Cyclosporin in the treatment of patients with atopic eczema: a systematic review and meta-analysis

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CRD summary
This review found that short-term use of cyclosporin can decrease the severity of atopic eczema in patients whose condition cannot be adequately controlled with conventional therapies. Limitations in the analysis mean that these conclusions should be interpreted with some degree of caution.

Authors' objectives
To determine the effectiveness of systemic cyclosporin for severe atopic eczema (AE).

Searching
MEDLINE, the Cochrane Skin Group’s Specialised Register and the Cochrane CENTRAL Register were searched from inception to August 2005, without any language restrictions, for published studies; the search terms were reported. The reference lists of retrieved articles were screened for additional relevant studies. Only full-text articles were included.

Study selection
Study designs of evaluations included in the review
Studies that included at least 5 patients were eligible for inclusion.

Specific interventions included in the review
Studies of cyclosporin were eligible for inclusion. The comparator treatments were topical tacrolimus 0.1%, placebo or different cyclosporin dosing regimens. One study compared continuous to intermittent treatment. The duration of treatment ranged from 6 weeks to 12 months.

Participants included in the review
Studies of patients with AE were eligible for inclusion. The included patients were aged from 2 to 70 years. Three studies were conducted in children, eight in adults, and four in adults and children. All of the studies were conducted in Europe. Criteria for the severity of AE in the included studies were refractory to or inadequately controlled by topical steroids or conventional therapies; some included objective score-oriented disability in addition to these criteria.

Outcomes assessed in the review
Studies that reported clinical end points were eligible for inclusion. The primary outcome was the change in mean clinical severity from baseline to 6 to 8 weeks following treatment. Adverse events and relapse rates were also considered in the review.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for relevance. Any disagreements were resolved through discussion.

Assessment of study quality
Two reviewers independently assessed study quality according to the following criteria: adequate case definition; definition of eligibility criteria; description of study population; randomisation and blinding; use of validated outcomes; adequate follow-up; conduct of intention-to-treat analysis. Studies were considered to be of a good quality if they fulfilled at least 6 criteria, of a moderate quality if they fulfilled 4 or 5 criteria, and of a poor quality if they fulfilled less than 4 criteria. Any disagreements were resolved through discussion.

Data extraction
Two reviewers independently extracted the data using a standardised data extraction form. Any disagreements were resolved through discussion. The data were extracted as the mean relative change in clinical severity from baseline. If
this was not reported in the paper, it was derived from the absolute severity scores at baseline and follow-up. For randomised controlled trials (RCTs), only the active treatment groups were considered in the primary analysis, although data were also extracted for the comparator groups. For crossover RCTs, only the study period prior to treatment was considered. Data on the frequency of adverse events were extracted as events per month of treatment. Chronic events were only counted once. Data on the frequency of withdrawals resulting from adverse events were also extracted.

**Methods of synthesis**

**How were the studies combined?**

Studies that used a composite score of clinical severity, including intensity and extent of AE, and from which it was possible to calculate relative changes in severity were included in the quantitative analysis. Relative changes in severity were pooled using the random-effects model of DerSimonian and Laird. Publication bias was investigated by plotting and regressing treatment effect on sample size.

**How were differences between studies investigated?**

Heterogeneity was assessed using the chi-squared test and through the visual assessment of forest plots. The influence of each individual study on the pooled estimate was investigated in a sensitivity analysis. Heterogeneity was investigated through meta-regression, including the following covariates: study type, inclusion of children, study quality, concomitant treatment and follow-up rate. The existence of a dose-response relationship was investigated by considering studies that reported on the mean relative effectiveness after 2 weeks of cyclosporin treatment. The studies were stratified by initial cyclosporin dose (<3 mg/kg body weight versus >3 mg/kg body weight).

**Results of the review**

Fifteen studies (602 patients) were included: 8 RCTs, including 3 crossover RCTs, and 7 uncontrolled open-label trials.

All 3 crossover RCTs and 3 of the 5 parallel-group RCTs were double-blinded. Two studies were considered to be of a good quality, five moderate and eight poor.

All studies reported a decrease in mean severity of AE of between 39% and 90% following 6 to 8 weeks of cyclosporin treatment. The pooled improvement in mean severity of AE from baseline to 6 to 8 weeks was 53% (95% confidence interval, CI: 47, 59; 12 studies: 5 controlled and 6 uncontrolled). There was strong evidence of heterogeneity (p=0.01). The meta-regression found no effect of study type (p=0.63), inclusion of children (p=0.91), study quality (p=0.76) or concomitant topical treatment with glucocorticosteroids (p=0.82) on the improvement in AE severity. The improvement in severity of AE from baseline to 2 weeks in those treated with a high cyclosporin dose (4 to 5 mg/kg body weight) was 40% (95% CI: 29, 51; based on 8 studies). There was a smaller improvement among those treated with the lower dose (2.5 to 3 mg/kg body weight): 22% (95% CI: 8, 36; based on 4 studies).

Three studies reported on relapse rates: around 50% of patients relapsed within 2 weeks, increasing to around 80% within 6 weeks.

In terms of adverse events, an increase in creatinine of more than 30% occurred in up to 11% of patient-months of cyclosporin treatment. Newly diagnosed infections were found in up to 6%, infections in up to 12%, and gastrointestinal symptoms in up to 40% of patient-months of treatment. Headache and parasthesia were also commonly reported. Up to 5% of patients withdrew per patient-month of treatment. Adverse events were more common in adults than in children and were more likely at higher doses of cyclosporin.

There was some evidence of publication bias (p=0.013).

**Authors’ conclusions**

Short-term use of cyclosporin can decrease the severity of AE in patients whose condition cannot be adequately controlled with conventional therapies. There was some evidence of publication bias, so these findings should be interpreted with caution. The effectiveness of cyclosporin is similar in adults and children; tolerability may be better in children. There is currently insufficient data to evaluate the long-term effectiveness and safety of cyclosporin in patients with AE.
CRD commentary
The review addressed a focused question that was supported by clearly defined inclusion criteria. The literature search was acceptable, but searching additional databases might have identified further relevant studies. The review was limited to full-length published articles, thus, as the authors acknowledged, there is a possibility of publication bias. Appropriate steps were taken to minimise bias and error at all stages of the review process. A detailed quality assessment was conducted and the results of this were presented and considered in the synthesis of the results.

Full details of the studies were tabulated clearly. A detailed analysis, including both qualitative and quantitative components, was carried out. A limitation of the quantitative analysis was that it only considered the cyclosporin treatment arms from the RCTs, thus ignoring the randomisation. Further analysis focusing more on the RCTs, including the comparator groups, may have been more informative, although this was discussed briefly in the qualitative analysis. In addition, differences between the comparator treatments may have made synthesis across studies impractical. Overall, the authors’ conclusions are supported by the information presented, but limitations in the analysis mean that they should be interpreted with some caution.

Implications of the review for practice and research
Practice: The authors stated that close long-term monitoring is required in all patients treated with cyclosporine, and that the findings of this review should help clinicians and patients to make informed decisions regarding the treatment of severe and refractory AE.

Research: The authors stated that further research with intention-to-treat analysis is required to investigate the long-term effectiveness and safety of cyclosporin in patients with AE.

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