REVIEW

Systematic review and meta-analysis of randomized clinical trials (RCTs) comparing topical calcineurin inhibitors with topical corticosteroids for atopic dermatitis: A 15-year experience

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Background: Calcineurin inhibitors are alternatives to corticosteroid for treatment of atopic dermatitis.

Objectives: We sought to compare the beneficial effects and adverse events associated with these therapies in treating patients with atopic dermatitis.

Methods: Four databases were searched for randomized clinical trials comparing topical calcineurin inhibitors versus corticosteroids in children and adults. Methodological quality was evaluated to assess bias risk. Clinical outcome and costs were compared.

Results: Twelve independent randomized clinical trials comparing calcineurin inhibitors (n = 3492) versus corticosteroids (n = 3462) were identified. Calcineurin inhibitors and corticosteroids had similar rates of improvement of dermatitis (81% vs 71%; risk ratio [RR] 1.18; 95% confidence interval [CI] 1.04-1.34; $P = .01$) and treatment success (72% vs 68%; RR 1.15; 95% CI 1.00-1.31; $P = .04$). Calcineurin inhibitors were associated with higher costs and had more adverse events (74% vs 64%; RR 1.28; 95% CI 1.05-1.58; $P = .02$) including a higher rate of skin burning (30% vs 9%; RR 3.27; 95% CI 2.48-4.31; $P < .00001$) and pruritus (12% vs 8%; RR 1.49; 95% CI 1.24-1.79; $P < .00001$). There were no differences in atrophy, skin infections, or adverse events that were serious or required discontinuation of therapy.

Limitations: Only a small number of trials reported costs.

Conclusion: Calcineurin inhibitors and corticosteroids have similar efficacy. Calcineurin inhibitors are associated with higher costs and have more adverse events, such as skin burning and pruritus. These results provide level-1a support for the use of corticosteroids as the therapy of choice for atopic dermatitis. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.02.1228.)

Key words: atopic dermatitis; calcineurin inhibitors; corticosteroids; meta-analysis; randomized controlled trial; systematic review.

Atopic dermatitis is a common inflammatory skin disorder characterized by itch, xerosis, and inflammation. Superinfection with *Staphylococcus aureus* resulting in edema and exudation is common. These symptoms interfere with most aspects of daily life. Topical corticosteroids remain the mainstay of treatment of atopic dermatitis.

Abbreviations used:

CI:	confidence interval
FDA:	Food and Drug Administration
RCT:	randomized clinical trial
RR:	risk ratio

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In 2000, topical immunomodulation by calcineurin inhibition was introduced to provide an alternative to topical corticosteroids.[1] Inhibition of calcineurin decreases the activity of transcription factors that control cell division, which reduces inflammation by means of selective prevention of T-cell activation. Pimecrolimus and tacrolimus are the calcineurin inhibitors that are currently being used in the treatment of atopic dermatitis in children and adults. These drugs enjoyed an initial surge of popularity fueled by aggressive advertising centered on the claim that, unlike topical corticosteroids, they would not produce cutaneous atrophy. This was dampened by the release of a Food and Drug Administration (FDA) Black Box warning. In 2005, the FDA raised concerns about the widespread use of 525,000 scripts (14% of prescriptions) for pimecrolimus and 69,000 scripts (7% of prescriptions) for tacrolimus,[2] particularly in regard to off-label prescribing to children and heavy direct-to-consumer advertising. Based on this, high-dose animal studies, and malignancy reports in the FDA's adverse event reporting system (25 malignancies, 13 lymphomas in >6.7 million potential patients), the committee concluded that calcineurin inhibitors carry a possible and plausible risk of the development of melanoma skin cancer, nonmelanoma skin cancer, and Hodgkin and non-Hodgkin lymphoma.[3]

In response to the warning, many dermatology associations have released position statements promoting the safety of calcineurin inhibitors and, since then, no evidence has been published demonstrating a causal relationship with the development of malignancy in human beings. Calcineurin inhibitors have been used in clinical practice for 15 years, but there is ongoing uncertainty about their role in the treatment of atopic dermatitis. Several randomized trials have compared clinical outcome of calcineurin inhibitors and corticosteroids for atopic dermatitis. Meta-analyses of these trials have so far only evaluated clinical outcomes and concluded that calcineurin inhibitors are as effective as corticosteroids.[4-6] Calcineurin inhibitors have a substantial cost premium,[7] but meta-analyses have so far failed to demonstrate superiority over corticosteroids to justify routine use.[4-6] Calcineurin inhibitors are currently not widely used as first-line therapy for atopic dermatitis, because of the perception that they have lower efficacy than corticosteroids.[6] Consequently, it is currently unknown whether calcineurin inhibitors or corticosteroids should be considered as standard therapy for atopic dermatitis. Previous meta-analyses have pooled studies published up until 2009 and since then 7 individual randomized clinical trials (RCTs) have been published. The current study aims to bring the evidence base up to date and determine the therapy of choice for atopic dermatitis by comparing clinical outcome and costs of topical calcineurin inhibitors with corticosteroids.

CAPSULE SUMMARY

- Calcineurin inhibitors were introduced as an alternative to corticosteroid for treatment of atopic dermatitis.
- Calcineurin inhibitors and corticosteroids have similar efficacy. Calcineurin inhibitors are associated with higher costs and have more adverse events.
- The findings provide level-1a support for use of corticosteroids as the therapy of choice for atopic dermatitis.

METHODS

Study selection

A systematic literature search with predefined search terms (Fig 1) was carried out in MEDLINE (from 1960), EMBASE (from 1980), Cochrane Library (issue 1, 2012), and the Web of Knowledge Conference Proceedings Citation Index–Science (from 1990) databases on April 5, 2015 (Fig 1). All identified articles were screened for cross-references. Language restrictions were not applied.

Inclusion criteria

Title and abstract of all identified articles were screened and selected according to the following inclusion criteria: study population—patients with atopic dermatitis; intervention—clearly documented topical treatment with calcineurin inhibitors or corticosteroids; study outcomes—at least 1 of the outcome measures reported below; study design—patients assigned to either calcineurin inhibitors or corticosteroids by random allocation; and publication—published as a full article in a peer-reviewed journal.

Exclusion criteria

Studies were excluded from analysis if they did not meet the inclusion criteria and it was impossible to extract or calculate appropriate data from the published results. Abstracts of RCTs were excluded as details on treatment, methodological quality, and the risk of bias of these studies could not be assessed.

Outcomes of interest and definitions

Efficacy outcomes were improvement of dermatitis and treatment success. Safety outcome included: adverse events, skin burning, pruritus,