Systemic treatment of severe atopic eczema: a systematic review

Schmitt J, Schakel K, Schmitt N, Meurer M

CRD summary
This review concluded that cyclosporin is consistently effective in treating atopic eczema refractory to topical treatment, and is recommended as the first option for these patients. There was insufficient evidence available for other potential treatments. This was a well-conducted review and the conclusions are likely to be reliable.

Authors' objectives
To determine which systemic immunosuppressive or immunomodulatory agent to use as first- and second-choice treatment for patients with severe atopic eczema.

Searching
MEDLINE was searched to 2005; the search terms were reported. The Cochran Skin Group's Specialised Register, the Cochrane CENTRAL Register and the bibliographies of review articles were also searched. Only full-text articles were included.

Study selection
Study designs of evaluations included in the review
Prospective clinical trials were eligible for inclusion. Case reports or series with fewer than 5 patients were excluded.

Specific interventions included in the review
Studies evaluating the effectiveness of systemic immunosuppressive or immunomodulatory agents were eligible for inclusion. The interventions evaluated were cyclosporin A, steroids, interferon gamma, intravenous immunoglobulin, azathioprine, infliximab, mycophenolate mofetile and Chinese herbal medicines. Doses and regimens varied across studies. Treatment duration varied from 6 weeks to 1 year.

Participants included in the review
Studies of patients with severe atopic eczema who did not respond adequately to topical treatments were eligible for inclusion. Where reported, participants were aged from 1 to 18 years in the studies of children, 17 to 73 years in the studies of adults, and 2 to 65 years in the studies of both adults and children.

Outcomes assessed in the review
No inclusion criteria were stated in relation to the outcomes. The primary outcome was change in clinical severity of eczema, in relation to the intensity and extent of skin lesions that were investigator-rated. The other outcomes evaluated were serious adverse events and withdrawals due to adverse events.

How were decisions on the relevance of primary studies made?
Two independent reviewers screened studies for inclusion; any disagreements were resolved by discussion.

Assessment of study quality
Study quality was evaluated in terms of appropriate case definition, the use of validated outcomes, follow-up rates, the use of intention-to-treat analysis, and the adequacy of randomisation, allocation concealment and blinding. The number of reviewers undertaking the validity assessment was not stated, but the assessment seems to have been conducted during the data extraction.

Data extraction
Two independent reviewers extracted the data using a standardised data extraction form; any disagreements were resolved by discussion. The change from baseline in mean objective clinical severity was calculated. The mean relative change in clinical severity was extracted or calculated using absolute scores at baseline and during treatment. Data were estimated from figures or graphs where necessary, and the distribution of relative individual responses abstracted if means were not reported.
Methods of synthesis
How were the studies combined?
The authors compared RCTs with uncontrolled studies by using the results of the treatment arm only, and only the first stage of RCTs with a crossover design. The study results were combined in a narrative.

How were differences between studies investigated?
Differences between the studies were discussed in the text and study details tabulated.

Results of the review
Twenty-seven studies (n=979) were included in the review. The study designs included were double-blind (n=560), evaluator blind (n=10) or open parallel (n=121) randomised controlled trials (RCTs), and open uncontrolled studies (n=288).

Of the 27 studies included, nine had follow-up of less than 80%, with three of these not using an intention-to-treat analysis, 11 RCTs did not report on randomisation concealment, and blinding was deemed inadequate in 9 studies, of which three were RCTs.

Effectiveness.
Cyclosporin A: 11 studies reported a decrease in disease activity with cyclosporine, with superiority over placebo in all 6 RCTs.

Systemic glucocorticosteroids: 2 RCTs in children reported short-term decreases in severity of 22% and 39% after treatment with beclomethasone dipropionate and flunisolide, respectively.

Interferon gamma: 2 poor-quality RCTs reported interferon as superior to placebo in children and adults. One uncontrolled study reported a 30% decrease in the intensity of lesions, while another uncontrolled study reported low response rates.

Intravenous immunoglobulin: 3 small studies reported limited responses to immunoglobulin.

Mycophenolate mofetile: 2 small uncontrolled studies reported short-term decreases in severity of 55% and 68% after 8 and 12 weeks’ treatment, respectively.

Azathioprine: one double-blind RCT reported a 27% decrease in disease activity after 12 weeks.

Infliximab: one small uncontrolled study reported a benefit of 50% or more in 2 out of 9 patients.

Chinese herbal medicines: 3 double-blind RCTs reported conflicting results, with 2 poor-quality studies reporting beneficial results and the third study reporting no difference between treatment and placebo.

Adverse events.
Most studies either did not report on serious adverse events, or reported that no serious adverse events occurred. Reported adverse events included abdominal pain, herpes simplex infection, acute cholecystitis, hypertension, haematurea, increased serum creatinine, serum sickle-like illness and serious infusion reaction. The proportion of patients withdrawing due to adverse events ranged from 0 to 10%.

Authors’ conclusions
Evidence showed cyclosporin to be consistently effective. It is recommended as the first option for patients with refractory atopic eczema. Insufficient evidence was available for the other potential treatments.

CRD commentary
The authors addressed a clear question, with inclusion criteria defined for the participants, intervention and study...
design. The search was limited, making publication bias a possibility, but the sources were relevant. In addition, since it is unclear whether language restrictions were applied, language bias cannot be ruled out. Each stage of the review was conducted in duplicate, thereby reducing the potential for error and bias. The decision to undertake a narrative synthesis seems appropriate given the clinical heterogeneity between the studies. The review had a number of limitations, particularly relating to the available evidence, which the authors acknowledged. This was a well-conducted review and the conclusions are likely to be reliable.

**Implications of the review for practice and research**
Practice: The authors recommended cyclosporin as the first option for patients with refractory atopic eczema.

Research: The authors stated that comparative studies, with standardised outcome measures including remission maintenance, are required. Long-term outcomes, particularly safety profiles, need evaluation.

**Funding**
Not stated.

**Bibliographic details**

**PubMedID**
17340015

**DOI**
10.2340/00015555-0207

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Clinical Trials as Topic; Dermatitis, Atopic /drug therapy /immunology; Humans; Immunosuppressive Agents /therapeutic use; Prospective Studies

**AccessionNumber**
12007001278

**Date bibliographic record published**
08/11/2007

**Date abstract record published**
01/09/2008

**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.