Two topical calcineurin inhibitors for the treatment of atopic dermatitis in pediatric patients: a meta-analysis of randomized clinical trials

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CRD summary
This review concluded that tacrolimus ointment and pimecrolimus cream were safe and effective in the treatment of atopic dermatitis in paediatric patients; tacrolimus ointments were superior to pimecrolimus cream. A possibility of publication bias, lack of reporting of some aspects of the review process and unclear adverse event data made the reliability of the authors' conclusions unclear.

Authors' objectives
To evaluate the efficacy and adverse effects of tacrolimus ointment and pimecrolimus cream in the treatment of paediatric atopic dermatitis.

Searching
MEDLINE, EMBASE, The Cochrane Library and CNKI were searched to December 2008 for studies published in any language. Search terms were reported. Abstract proceedings were searched. Investigators and pharmaceutical companies were contacted.

Study selection
Randomised controlled trials (RCTs) of paediatric patients (less than 18 years) with a reliable diagnosis of atopic dermatitis that compared locally applied tacrolimus ointment or pimecrolimus cream with placebo or other medicines were eligible for inclusion.

Primary outcomes of interest were investigators' global assessment (IGA) or physician's global evaluation (PGE); secondary outcomes were modified or unmodified eczema area and severity index (EASI) quality of life and adverse events.

Participant age ranged from three months to 17 years. Atopic dermatitis was described as mild, moderate or severe. The included interventions were 0.1% (with or without 0.3%) or 0.03% tacrolimus twice daily, 1% hydrocortisone, 1% hydrocortisone acetate, 1% pimecrolimus, 0.1% methylprednisolone aceponate and corticosteroids. These were compared with each other or a vehicle control. The outcomes reported were IGA, EASI, modified EASI, PGE, quality of life, pruritus, sleep, flare.

The authors did not state how papers were selected for the review.

Assessment of study quality
Methodological quality was assessed independently by two reviewers using the Jadad scale of randomisation, blinding, withdrawals and dropouts to give a quality score out of five. A score of 3 to 5 indicated high quality.

Disagreements were resolved by discussion or consultation with a third reviewer.

Data extraction
Odds ratios (ORs) and 95% confidence intervals (CIs) were extracted for outcomes.

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
Odds ratios and 95% CIs were pooled in a meta-analysis. A fixed-effect model was used in the absence of heterogeneity; a random-effects model was used where heterogeneity was present. Heterogeneity was assessed using
X² test and I² statistic.

**Results of the review**

Twenty RCTs were included in the review (n=6,288, range 21 to 713). All trials received a Jadad score of at least 3.

Tacrolimus was associated with a significantly better response than control (OR 4.56, 95% CI 2.80 to 7.44; four RCTs), 1% hydrocortisone acetate (OR 3.92, 95% CI 2.96 to 5.20; number of RCTs unclear, results for tests of heterogeneity not reported) and 1% pimecrolimus (OR 1.58, 95% CI 1.18 to 2.12; three RCTs).

Pimecrolimus was associated with a significantly better response than control (OR 3.21, 95% CI 2.48 to 4.14; six RCTs). There was no significant difference in efficacy outcomes with 0.03% compared with 0.1% tacrolimus and with pimecrolimus compared with corticosteroids. Heterogeneity was not significant for any analyses except tacrolimus 0.1% versus 0.03% (I²=56.8) and tacrolimus versus control (I²=57.9)

Quality of life scores were significantly better with 0.1% and 0.03% tacrolimus than with control in children and toddlers in one study (p<0.05). Another study found better quality of life scores with tacrolimus in children, but not toddlers (p<0.05). One study found that 1% pimecrolimus cream had a significantly beneficial effect on the quality of life of parents compared with control.

Adverse events were described as similar with 1% pimecrolimus cream (5% to 86%, 27 withdrawals due to adverse events), tacrolimus ointment (13% to 39%, 11 withdrawals with 0.1% tacrolimus; 15% to 84%, 29 withdrawals with 0.03 tacrolimus) and control (not reported); major adverse events reported were burning and pruritus (text and tables differed).

**Authors' conclusions**

Both tacrolimus ointment and pimecrolimus cream were safe and effective in the treatment of atopic dermatitis in paediatric patients. Tacrolimus ointments were superior to pimecrolimus cream.

**CRD commentary**

The review question was well defined and supported by explicit inclusion criteria. Relevant databases were searched without language restrictions, which reduced the risk of language bias. Only published studies were sought. Publication bias could not be ruled out. Study quality was assessed by two reviewers; it was unclear whether similar steps were taken to reduce reviewer error and bias during study selection and data extraction. Heterogeneity was assessed; sources were not explored where present. Conclusions were made regarding safety, but the reporting of data for this was unclear. The authors stated that all of the trials were sponsored by Fujisawa or Novartis, so bias toward positive results was possible. The authors declared that they had no conflicts of interest with Fujisawa or Novartis.

A possibility of publication bias, lack of reporting of some aspects of the review process and unclear adverse event data made the reliability of the authors' conclusions unclear.

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

**Practice:** The authors stated that the results of the review should be integrated with doctors' experiences and actual clinical experiences as a guide to clinical practice.

**Research:** The authors stated that more large-scale clinical trials were needed.

**Bibliographic details**


**PubMedID**

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.