTs of the effectiveness of pimecrolimus compared with mild topical corticosteroids for mild to moderate atopic dermatitis (particularly in children and infants); large good-quality RCTs of pimecrolimus applied in the early stages of atopic dermatitis compared to short bursts of mild topical corticosteroids for prevention of flares; studies of the effectiveness of topical corticosteroids in cases of steroid resistance; and very long-term studies of the safety of topical calcineurin inhibitors for suspected cancer.]

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