

Topical cyclosporine for atopic keratoconjunctivitis (Review)

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Topical cyclosporine for atopic keratoconjunctivitis

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ABSTRACT

Background

Atopic keratoconjunctivitis (AKC) is a chronic ocular surface non-infectious inflammatory condition that atopic dermatitis patients may suffer at any time point in the course of their dermatologic disease and is independent of its degree of severity. AKC is usually not self resolving and it poses a higher risk of corneal injuries and severe sequelae. Management of AKC should prevent or treat corneal damage. Although topical corticosteroids remain the standard treatment for patients with AKC, prolonged use may lead to complications. Topical cyclosporine A (CsA) may improve AKC signs and symptoms, and be used as a corticosteroid sparing agent.

Objectives

To determine the efficacy and gather evidence on safety from randomised controlled trials (RCTs) of topical CsA in patients with AKC.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2012, Issue 6), MEDLINE (January 1946 to July 2012), EMBASE (January 1980 to July 2012), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to July 2012), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (January 1937 to July 2012), OpenGrey (System for Information on Grey Literature in Europe) (www.opengrey.eu/), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov), the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictcp/search/en), the IFPMA Clinical Trials Portal (http://clinicaltrials.ifpma.org/no_cache/en/myportal/index.htm) and Web of Science Conference Proceedings Citation Index- Science (CPCI-S). We did not use any date or language restrictions in the electronic searches for trials. The electronic databases were last searched on 9 July 2012. We also handsearched the following conference proceedings: American Academy of Ophthalmology, Association for Research in Vision and Ophthalmology, International Council of Ophthalmology and Societas Ophthalmologica Europaea from 2005 to July 2011.

Selection criteria

We included randomised controlled trials only.

Data collection and analysis

Two review authors independently extracted data. Due to the small number of studies and the diversity of outcome measures, interventions and participants, we presented results narratively.

Main results

We found three RCTs with a total of 58 participants that were eligible for inclusion. There was significant variability between the trials in interventions, methodology and outcome measures and therefore we did not perform meta-analysis.

One study reported on the use of 2% CsA in maize oil and two on the use of a commercial emulsion of 0.05% CsA. Of these three studies, one showed a beneficial effect of topical CsA in controlling signs and symptoms of AKC, one in controlling signs of AKC and one did not show evidence of an improvement. Only two studies analysed the effect of topical CsA in reducing topical steroid use; one showed a significant reduction in topical steroid use with CsA, but the other did not show evidence of this improvement. No serious adverse events were reported in the trials.

Authors' conclusions

This systematic review highlights the relative scarcity of controlled clinical trials assessing the efficacy of topical CsA therapy in AKC and suggests that evidence on the efficacy and safety of topical CsA treatment in patients with CsA remains limited. However, the data suggest that topical CsA may provide clinical and symptomatic relief in AKC and may help to reduce topical steroid use in patients with steroid-dependent or steroid-resistant AKC. No serious adverse events were reported. Reported adverse events in patients treated with topical CsA include intense stinging and eyelid skin maceration. One patient in the placebo group developed a severe allergic response to maize antigens. However, the total number of patients in the trials was too small to assess the safety of this treatment.

Additional well-designed and powered RCTs of topical CsA in AKC are needed. Ideal study designs should include adequate randomisation and concealment of allocation; masking of participants, personnel and outcome assessors; adequate follow-up periods and minimisation of attrition bias; and comparison groups with similar clinical and epidemiologic characteristics. Samples should be large enough to provide sufficient statistical power to assess the safety of CsA and to detect clinically relevant treatment effect sizes of the primary outcomes. Analyses should be appropriate to the study's design and outcome measures. Moreover, standardisation of outcome measures and follow-up periods across studies would be beneficial to maximise study comparability.

PLAIN LANGUAGE SUMMARY

Topical treatment with cyclosporine A eyedrops for inflammation of the surface of the eye

Atopic keratoconjunctivitis (AKC) is an inflammatory disorder of the ocular surface that can be suffered by 67.5% of atopic dermatitis patients. It is a chronic condition that often requires long-term treatment in order to avoid ocular complications that may lead to visual loss. This condition is frequently treated with steroid eyedrops, but long-term treatment with such drugs can produce severe side effects, such as the development of cataracts, glaucoma or severe infections of the eye. Topical treatment with cyclosporine A (CsA) eyedrops may be useful to control signs and symptoms of atopic keratoconjunctivitis, and to reduce the need for steroid eyedrops.

Three eligible studies with a total of 58 participants were included in this review. One study was conducted in the UK, one in Australia and one had multicentre sites in the UK and US. These studies varied significantly in interventions, methodology and reported outcomes. One study used 2% CsA in maize oil, and two used a commercial emulsion of 0.05% CsA. Of these three studies, two showed a beneficial effect of topical CsA in controlling signs of AKC, and one did not find evidence of this improvement. One study showed a beneficial effect of topical CsA in controlling symptoms of AKC, but the other two did not find evidence of this improvement. Only two studies analysed the effect of topical CsA in reducing topical steroid use; one showed a significant reduction in topical steroid use with CsA, but the other could not find evidence of this improvement. The data suggest that topical CsA may provide clinical and symptomatic relief in AKC and may help to reduce topical steroid use in patients with steroid-dependent or steroid-resistant AKC. Moreover, no serious adverse events were detected. However, this review has identified a need for more randomised controlled trials to provide further reliable evidence on the efficacy and safety of topical treatment with CsA eyedrops for patients with AKC. These trials should include larger samples of patients with AKC, and their follow-up periods should be long enough to draw conclusions on the long-term efficacy and safety of this therapy.

BACKGROUND

Description of the condition

Approximately 2% to 5% of general practice consultations are related to the eye (Dart 1986; McCormick 1995; McDonnell 1988). Allergic keratoconjunctivitis is one of the most frequent eye disorders, affecting up to 18% of people in some urban populations such as Mexico Distrito Federal (López Pérez 2009). This disease may present with local signs and symptoms, such as red eye, itching or tearing (Ono 2005). Atopic keratoconjunctivitis (AKC) is a severe form of allergic keratoconjunctivitis that is usually not self resolving and it poses a higher risk of corneal injuries and severe sequelae (Power 1998). Three per cent of the population has atopic dermatitis and up to 67.5% of these patients have ocular disease, usually AKC (Dogru 1999).

Unlike vernal keratoconjunctivitis, there is no universally agreed case definition for AKC. AKC has been defined as a chronic ocular surface non-infectious inflammatory condition with the following clinical characteristics (Calonge 2007; Guglielmetti 2010):

- always associated with other atopic conditions (typically atopic dermatitis, periocular eczema or asthma);
- occurring at any time point in the course of the associated atopic disease and independent of its degree of severity;
- evidence of corneal involvement at some time in the course of the disease.

Itching is the most prevalent symptom; other symptoms include watering, mucous discharge, redness, blurring of vision, photophobia and pain. Signs involve alterations to the lids, such as eczema, blepharitis, trichiasis and punctual ectropion. Conjunctival involvement is also frequent, with subepithelial fibrosis, giant papillae, symblepharon (adhesion of the eye lids to the eyeball) and follicles. Corneal damage may be present in AKC and can be sight-threatening; it includes superficial punctate keratitis, present in 100% of patients; neovascularisation in 64.9%; persistent epithelial defects in 10.8%; and filamentary keratitis in 2.7% of cases (Tuft 1991). Management of AKC should prevent or treat such corneal damage. Whenever therapeutic strategies fail to do so, AKC patients may develop corneal scarring, corneal neovascularisation or irregular astigmatisms which compromise their visual acuity (Power 1998). Other anterior segment complications are keratoconus and cataract (Foster 1990; Tuft 1991). Posterior segment complications, such as atopic retinal detachment, have also been reported, mostly in atopic patients of Asian descent (Yoneda 1995).

Topical corticosteroids remain the standard treatment for patients with AKC, as their use produces a rapid relief of the symptoms and some signs. Nevertheless, the prolonged use of this therapy may lead to a wide range of complications, such as secondary glaucoma, cataracts or increased susceptibility to infection, including herpes simplex keratitis (Bonini 2000).

Description of the intervention

Some studies have suggested that topical cyclosporine A (CsA) at concentrations ranging from 0.05% to 2% has been useful in treating severe allergic ocular diseases, including AKC (Ebihara 2009; Hingorani 1998; Nochez 2009; Ozcan 2007). The treatment consists of the instillation of an eyedrop of CsA two (Nochez 2009) to four (Ebihara 2009) times daily, in order to achieve a sustained control of the inflammation. AKC is a chronic disease so long-term immunomodulatory therapy is the rule. Recurrence of signs and symptoms is frequent after discontinuing treatment. Immunomodulatory treatment should be gradually tapered when symptoms are alleviated. If the remission period becomes long, control can be continued with a mast cell stabiliser or antihistamine eyedrop only (Takamura 2011). Studies have shown that the treatment may be useful for up to six months (Ebihara 2009), but its efficacy is unclear for longer treatments. Daily cost of the treatment with a commercial formulation of 0.05% CsA (Restasis, Allergan) has been calculated to be USD 3.50 (United States Dollars) and its yearly cost, USD 1276 (Brown 2009). It has been found to be cost-effective in other ocular surface disorders such as dry eye syndrome (Brown 2009).

There are different formulations of CsA used and reported in various studies, which affect the tolerability of the medication:

- 0.05% CsA (Restasis, Allergan) is an emulsion which is well tolerated but very weak.
- 2% CsA in maize oil is manufactured at compounding pharmacies. It frequently causes stinging, so it is often not well tolerated.
- 0.2% cyclosporine ointment (Optimmune) is obtainable in the UK. Although it is marketed as a veterinary preparation for use in dogs, it is used in patients at some hospitals. It is slightly better tolerated than the 2% maize oil drops.
- 1% CsA in artificial tears can be prepared by hospital pharmacies.

Lack of stability of higher concentrations of cyclosporin in aqueous emulsion is stated as the reason why it is not available commercially in a concentration higher than 0.05%.

Restasis is not easily available in Europe and other countries. In Australia, the prescription of Restasis for AKC requires special authority (government) approval. Lack of availability or difficulty with obtaining topical CsA, along with the rarity of AKC, may explain why there are few studies evaluating the efficacy of topical CsA.

How the intervention might work

AKC is caused by the infiltration of T-cells in the conjunctival tissues (Offiah 2009). An increased production of interleukin-2 (IL2) in CD4+ T-cells has been associated with the abnormal cell response observed in AKC (Leonardi 2000).

Cyclosporine A acts as an immunomodulator, decreasing the replication of CD4+ T-cells by inhibiting the expression of the IL2 receptor. It has also shown some activity on eosinophils and mast cells, which may be important in allergic inflammation (Friedlander 1988; Hingorani 1999; Whitcup 1996).

As CsA down-regulates the expression of the IL2 receptor in CD4+ T-cells, it may represent a useful option in the treatment of AKC. In fact, some clinical trials have shown topical CsA to be useful in the treatment of AKC (Akpek 2004; Hingorani 1998) and other severe allergic eye disorders like vernal keratoconjunctivitis (Kiliç 2006; Spadavecchia 2006).

Why it is important to do this review

As stated above, corticosteroid eyedrops provide fast relief for ocular allergy signs and symptoms. However, AKC is a severe and chronic form of ocular allergy and 70% of patients treated with either oral antihistamines, topical mast cell stabilisers or intermittent corticosteroid eyedrops develop significant keratopathy (Power 1998), in spite of the use of these treatments.

Furthermore, long-term use of topical steroids is associated with known adverse effects such as cataracts or high intraocular pressure. Delayed corneal wound healing is also associated with the use of steroid drops and may increase the risk of developing an infectious keratitis (Barba 2000).

Some randomised clinical trials have found that topical CsA may improve AKC signs and symptoms, even in severe cases refractory to topical steroids (Akpek 2004; Hingorani 1998), and that this treatment may be an effective and safe corticosteroid sparing agent in AKC (Hingorani 1998). Other randomised clinical trials have failed to show these benefits (Daniell 2006). Nevertheless, AKC is a severe and rare form of ocular allergy. This may explain the small number of trials studying the effectiveness of topical CsA in this disease (Chambless 2004). Although most of these trials point towards the efficacy of topical CsA in this disease, the sample size used was usually small, and there was heterogeneity in the reported results (Akpek 2004; Daniell 2006; Hingorani 1998). A systematic review is therefore needed, in order to better understand the efficacy and safety of topical CsA therapy for AKC.

OBJECTIVES

To determine the efficacy and gather evidence on safety from randomised controlled trials (RCTs) of topical cyclosporine A in patients with atopic keratoconjunctivitis.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs only. We excluded trials in which one eye was treated with topical CsA and compared to the other eye (because it may have a systemic effect and it will not be possible to measure relevant outcomes, such as impact on quality of life). However, if we did find these study designs, we planned to include them in the sensitivity analysis, in order to determine the impact of their exclusion in the results of the meta-analysis (see 'Sensitivity analysis').

Types of participants

We included trials with participants of any age who had a clinical diagnosis of AKC of any duration.

Types of interventions

This review included trials in which any concentration of topical CsA, alone or combined with other treatments, was compared to no treatment, placebo or any other intervention (such as eosinophil stabilising agents or antihistamines). We considered studies using CsA combined with other treatments as eligible only if the specific effects of CsA could be addressed, that is, the use of CsA was the only difference between the intervention and control arms. This review did not include studies comparing different concentrations or routes of administration of CsA.

Types of outcome measures

Primary outcomes

- Symptoms improvement (reported by the participant), such as itching, tearing, discomfort, mucous discharge, photophobia, foreign body sensation or pain, at the end of the follow-up period. We admitted any type of data, provided that the outcome was measured with a reproducible scale, described in the methods section of the trial.

Secondary outcomes

- Topical steroid use after three months of treatment (continuous data, if possible).
- Clinical signs (assessed by the clinician), such as hyperaemia, swelling, papillae and giant papillae for the tarsal conjunctiva, hyperaemia and oedema for the bulbar conjunctiva, or corneal involvement (e.g. epithelial disease, opacity, stromal thinning, neovascularisation) at the end of the follow-up period. We considered any type of data.
- Adverse effects (see 'Glossary'; Table 1), particularly malignancy (dichotomous data). If a variety of adverse effects

were detected, in order to address adverse effects in a more organised manner, we planned to narrow down the broad focus into all adverse effects that either the patient or the clinician considered to be serious (Loke 2011). We tabulated and described other adverse effects related to CsA therapy reported in the included studies.

- Recurrence of the disease. We admitted any method of measuring the frequency of this outcome, for example, time to recurrence, rates of recurrences or symptom-free duration.
- Quality of life measures (measured with a validated tool).

For symptoms and clinical signs, as there is no standard scale for measuring symptomatic or clinical relief, we admitted any method of measurement that was presented in the trials and any metric for quantifying these outcomes, such as total ocular symptom scores or individual ocular symptoms. Clinician assessed improvement should be preferably ascertained using slit-lamp examination.

In general, there was no restriction on the length of follow-up in the trials. However, when assessing the recurrence of the disease, only those studies with at least one-month follow-up were eligible for analysis. If no study fulfilled this criteria, we considered the inclusion of studies with a shorter follow-up for the assessment of the recurrence of the disease.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 6, part of *The Cochrane Library*. www.thecochranelibrary.com (accessed 9 July 2012), MEDLINE (January 1946 to July 2012), EMBASE (January 1980 to July 2012), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to July 2012), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (January 1937 to July 2012), OpenGrey (System for Information on Grey Literature in Europe) (www.opengrey.eu/), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov), the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictcp/search/en) the IFPMA Clinical Trials Portal (http://clinicaltrials.ifpma.org/no_cache/en/myportal/index.htm) and Web of Science Conference Proceedings Citation Index- Science (CPCI-S). We did not use any date or language restrictions in the electronic searches for trials. The electronic databases were last searched on 9 July 2012. See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), LILACS (Appendix 4), CINAHL (Appendix 5), OpenGrey, (Appendix 6) mRCT (Appendix 7), ClinicalTrials.gov (Appendix 8), ICTRP (Appendix 9), IFPMA Clinical Trials Portal (Appendix 10) and CPCI-S (Appendix 11).

Searching other resources

We handsearched the following conference proceedings from 2005 to 8 July 2011:

- American Academy of Ophthalmology;
- Association for Research in Vision and Ophthalmology;
- International Council of Ophthalmology; and
- Societas Ophthalmologica Europaea.

On 7 July 2011 we checked the reference lists of all included studies to identify further potentially relevant studies and searched the ISI Science Citation Index to identify articles that have cited the studies that are included in the review.

On 5 July 2011 we contacted experts who are active in the field and primary authors of included studies and relevant reviews to identify further published or non-published studies eligible for inclusion. We also contacted the following pharmaceutical companies for unpublished trials: Allergan Inc., F. Hoffmann-La Roche Ltd., Novartis International AG.

Data collection and analysis

Selection of studies

Two review authors independently checked the titles and abstracts resulting from the searches. Using a form developed to document the process, we divided the titles and abstracts into three groups: 'exclude', 'unsure' or 'include'. We marked all those titles classified as 'unsure' or 'include' and retrieved their full-text versions for definitive assessment of eligibility. At this stage, we only excluded those papers classified by both review authors as 'exclude'.

We planned to obtain further information about any trial that had been published only as an abstract. If a full report was not available, and the information could not be obtained from the authors, we excluded the abstract. If relevant, we reported the trial characteristics in the '[Characteristics of excluded studies](#)'.

Using another form developed to document the process, we classified the full-text copies into three groups ('exclude', 'unsure' or 'include'), according to pre-stated criteria (see '[Criteria for considering studies for this review](#)'). We resolved any disagreements through discussion. If we could not reach a consensus, we consulted a third review author (JLA) or the editorial base of the Cochrane Eyes and Vision Group (CEVG). If relevant, we documented the disagreements. If there was insufficient information to determine the eligibility of a study (full text classified as 'unsure'), we asked the authors for clarification. We detailed in '[Characteristics of excluded studies](#)' all relevant studies labelled as 'excluded' after the assessment of the full text, with the reasons for their exclusion.

Review authors were not masked to trial results or publication details during the selection of the studies.

Data extraction and management

Two review authors independently performed the extraction of data from trial reports, using pre-designed data extraction forms. We extracted information about the methods used in the trial reports and the following details:

- participants (age, gender, setting, number in each group, comparability at baseline, etc);
- interventions (dosage, schedule, compliance, comparison group, timing, etc);
- outcomes (primary and secondary outcomes, adverse effects);
- results;
- risk of bias;
- other information (such as funding).

The review authors resolved discrepancies on the data extraction through discussion. If there was no consensus, a third review author (JLA) or the editorial base of the CEVG settled the discrepancies.

One review author entered the data in to RevMan (RevMan 2011) and another author manually checked the entered data.

Assessment of risk of bias in included studies

We assessed the risk of bias of each included study, according to the criteria of The Cochrane Collaboration's tool for assessing risk of bias, as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a) (see 'Differences between protocol and review'). We considered the following domains.

1. Random sequence generation (selection bias).
2. Allocation concealment (selection bias).
3. Blinding (masking) for participants and personnel (performance bias).
4. Blinding (masking) of outcome assessment (detection bias)*.

5. Incomplete outcome data (attrition bias).
6. Selective outcome reporting (reporting bias).

* We made assessments for each class of outcomes (patient reported outcomes and non-patient reported outcomes)

Two review authors (JJGL and RML), not masked to the study details, independently labelled each domain as 'low risk', 'high risk' or 'unclear risk' of bias.

We resolved disagreements by discussion and consensus and, if necessary, with the involvement of a third author (JLA) or the CEVG editorial base. We reported relevant discrepancies in the assessments.

We summarised the overall risk of bias for each outcome (or class of similar outcomes) in two different manners (Higgins 2011a):

- within each study across domains: we defined each outcome (or class of outcomes) as having a 'low risk of bias' only if it met all the domains; as 'high risk of bias' if it demonstrated high risk of bias for one or more of them; or as 'unclear risk of bias' if it

demonstrated unclear risk of bias for at least one domain without any of them described as 'high risk of bias'.

- across studies: we defined each outcome (or class of outcomes) as having a 'low risk of bias' if most information was from studies at low risk of bias; as 'high risk of bias' if the proportion of information from studies at high risk of bias was sufficient to affect the interpretation of the results; or as 'unclear risk of bias' if most information was from studies at low or unclear risk of bias.

We tried to obtain the information from the trial reports. If any domain was graded as 'unclear', JJGL wrote to the authors for clarification. If clarification was not obtained in less than 30 days, we assigned a grading to the outcome, based on the consensus between the review authors.

Finally, we incorporated the results of the 'Risk of bias' assessment into the review through systematic narrative description and commentary. We planned to explore the effect of the risk of bias in the meta-analysis (see 'Sensitivity analysis').

Measures of treatment effect

We analysed data using guidance from Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We reported study results with their associated 95% confidence intervals (CI).

Measures of treatment effect depended on the types of data presented in the individual studies:

- for dichotomous data, we reported the odds ratio (OR);
- for counts of rare events and rates we reported the OR;
- for counts of more common events we reported in the same way as continuous outcome data (see below);
- for continuous data we used the mean difference (MD) with standard deviations (SD). If different scales are used to measure continuous outcomes, we calculated a standardised mean difference (SMD);
- for time-to-event data, we reported the hazard ratio (HR), if possible.

Unit of analysis issues

Atopic keratoconjunctivitis usually presents with symptoms in both eyes. For this reason, analysis of these studies can be difficult: people have two eyes and different studies deal with this in different ways. Moreover, it is not always evident from a trial report whether eyes or participants are being analysed and review authors may need to contact study authors in order to clarify what has been done (Cochrane Eyes and Vision Group module 2011).

We did not assume that two eyes in an individual are independent data. We determined whether the data were correctly analysed by looking for potential 'unit of analysis errors' (Table 1). Comparisons that randomise participants, but the unit of analysis is the eye, do not account for clustering during analysis and have 'unit of

analysis errors', resulting in potential artificially extreme P values and over narrow confidence intervals (Deeks 2011; Ukoumunne 1999).

We considered data to have been analysed correctly if either:

- the analysis was conducted at the same level as the allocation; or
- the analysis was conducted at the level of the eye, but appropriate statistical correction for the clustering was performed.

If we determined the data analysis to have been performed incorrectly, we extracted the data and performed analyses using Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b) as a guide.

Dealing with missing data

We described missing outcomes of the included studies by reporting proportions of randomised participants for whom no outcome data were obtained (with reasons) by outcome and by randomised group. We addressed the potential impact of the missing outcomes on the results of the included studies in the assessment of risk of bias and we described its impact on the findings of the review in the discussion section.

For all outcomes, we tried to carry out analyses on an intention-to-treat (ITT) basis (Table 1). We contacted the primary authors to request missing data and for clarification of issues. If, finally, this information could not be obtained, we performed an 'available case analysis' (Table 1). If possible, we 're-included' avoidable exclusions done by the authors of the included studies (Higgins 2011b, section 16.2). We planned to perform sensitivity analyses to assess how sensitive results are to changes in the assumptions made in the 'available case analysis' (see 'Sensitivity analysis'). We planned to consider variation in the degree of missing data across studies as a potential source of heterogeneity by performing a subgroup analysis (see 'Subgroup analysis and investigation of heterogeneity').

Assessment of heterogeneity

We planned to check for heterogeneity by examining:

1. the characteristics of the studies;
2. the forest plot of results of the studies. We displayed graphically the results of the studies and we will check the symmetry of their results visually;
3. the results of the χ^2 test for statistical heterogeneity (a significant P value will be considered for $P < 0.10$);
4. the results of the I^2 statistic for the quantification of the heterogeneity. The I^2 statistic describes the percentage total variation across studies that is due to heterogeneity rather than chance. We judged the importance of the observed value of I^2 depending on the magnitude and direction of effects and the strength of evidence for heterogeneity (moderate to high heterogeneity was defined as $I^2 \geq 50\%$) (Deeks 2011).

Assessment of reporting biases

We attempted to minimise reporting bias:

- by including both published and unpublished studies;
- in the case of studies with multiple publications, by extracting data on outcomes from the publication with the most mature data;
- by not excluding studies solely on the basis of the publication language.

We had planned to create funnel plots for the assessment of reporting bias, provided 10 or more studies were included in the review. However, there were not sufficient studies to do so. Details of the planned assessment of reporting bias in future updates of this review are described in Appendix 12.

Data synthesis

We had planned to meta-analyse data from included studies, but because of the small number of studies and the diversity of outcome measures (outcomes were measured using different scales and different signs and symptoms were evaluated in each study), interventions (0.05% and 2% CsA were used in different studies; vehicle or artificial tears were used as control in different studies) and participants (one study also included patients with vernal keratoconjunctivitis) we decided to present the results narratively. Details of planned meta-analysis in future updates of this review are described in Appendix 12.

Subgroup analysis and investigation of heterogeneity

We had planned to undertake subgroup analysis based on the CsA concentration used ($< 0.1\%$ versus $> 0.1\%$). However, there were not sufficient studies to do so. In future updates of this review we will try to explain heterogeneity by considering this factor for subgroup analysis.

Sensitivity analysis

There were not enough studies to undertake sensitivity analyses. Details of the planned sensitivity analyses in future updates of this review are described in Appendix 12.

RESULTS

Description of studies

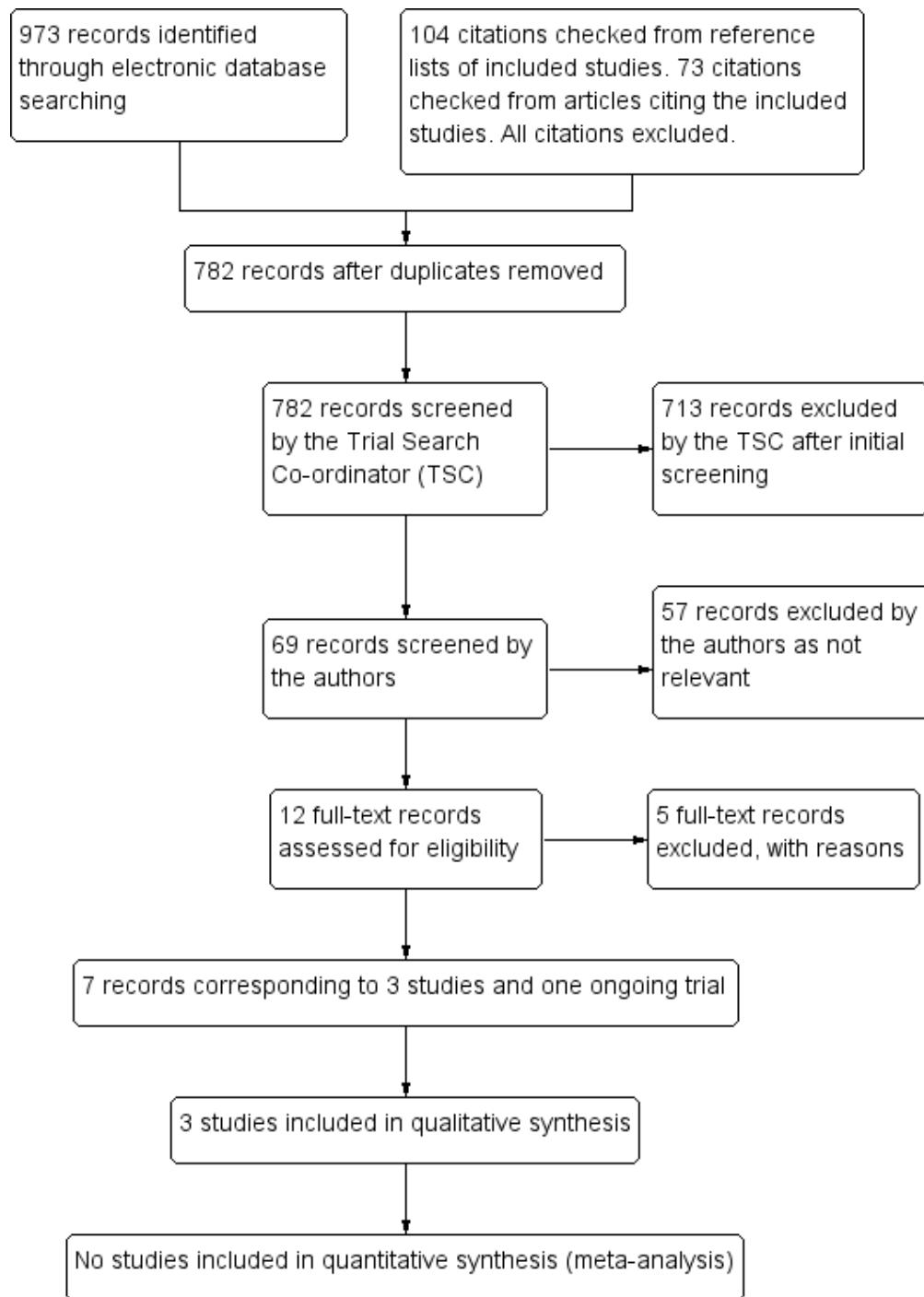
See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

See: 'Characteristics of included studies'; 'Characteristics of excluded studies'; 'Characteristics of ongoing studies'.

Results of the search

The electronic searches retrieved a total of 782 records ([Figure 1](#)). The Trials Search Co-ordinator scanned the search results and removed 713 records as they were not relevant to the scope of the review. We assessed the remaining 69 records and obtained the full text of 12 records for detailed evaluation. After reading the full texts or contacting the authors, we considered that five reports did not meet the inclusion criteria. The primary reasons for their exclusion were as follows: comparing different concentrations of topical CsA ([Velasco 2003](#)), not including patients with AKC ([NCT00833495](#); [NCT01120132](#)), not being RCTs ([Bellini 2008](#); [Tomida 2002](#)). The remaining seven reports, corresponding to four studies (one is still ongoing), were included in the review. However, we combined no data for any of the review outcomes for statistical analysis.

Figure 1. Results from searching for studies for inclusion in the review.



In addition we assessed 104 records from the reference lists of included studies, 73 records from articles citing the included studies and we contacted one expert. However, searching these resources and handsearching of conference proceedings provided no additional records relevant to the review.

Included studies

Three clinical trials (Akpek 2004; Daniell 2006; Hingorani 1998) with a total of 58 participants met the criteria for being included in this review. Their most relevant features are detailed in the 'Characteristics of included studies' table.

Akpek 2004 (22 participants) compared 0.05% CsA (Restasis, Allergan) to preservative-free artificial tears (Refresh Tears, Allergan) (both used one drop six times daily for the first two weeks and four times daily for the following two weeks in both eyes) in adult patients with a diagnosis of AKC (based on the criteria by Hogan (Hogan 1952)) refractory to topical corticosteroid eyedrops for at least two weeks. Participants with additional causes of ocular inflammation and those with systemic diseases other than atopic dermatitis who were taking systemic corticosteroids, antihistamines, non-steroidal anti-inflammatory drugs or immunosuppressives were excluded. Contact lens wearers were also excluded. Ten patients were randomised to receive topical CsA eyedrops and 12 to receive artificial tears. Patients were reviewed at days seven, 14, 28 and 35.

Daniell 2006 compared 0.05% CsA (Restasis, Allergan) to placebo (vehicle, Allergan) (both used one drop four times daily in both eyes) in 40 patients with a clinical diagnosis of AKC (18 patients) or vernal keratoconjunctivitis (22 patients) who were steroid-dependent. Participants were excluded if they were using systemic steroid or immunosuppressive drugs or non-steroidal anti-inflammatory medication or had associated ocular infections or coexisting ocular diseases such as corneal diseases, glaucoma or optic atrophy. If patients were using topical or systemic CsA, this medication was discontinued two weeks before the start of the trial. Patients were also excluded if they have had periocular injections of steroids or ocular surgery within a period of six months, if they were using steroid eyedrops for reasons other than allergic eye disease, or if they were pregnant or lactating mothers. Although this study also included patients with vernal keratoconjunctivitis, the authors of the study provided our review team with the data for the participants with AKC included in their trial (10 participants in the intervention group and eight participants in the control

group). Patients were reviewed at week one and then monthly for three months.

Hingorani 1998 (21 participants) compared 2% CsA in maize oil to maize oil (both used one drop four times daily in both eyes) in patients with a clinical diagnosis of AKC who had been unable to cease topical corticosteroid use despite the use of other agents. Participants were excluded if they were using systemic steroids, immunosuppressives or non-steroidal anti-inflammatory drugs; if they were using steroid eyedrops for reasons other than allergic eye disease; or if they had undergone ocular surgery in the previous six months. Twelve participants were randomised to receive topical CsA eyedrops and nine to receive placebo. Patients were reviewed at week one and then monthly for three months.

Ongoing studies

There is one study (NCT00884585) that is currently being conducted. See the 'Characteristics of ongoing studies' table for further details.

Excluded studies

We excluded the remaining studies, listed in the 'Characteristics of excluded studies' table with reasons for exclusion. Main reasons for exclusion were not being a randomised trial (Bellini 2008; Ebihara 2009; Holland 1993; Nochez 2009; Ozcan 2007; Tesse 2010; Tomida 2002), not including patients with AKC (NCT00833495; NCT01120132; Spadavecchia 2006) and comparing two different concentrations of CsA (Velasco 2003).

Risk of bias in included studies

We summarised the risk of bias of the included studies in Figure 2 ('Risk of bias' graph) and Figure 3 ('Risk of bias' summary). Figure 2 shows the percentage of studies with each of the judgements ('low risk', 'high risk', 'unclear risk' of bias) for each domain. Figure 3 presents all of the judgements in a cross-tabulation of study by domain. Regarding the domain 'Blinding (masking) of outcome assessment' we made the assessments for each class of outcomes ('patient reported outcomes' or 'non-patient reported outcomes'). On the basis of our assessment, all the outcomes were defined as having an 'unclear risk of bias', as they demonstrated unclear risk of bias for at least one domain without any of the remaining domains described as 'high risk of bias'.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

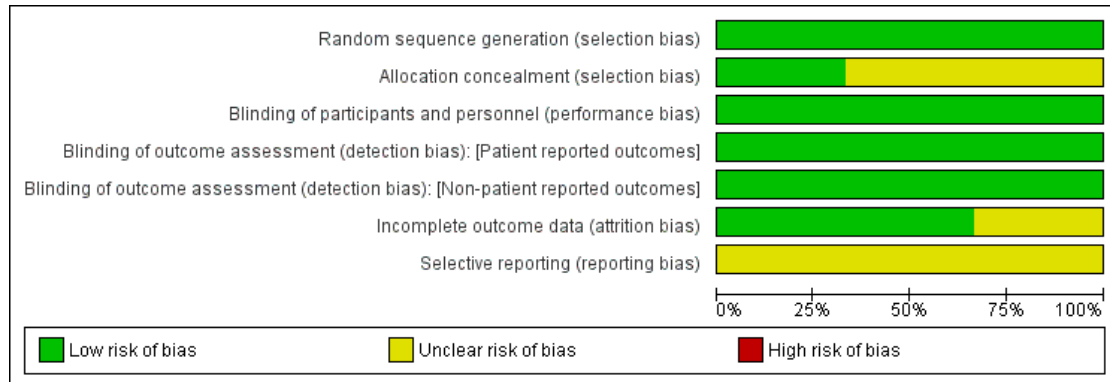


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias): [Patient reported outcomes]	Blinding of outcome assessment (detection bias): [Non-patient reported outcomes]	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Akpek 2004	+	?	+	+	+	+	?
Daniell 2006	+	?	+	+	+	?	?
Hingorani 1998	+	+	+	+	+	+	?

Allocation

Random sequence generation

We judged the sequence generation to be at low risk of bias for the three studies (Akpek 2004; Daniell 2006; Hingorani 1998); all used a computer-generated randomisation scheme.

Allocation concealment

We judged allocation concealment to be at low risk of bias for one study (Hingorani 1998), which kept the allocation coding under lock by a senior pharmacist, who was independent of the trial and who did not meet the involved patients. We considered that the allocation concealment of the remaining two trials (Akpek 2004; Daniell 2006) was at unclear risk of bias; although these reports stated that the allocation coding was “undisclosed until all patients had completed the study”, the methods for allocation concealment were not described, so there was insufficient information to permit judgement about this domain.

The patient was the unit of assignment and analysis for all studies. However, only one study (Akpek 2004) specified how the information obtained from each single patient evaluated was aggregated: “Persons were classified according to the status of the worse eye, and the worse eye was defined separately for symptoms and signs based on the composite score for each”.

Blinding

We judged masking (blinding) of participants, personnel and outcome assessors to be at low risk of bias for the three included studies (Akpek 2004; Daniell 2006; Hingorani 1998); the masking was probably effective in all the studies as both study arms used similar vials to hold the treatments, applied with the same mode, vehicle, number and schedule.

Incomplete outcome data

We judged this domain to be at low risk of bias for two studies (Akpek 2004; Hingorani 1998) and at unclear risk of bias for Daniell 2006.

Akpek 2004: 100% of the randomised participants were analysed in the intervention group (10/10) and 83.3% in the control group (10/12). An available case analysis was performed according to the original assignment group. Although missing outcome data were not balanced in numbers across study arms, we judged that plau-

sible outcomes among missing participants would not be enough to have a clinically relevant impact on observed effect size.

Hingorani 1998: there were no losses to follow-up or withdrawals and all the participants were analysed according to their original group assignment.

Daniell 2006: three of 20 participants in the CsA group (one was lost to follow-up after enrolment and two withdrew for personal reasons; two with AKC and one with vernal keratoconjunctivitis) and two of 20 in the placebo group (one was found not to meet the study criteria after randomisation and one withdrew for personal reasons; one with AKC and one with vernal keratoconjunctivitis) discontinued the follow-up. An available case analysis was performed according to the original assignment group. We considered that there was insufficient reporting of attrition/exclusions to permit judgement of ‘low risk’ or ‘high risk’ of bias.

Selective reporting

We did not have access to study protocols or other related materials, so we were unable to fully assess the risk of bias for selective outcome reporting. The published reports analysed all the outcomes that were mentioned in the methods section but there was no convincing text suggesting that these reports included all pre-specified outcomes.

Effects of interventions

Symptoms improvement

Akpek 2004 reported for each study arm the changes from baseline in the median severity scores of each symptom (three-point scale: 0, 1, 2 and 3 points; higher scores denoting increased symptoms) after a treatment period of four weeks. Median score for itching decreased from 2.0 to 1.0 in the cyclosporine A (CsA) group and from 1.5 to 1.0 in the placebo group ($P = 0.089$). Median score for tearing decreased from 2.0 to 0.5 in the CsA group and from 1.5 to 1.0 in the placebo group ($P = 0.20$). Median score for discomfort decreased from 1.5 to 0.5 in the CsA group and from 2.0 to 1.5 in the placebo group ($P = 0.14$). Median score for mucous discharge decreased from 1.5 to 0.5 in the CsA group and from 1.5 to 1.0 in the placebo group ($P = 0.13$). Median score for photophobia decreased from 0.5 to 0.0 in the CsA group and stayed at 2.0 in the placebo group ($P = 0.40$). Moreover, the median of the composite score for all the symptoms (composite range: 0 to 15, using a four-point scale for each symptom, higher scores denoting increased symptoms) was also reported, which decreased four points in the CsA group and 0.5 points in the placebo group ($P = 0.048$).

Daniell 2006 reported an initial symptom score (higher scores denoting increased symptoms reports, scale not described) of 5.9

(standard deviation (SD) 4.3) for patients receiving placebo and 6.1 (SD 4.0) for patients receiving CsA ($P = 0.9$). The final symptom score after a three-month treatment period was 2.1 (SD 2.9) for the placebo group and 2.8 (SD 3.1) for the CsA group ($P = 0.5$).

[Hingorani 1998](#) reported that there were no differences in the initial or final symptom scores (four-point scale: 0, 1, 2, 3, 4; higher scores denoting increased symptoms reports) measured by the patients or the clinicians between patients receiving CsA or placebo for three months. Initial patient-measured mean symptom score was 11.3 (standard error (SE) 1.3) in the CsA group and 10.3 (SE 1.6) in the placebo group. Initial clinician-measured mean symptom score was 10.8 (SE 1.6) in the CsA group and 9.5 (SE 2.2) in the placebo group. Final patient-measured mean symptom score was 6.2 (SE 2.0) in the CsA group and 8.5 (SE 2.0) in the placebo group. Final clinician-measured mean symptom score was 5.4 (SE 1.3) in the CsA group and 9.0 (SE 1.6) in the placebo group. Change in composite symptom score between the CsA and placebo groups was not compared.

Clinical signs

[Akpek 2004](#) reported median sign scores (for bulbar conjunctival hyperaemia, upper tarsal conjunctival papillae, punctate keratitis, corneal neovascularisation, cicatrising conjunctivitis, blepharitis and a composite sign score) for participants treated with CsA or placebo before and after a treatment period of four weeks (three-point scale: 0, 1, 2 and 3 points; higher scores denoting increased clinical sign reports). Median score for bulbar conjunctival hyperaemia decreased from 2.0 to 1.0 in the CsA group and from 1.5 to 1.0 in the placebo group ($P = 0.017$). Median score for upper tarsal conjunctival papillae decreased from 3.0 to 1.5 in the CsA group and from 2.0 to 2.0 in the placebo group ($P = 0.005$). Median score for punctate keratitis decreased from 3.0 to 0.5 in the CsA group and increased from 1.0 to 1.5 in the placebo group ($P = 0.007$). Median score for corneal neovascularisation remained 0.0 in the CsA group and increased from 0.5 to 1.0 in the placebo group ($P = 0.051$). Median score for cicatrising conjunctivitis remained 0.0 in the CsA group and 1.0 in the placebo group ($P = 0.99$). Median score for blepharitis conjunctivitis decreased from 2.5 to 1.0 in the CsA group and remained 2.0 in the placebo group ($P = 0.055$). Median change in composite sign score was 5 in the CsA group and -1 in the placebo group ($P = 0.002$).

[Daniell 2006](#) reported no significant differences between patients receiving placebo or CsA in the baseline sign score ($P = 0.7$) or the final sign score ($P = 0.6$). Higher scores denote increased clinical sign reports but the scale was not described.

[Hingorani 1998](#) reported no significant differences in the total clinical sign score or in any of the individual scores at baseline (higher scores denoting increased symptoms reports) between patients receiving CsA or placebo (four-point scale: 0, 1, 2, 3 and 4 points, for all signs but meibomian gland dysfunction, which used

a three-point scale: 0, 1, 2 and 3 points; higher scores denoting increased clinical sign reports). Initial mean total clinical sign score was 27.3 (SD 3.6) in the CsA group and 26.8 (SD 3.2) in the placebo group ($P > 0.05$). Final mean total clinical sign score was 13.3 (SD 1.8) in the CsA group and 25.2 (SD 2.9) in the placebo group ($P = 0.004$). The mean improvement in total clinical sign score was significantly greater in the CsA group (14.0, SD 3.4) than in the placebo group (1.5, SD 1.9; $P = 0.02$).

Topical steroid use after three months of treatment

In the [Daniell 2006](#) study, initial weekly steroid drop usage (drug score = number of drops per week multiplied by five for prednisolone acetate 1%, by four for dexamethasone 0.1%, by three for fluoromethalone 0.1%, by two for prednisolone phosphate 0.3%, and by one for prednisolone phosphate 0.1%) was significantly more elevated in the CsA group (99.3, SD 45.1) than in the placebo group (66.5, SD 45.9; $P = 0.05$). No significant differences were observed in the final weekly steroid drop usage between the CsA group (42.0, SD 44.7) and the placebo group (39.9, SD 45.8; $P = 0.9$). Also, the reduction in the placebo group was not significantly different from that in the CsA group ($P = 0.6$).

In the [Hingorani 1998](#) study, nine out of 12 patients using topical 2% CsA four times daily were able to cease steroid therapy; while only one of nine patients in the placebo group could discontinue steroid therapy ($P = 0.01$). Initial weekly steroid drop usage (weekly steroid drop usage score = number of drops per week multiplied by five for prednisolone acetate 1%, by four for dexamethasone 0.1%, by three for fluoromethalone 0.1%, by two for prednisolone phosphate 0.3%, and by one for prednisolone phosphate 0.1%) was significantly more elevated in the CsA group (88.1, SD 15.2) than in the placebo group (41.2, SD 7.1; $P = 0.04$). The final weekly steroid use was significantly lower in the CsA group (2.6, SD 1.4) than in the placebo group (27.7, SD 17.7; $P = 0.005$). The mean reduction was significantly greater in the CsA group (85.5, SD 14.7) than in the placebo group (13.9, SD 16.0; $P = 0.005$).

Adverse events

No serious adverse events were identified in the trials.

One patient in the placebo group complained of headaches while using medication in [Akpek 2004](#).

In [Hingorani 1998](#), blurring of vision lasting from 30 seconds to three hours after instillation was the most common adverse event, presenting in nine of nine patients in the placebo group, and in five of 12 patients in the CsA group ($P = 0.01$). Some stinging on drop instillation was observed in 12 of 12 patients in the CsA group, and in two of nine patients in the placebo group ($P = 0.0006$). Intense stinging was experienced by nine of 12 CsA patients, and one of nine placebo patients ($P = 0.01$). Other adverse events were tearing (five CsA patients and two placebo patients), increased

discharge (one CsA and one placebo patient), redness (two placebo patients) and puffiness of the lids (one CsA patient). One CsA patient developed lid skin maceration. One placebo patient had a marked allergic reaction of the lid skin and conjunctiva, due to sensitivity to maize antigens. Four placebo patients and five CsA patients were unable to tolerate the drops more than two to three times daily.

Recurrence of the disease and quality of life

None of the included studies considered these outcomes.

DISCUSSION

Summary of main results

The electronic searches identified three single randomised clinical trials of the use of topical cyclosporine A (CsA) in the treatment of atopic keratoconjunctivitis (AKC) that met our inclusion criteria. Of these, one reported on the use of 2% CsA in maize oil (Hingorani 1998), and two on the use of a commercial emulsion of 0.05% CsA (Akpek 2004; Daniell 2006). Of these three studies, one showed a beneficial effect of topical CsA in controlling signs and symptoms of AKC (Akpek 2004), a second one showed a beneficial effect in controlling signs but not symptoms (Hingorani 1998), and one failed to show this improvement (Daniell 2006). However, in Akpek 2004, sign scores were consistently higher in the CsA group than in the placebo group. Thus, this study may be overestimating the effect of topical CsA for controlling the clinical signs of AKC. Only two studies analysed the effect of topical CsA in reducing topical steroid use (Daniell 2006; Hingorani 1998); Hingorani 1998 showed a significant reduction in topical steroid use with CsA, but Daniell 2006 failed to show this improvement. Although the literature does not unequivocally validate topical CsA as an effective treatment for AKC, the combined evidence lends support to its usefulness in AKC management.

No serious adverse events were identified in the trials but evidence on the safety of topical CsA in AKC is very limited, mainly because the sample size was probably insufficient to draw conclusions on the safety of topical CsA treatment in patients with AKC.

Overall completeness and applicability of evidence

All three included studies address the main objectives of this review. Some secondary outcomes, such as recurrence of the disease and quality of life measures, are not addressed in any of the three trials. Meta-analysis of the three included studies was not possible due to significant clinical and methodological heterogeneity. As a

result, the evidence for topical CsA in the treatment of AKC is incomplete.

Nevertheless, there is a general trend across studies showing the benefit of topical CsA; only Daniell 2006 reported no improvement in signs, symptoms or topical steroid use following topical CsA treatment. It should be noted, however, that Daniell 2006 was the one included study to recruit patients with a clinical diagnosis of AKC or vernal keratoconjunctivitis. However, topical CsA has been useful in patients with vernal keratoconjunctivitis (Kiliç 2006; Spadavecchia 2006), so this alone cannot explain the different results observed in this study. Additionally, the small number of participants in the three trials has resulted in inadequate evidence.

Quality of the evidence

We judged that the sequence generation was adequate in all the included studies (Akpek 2004; Daniell 2006; Hingorani 1998). We considered the concealment of allocation to be adequate in one study (Hingorani 1998) and unclear for the remainder (Akpek 2004; Daniell 2006). The participants, personnel and outcome assessors were masked in all the studies (Akpek 2004; Daniell 2006; Hingorani 1998). We considered two studies low risk for attrition bias (Akpek 2004; Hingorani 1998) and unclear for Daniell 2006. There was insufficient information to permit judgement of risk of bias due to selective outcome reporting (Akpek 2004; Daniell 2006; Hingorani 1998).

Two studies (Akpek 2004; Daniell 2006) used an available case analysis when dealing with missing data. We could not re-include lost patients in the analysis, as these data were not available from the authors.

Variability in the tools for measuring signs and symptoms of AKC (a different scale for each study was used) and in the CsA posology (2% CsA four times daily (Hingorani 1998); 0.05% CsA six times daily (Akpek 2004); and 0.05% CsA four times daily (Daniell 2006)) makes comparisons between studies problematic and limits the interpretability of the findings.

Follow-up periods were also variable across studies (one month for Akpek 2004; three months for Daniell 2006; and multiple measures at one week, one, two and three months for Hingorani 1998, main measure not mentioned) and therefore assessing the long-term clinical effectiveness of topical CsA in the treatment of chronic AKC was not possible.

The three included studies (Akpek 2004; Daniell 2006; Hingorani 1998) used the patient as the unit of analysis. They used pooled data from both eyes in each individual. The main disadvantage of pooling or averaging results from right and left eyes is a 'loss' of information and hence a loss of efficiency, analogous to that which may occur when only a single eye from each individual is used in the analysis. Nevertheless, the amount of information 'wasted' by the pooling or averaging of findings will be less than that which occurs when only one eye is included (Newcombe 1987). It will

depend on the degree of correlation between the right and left eyes, with the greatest loss occurring when this correlation is low (Murdoch 1998). Pooling or averaging the findings from the two eyes may be appropriate in studies of risk factors which operate at the individual level, for example, a study of age and allergic conjunctivitis. It would not be appropriate for studies of factors which operate at the ocular level, for example, in studies of the impact of a topical therapy or ocular surgery. While pooling information seems to be a useful approach for presenting a clinical picture of disease in individuals, findings must be examined cautiously. If uniocular findings are given the same weight as binocular findings the results will not provide a good index of threat to vision. The use of an overall summary of ocular findings for each individual is often an inefficient use of data and will, in some circumstances, be an inappropriate use of data. Careful interpretation of the results will be required (Murdoch 1998).

Finally, the low number of participants may have not allowed the differences in the outcomes to become significant.

Potential biases in the review process

Limitations of this review are an important clinical heterogeneity of the included studies and potential publication bias. Moreover, every healthcare intervention may have unintended consequences. A systematic review should also assess these consequences, in order to achieve a balanced perspective of the effects of the intervention (Loke 2011). A rigorous systematic review of the safety of an intervention may require applying methods different to those used for efficacy outcomes. This might mean considering a variety of study designs (such as cohort studies, case-control studies or even case reports), checking additional sources of information, designing highly sensitive searches or assessing the risk of bias of the included studies with specific tools (Golder 2009; Loke 2011).

Agreements and disagreements with other studies or reviews

To the best of our knowledge, this is the first systematic review investigating the efficacy and safety of topical CsA in patients with AKC. The results of this review agree with those of large epidemiologic studies such as Ebihara 2009 (including a cohort of 594 patients), which found that 0.1% topical CsA can be effective for the treatment of AKC. However, this large epidemiologic study reported an incidence of adverse events in the AKC group of 12%.

Implications for practice

This systematic review shows a relative scarcity of controlled clinical trials assessing the efficacy of topical cyclosporine A (CsA) therapy in atopic keratoconjunctivitis (AKC) and suggests that evidence on the efficacy and safety of topical CsA treatment in patients with CsA remains limited. However, the data suggest that topical CsA may provide clinical and symptomatic relief in AKC and may help to reduce topical steroid use in patients with steroid-dependent or steroid-resistant AKC. On the other hand, no serious adverse events were identified in the trials (although the sample size of the included studies was probably insufficient to draw conclusions on the safety of topical CsA treatment in patients with AKC).

Implications for research

The major limiting factor in our ability to evaluate the effects of topical CsA in the treatment of AKC remains a scarcity of randomised clinical trials in the area. Moreover, a lack of adequate standardisation across studies with respect to study design, follow-up periods and outcomes assessment further complicates any comparisons.

AKC is a chronic disease which requires long-term treatment. Since topical CsA has shown a possible benefit for a period of at least three months (Hingorani 1998), a relatively long follow-up period (up to at least one year) should be used in order to evaluate the full therapeutic effect of topical CsA.

Signs and symptoms of patients with AKC were measured with different scales across the three trials included in this review. We suggest that future trials use a standardised method for measuring signs and symptoms of patients with AKC, such as the standardised scale proposed by the International Ocular Inflammation Society (BenEzra 2006).

Finally, the sample size from the current trials is very low. New trials should have a larger sample size, in order to be able to precisely determine the effects of topical CsA (including adverse events).

In our opinion, additional well-designed randomised controlled trials of topical CsA in AKC are needed. Ideal study designs should include adequate randomisation and concealment of allocation; masking of participants, personnel and outcome assessors; adequate follow-up periods and minimisation of attrition bias; and appropriate comparison groups. Samples should be large enough to provide sufficient statistical power to detect clinically relevant treatment effect sizes of the primary outcomes, and analyses should be appropriate to the study's design and outcome measures. Moreover, standardisation of outcome measures and follow-up periods across studies would be beneficial to maximise study comparability.

AUTHORS' CONCLUSIONS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Akpek 2004

Methods	Study design: randomised, controlled, parallel clinical trial with blinded participants, personnel and outcome assessors Period of study: not reported Sample size predetermination: not reported Unit of randomisation: patient Unit of analysis: patient (Quote: "Individuals, rather than eyes, were the unit of analysis because eyes were not examined independently, [...]. Persons were classified according to the status of the worse eye, and the worse eye was defined separately for symptoms and signs based on the composite score for each") Analysis strategy: not reported (an available case analysis according to the original group assignment was performed)
Participants	Setting: multicentre (patients attended at specialised hospitals). Patients recruited from outpatient clinic Country: United Kingdom, United States Inclusion criteria: adult patients with a clinical diagnosis of AKC and persistent symptomatology after more than 2 weeks of topical corticotherapy Exclusion criteria: other causes of ocular inflammation; systemic diseases different from atopia; systemic use of corticosteroids, immunosuppressive drugs, antihistamines or non-steroidal antiinflammatory drugs; contact lens wearers Number of subjects assessed for potential enrolment: not reported Number of randomised patients: 22 Number allocated to the intervention group: 10 participants. Number allocated to the control group: 12 participants Mean age (years): 22 to 73. Intervention group: 42.3 years. Control group: 42.9 years Gender (male/female): 59.1/40.9. Intervention group: 60/40. Control group: 58.3/41.7 Mean AKC duration (years): 12 (range: 3 to 360 months). Intervention group: 8. Control group: 12.5 Median score symptoms at baseline: Intervention group: 8. Control group: 8 Median score signs at baseline: Intervention group: 10. Control group: 10 Lost to follow-up: 1 participant in the control group Withdrawals: 1 participant in the control group Participants analysed: 20 out of 22 (91%). Intervention group = 10/10 (100%). Control group: 10/12 (83%)
Interventions	Intervention group: 0.05% CsA (Restasis, Allergan Inc., Irvine CA) 1 drop in each eye 6 times daily for 2 weeks and 4 times daily 2 more weeks Control group: artificial tear (Refresh Tears, Allergan Inc., Irvine CA) 1 drop in each eye 6 times daily for 2 weeks and 4 times daily 2 more weeks Co-interventions: while taking the test medication, patients stayed on their pre-enrolment topical therapy (corticosteroid or corticosteroid plus mast cell stabiliser) between day 0 and day 28. During days 29 to 35, no test medication was administered, but pre-enrolment medications continued

Outcomes	1. Improvement in signs measured 4 weeks after the beginning of the treatment: bulbar conjunctival hyperaemia, tarsal conjunctival papillary hypertrophy, punctate keratitis, neovascularisation of the cornea, cicatrising conjunctivitis, blepharitis 2. Improvement in symptoms measured 4 weeks after the beginning of the treatment: itching, tearing, discomfort, discharge, photophobia 3. Adverse events reported by the patients	
Notes	Funding: supported, in part, by an unrestricted research grant from Allergan Inc. Dr Schein is supported in part by a National Institutes of Health grant (no. K24EY00395) and the Burton Grossman Fund for Preventive Ophthalmology	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned, based on a predetermined randomization list generated by computer, [...]"
Allocation concealment (selection bias)	Unclear risk	Quote: "Allocation coding was undisclosed until all patients had completed the study." Comment: Insufficient information to permit judgement. The method of concealment is not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both patients and physicians were masked to the identity of the drops used for the duration of the trial. Drops were in identical single-use droppers, labelled in a masked fashion."
Blinding of outcome assessment (detection bias) [Patient reported outcomes]	Low risk	Quote: "Both patients and physicians were masked to the identity of the drops used for the duration of the trial. Drops were in identical single-use droppers, labelled in a masked fashion."
Blinding of outcome assessment (detection bias) [Non-patient reported outcomes]	Low risk	Quote: "Both patients and physicians were masked to the identity of the drops used for the duration of the trial. Drops were in identical single-use droppers, labelled in a masked fashion."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Two of the 22 randomised patients contributed no follow-up data. One of these patients was lost to follow-up after the enrolment visit. A second patient opted to withdraw from the study after the

		first follow-up visit to resume contact lens wear for bilateral keratoconus. Both patients were assigned to the placebo.” Comment: plausible effect size among missing outcomes not enough to have a clinically relevant impact on observed effect size
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of ‘low risk’ or ‘high risk’

Daniell 2006

Methods	Study design: randomised, controlled, parallel clinical trial with blinded participants, personnel and outcome assessors Period of study: not reported Sample size predetermination: not reported Unit of randomisation: patient Unit of analysis: patient (but it was not reported according to which eye persons were classified) Analysis strategy: not reported (an available case analysis according to the original group assignment was performed)
Participants	Setting: unicentric. Patients recruited from the Royal Victorian Eye and Ear Hospital corneal clinic (specialised hospital). Patients were also recruited from that centre Country: Australia Inclusion criteria: patients with corticoid-dependent AKC or vernal keratoconjunctivitis Exclusion criteria: coexisting ocular disease or infection; systemic use of corticosteroids, immunosuppressive drugs or non-steroidal anti-inflammatory drugs; intra or periocular injections in the previous 6 months; ocular surgery in the previous six months; topical corticosteroid use for reasons different from AKC; pregnant or lactating mothers Number of subjects assessed for potential enrolment: not reported Number of randomised patients: 40 (18 with AKC and 22 with vernal keratoconjunctivitis) Number allocated to the intervention group: 20 participants. Number allocated to the control group: 20 participants Mean age (years) ± standard deviation (of analysed patients): Intervention group: 26.2 ± 18. Control group: 26.2 ± 16.3 Gender (male/female): Intervention group: 15/2. Control group: 13/5 Mean AKC duration: not reported Mean symptom score at baseline: Intervention group: 6.1. Control group: 5.9 Mean sign score at baseline: Intervention group: ≈ 5.8. Control group: ≈ 5.5 Lost to follow-up: 1 participant in the intervention group Withdrawals: 2 participants in the intervention group (all of them for personal reasons) . 2 participants in the control group (one for personal reasons and one found not to be eligible) Participants analysed: 35 out of 40 (87.5%; 15 with AKC and 20 with vernal keratoconjunctivitis). Intervention group = 17/20. Control group: 18/20

Interventions	Intervention group: 0.05% CsA (Restasis, Allergan Inc., Irvine CA) 1 drop in both eyes 4 times daily for three months Control group: vehicle 1 drop in both eyes 4 times daily for 3 months Co-interventions: topical steroid drops modulated according to the clinical response
Outcomes	1. Improvement in symptoms (measured at week 1 and months 1, 2 and 3, main measurement not defined): itching, tearing, redness, soreness (burning, discomfort, foreign body sensation), discharge, photophobia 2. Improvement in signs (measured at week 1 and months 1, 2 and 3, main measurement not defined): ptosis, lid skin dermatitis, lid margin thickening, lid margin distortion, lid margin hyperaemia; hyperaemia and oedema for the bulbar conjunctiva, hyperaemia, infiltration and papillae for the inferior conjunctiva, and subepithelial conjunctival scarring, cicatrization, hyperaemia, infiltration and papillae for the superior tarsal conjunctiva; tear film deficiency, corneal epithelial disease, corneal opacity, corneal stromal thinning, corneal neovascularisation and corneal lipid deposition 3. Ability to reduce or cease topical corticotherapy (measured at week 1 and months 1, 2 and 3, main measurement not defined). "Drug score" was used to measure weekly steroid drop usage, calculated as the number of drops per week multiplied by 5 for prednisolone acetate 1%, by 4 for dexamethasone 0.1%, by 3 for fluoromethalone 0.1%, by 2 for prednisolone phosphate 0.3%, and by 1 for prednisolone phosphate 0.1%
Notes	Funding: This work was partly supported by Allergan Australia, who supplied the cyclosporin and placebo drops. The authors stated that they had no commercial interest in the findings presented in this paper

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned randomly based on a predetermined randomisation list generated by computer [...]"
Allocation concealment (selection bias)	Unclear risk	Quote: "Allocation coding was undisclosed until all patients had completed the study." Comment: Insufficient information to permit judgement. The method of concealment is not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Participants and physicians were masked to the identity of the drops used for the duration of the trial. Identical unit dose vials were used to hold the study treatments."
Blinding of outcome assessment (detection bias) [Patient reported outcomes]	Low risk	Quote: "Participants and physicians were masked to the identity of the drops used

Daniell 2006 (Continued)

		for the duration of the trial. Identical unit dose vials were used to hold the study treatments.”
Blinding of outcome assessment (detection bias) [Non-patient reported outcomes]	Low risk	Quote: “Participants and physicians were masked to the identity of the drops used for the duration of the trial. Identical unit dose vials were used to hold the study treatments.”
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Five participants discontinued the follow-up: 3 participants in the CsA group (1 was lost to follow-up after enrolment and 2 withdrew for personal reasons); and 2 participants in the placebo group (1 was found not to meet the study criteria after randomisation and 1 withdrew for personal reasons) Comment: insufficient reporting of attrition/exclusions to permit judgement of ‘low risk’ or ‘high risk’
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of ‘Low risk’ or ‘High risk’

Hingorani 1998

Methods	Study design: randomised, controlled, parallel clinical trial with blinded participants, personnel and outcome assessors Period of study: not reported Sample size predetermination: not reported Unit of randomisation: patient Unit of analysis: patient (but it was not reported according to which eye persons were classified) Analysis strategy: not reported but an available case analysis according to the original group assignation was performed
Participants	Setting: unicentric. External Disease Service of Moorfields Eye Hospital. Patients were also recruited from that centre Country: United Kingdom Inclusion criteria: patients with a clinical diagnosis of AKC who could not stop topical corticotherapy after other interventions (e.g. mast cell stabilisers or artificial tears) Exclusion criteria: use of systemic corticosteroids, immunosuppressants or non-steroidal antiinflammatory drugs; history of ocular surgery during the previous 6 months, use of topical corticosteroids for reasons different from AKC Number of subjects assessed for potential enrolment: not reported Number of randomised patients: 21 Number allocated to the intervention group: 12 participants. Number allocated to

	the control group: 9 participants Mean age (years) ± standard deviation (of analysed patients): Intervention group: 33.9.2 ± 3.9. Control group; 35.7 ± 4.6 Gender (male/female): Intervention group: 8/4. Control group: 4/5 Mean AKC duration: not reported Mean total symptom score at baseline: a) Measured by the patient: Intervention group: 11.3 ± 1.3. Control group: 10.3 ± 1.6. b) Measured by the clinician: Intervention group: 10.8 ± 1.6. Control group: 9.5 ± 2.2 Mean total sign score at baseline: Intervention group: 27.3 ± 3.6. Control group: 26.8 ± 3.2 Lost to follow-up or withdrawals: none Participants analysed: 100% (according to their original group assignment)	
Interventions	Intervention group: 2% CsA in maize oil 1 drop in both eyes 4 times daily for 3 months Control group: vehicle (maize oil) 1 drop in both eyes 4 times daily for 3 months Co-interventions: topical steroid drops modulated according to the clinical response	
Outcomes	1. Improvement in symptoms (measured at week 1 and months 1, 2 and 3, main measurement not defined): itching, soreness (burning, discomfort), redness, tearing, discharge, blurring of vision and photophobia 2. Improvement in signs (measured at week 1 and months 1, 2 and 3, main measurement not defined): lids (ptosis, lid skin dermatitis, lid margin hyperaemia, lid margin thickening and rounding, meibomian gland abnormality, lid margin anatomic distortion); conjunctiva (hyperaemia and oedema for the bulbar conjunctiva, hyperaemia, infiltration and papillae for the superior and inferior conjunctiva, and subepithelial conjunctival scarring, cicatrisation for the superior tarsal conjunctiva); cornea (tear film deficiency, epithelial disease, opacity, stromal thinning, neovascularisation and lipid deposition) 3. Ability to reduce or cease topical corticotherapy (measured at week 1 and months 1, 2 and 3, main measurement not defined). “Drug score” was used to measure weekly steroid drop usage, calculated as the number of drops per week multiplied by 5 for prednisolone acetate 1%, by 4 for dexamethasone 0.1%, by 3 for fluoromethalone 0.1%, by 2 for prednisolone phosphate 0.3%, and by 1 for prednisolone phosphate 0.1% 4. Adverse events reported by the patients	
Notes	Funding: Supported by a grant from Moorfields Eye Hospital Research Fund. No commercial interests reported	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Patients were assigned randomly (by computer-generated randomisation)”
Allocation concealment (selection bias)	Low risk	Quote: “Allocation coding was kept under lock by a senior pharmacist, who was independent of the trial and who did not meet the involved patients. Once the code was broken, the original coding was retained

Hingorani 1998 (Continued)

		under lock in the pharmacy for confirmation of the data"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both patients and clinicians were masked to the identity of the drops used, and drops were identical in appearance and in identical bottles"
Blinding of outcome assessment (detection bias) [Patient reported outcomes]	Low risk	Quote: "Both patients and clinicians were masked to the identity of the drops used, and drops were identical in appearance and in identical bottles"
Blinding of outcome assessment (detection bias) [Non-patient reported outcomes]	Low risk	Quote: "Both patients and clinicians were masked to the identity of the drops used, and drops were identical in appearance and in identical bottles"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up or withdrawals were reported. 100% of the participants were analysed (according to their original group assignation)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'

AKC: atopic keratoconjunctivitis

CsA: topical cyclosporine A

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bellini 2008	Not a randomised controlled trial
Ebihara 2009	Not a randomised controlled trial
Holland 1993	Not a randomised controlled trial
NCT00833495	Patients have mild allergic conjunctivitis, not atopic keratoconjunctivitis
NCT01120132	Patients have mild allergic conjunctivitis, not atopic keratoconjunctivitis
Nochez 2009	Not a randomised controlled trial

(Continued)

Ozcan 2007	Not a randomised controlled trial
Spadavecchia 2006	Patients have severe vernal keratoconjunctivitis, not atopic keratoconjunctivitis
Tesse 2010	Not a randomised controlled trial
Tomida 2002	Not a randomised controlled trial
Velasco 2003	Compares different concentrations of topical cyclosporine A

Characteristics of ongoing studies [ordered by study ID]

NCT00884585

Trial name or title	Efficacy and safety study of cyclosporine 0.010% to treat atopic keratoconjunctivitis
Methods	Multicentre, randomised, parallel-group clinical trial with masked participants, personnel and outcomes assessors
Participants	Patients with a clinical diagnosis of atopic keratoconjunctivitis
Interventions	Cyclosporine ophthalmic solution 0.010% (1 drop in both eyes 4 times daily for 3 months) compared with placebo (its vehicle): 1 drop in both eyes 4 times daily for 3 months
Outcomes	The proportion of patients with a 2 or more improvement in punctate corneal staining score (time frame: month 2)
Starting date	1 May 2009
Contact information	Allergan Therapeutic Area Head: clinicaltrials@allergan.com
Notes	Ongoing study but not recruiting participants

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Glossary

Adverse effect	Unfavourable outcome that occurs during or after the use of a drug or other intervention for which the causal relation between the intervention and the event is at least a reasonable possibility (Loke 2011).
Available case analysis	Analysis that includes data on only those whose results are known, using as a denominator the total number of people who had data recorded for the particular outcome in question (Higgins 2011a).
Funnel plot	Simple scatter plot of the intervention effect estimates from individual studies against some measure of each study's size or precision (Sterne 2011).
Intention-to-treat analysis	Analysis that fulfils the next principles: 1. keeps participants in the intervention groups to which they were randomised, regardless of the intervention they actually received; 2. there is a measurement of outcome data on all participants; and 3. includes all randomised participants in the analysis (Higgins 2011a).
Unit of analysis errors	An error made in statistical analysis when the analysis does not take account of the unit of allocation. In some studies, the unit of allocation is not a person, but is instead a group of people, or parts of a person, such as eyes or teeth. Sometimes the data from these studies are analysed as if people had been allocated individually. Using individuals as the unit of analysis when groups of people are allocated can result in overly narrow confidence intervals. In meta-analysis, it can result in studies receiving more weight than is appropriate (Green 2005).
Small-study effects	A tendency for estimates of the intervention effect to be more beneficial in smaller studies (Sterne 2011).

APPENDICES

Appendix I. CENTRAL search strategy

#1 MeSH descriptor Keratoconjunctivitis
#2 MeSH descriptor Conjunctivitis,
#3 conjunctiv*
#4 keratoconjunctiv*
#5 (#1 OR #2 OR #3 OR #4)
#6 MeSH descriptor Immunosuppressive Agents
#7 immunosuppress*
#8 MeSH descriptor Cyclosporine
#9 c?closporin*
#10 (#6 OR #7 OR #8 OR #9)

#11 (#5 AND #10)

Appendix 2. MEDLINE (OvidSP) search strategy

1 randomized controlled trial.pt.
2 (randomized or randomised).ab,ti.
3 placebo.ab,ti.
4 dt.fs.
5 randomly.ab,ti.
6 trial.ab,ti.
7 groups.ab,ti.
8 or/1-7
9 exp animals/
10 exp humans/
11 9 not (9 and 10)
12 8 not 11
13 keratoconjunctivitis/
14 conjunctivitis, allergic/
15 conjunctiv\$.tw.
16 rhinoconjunc\$.tw.
17 keratoconjunctiv\$.tw.
18 or/13-17
19 exp immunosuppressive agents/
20 immunosuppress\$.tw.
21 exp cyclosporine/
22 c?cyclosporin\$.tw.
23 or/19-22
24 18 and 23
25 12 and 24

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville ([Glanville 2006](#)).

Appendix 3. EMBASE (OvidSP) search strategy

1 exp randomized controlled trial/
2 exp randomization/
3 exp double blind procedure/
4 exp single blind procedure/
5 random\$.tw.
6 or/1-5
7 (animal or animal experiment).sh.
8 human.sh.
9 7 and 8
10 7 not 9
11 6 not 10
12 exp clinical trial/
13 (clin\$ adj3 trial\$).tw.
14 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
15 exp placebo/
16 placebo\$.tw.
17 random\$.tw.
18 exp experimental design/
19 exp crossover procedure/

20 exp control group/
 21 exp latin square design/
 22 or/12-21
 23 22 not 10
 24 23 not 11
 25 exp comparative study/
 26 exp evaluation/
 27 exp prospective study/
 28 (control\$ or prospectiv\$ or volunteer\$).tw.
 29 or/25-28
 30 29 not 10
 31 30 not (11 or 23)
 32 11 or 24 or 31
 33 keratoconjunctivitis/
 34 atopic keratoconjunctivitis/
 35 allergic conjunctivitis/
 36 conjunctiv\$.tw.
 37 keratoconjunctiv\$.tw.
 38 or/33-37
 39 immunosuppressive agent/
 40 immunosuppress\$.tw.
 41 exp cyclosporine/
 42 exp cyclosporine A/
 43 c?closporin\$.tw.
 44 or/39-43
 45 38 and 44
 46 32 and 45

Appendix 4. LILACS search strategy

keratoconjunctivitis or conjunctivitis and cyclosporin\$ or ciclosporin\$

Appendix 5. CINAHL (EBSCO) search strategy

S24 S12 and S23
 S23 S17 and S22
 S22 S18 or S19 or S20 or S21
 S21 TX ciclosporin*
 S20 TX ciclosporin*
 S19 TX immunosuppress*
 S18 (MH "Immunosuppressive Agents+")
 S17 S13 or S14 or S15 or S16
 S16 TX keratoconjunctiv*
 S15 TX conjunctiv*
 S14 (MM "Conjunctivitis")
 S13 (MM "Keratoconjunctivitis")
 S12 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11
 S11 TX allocat* random*
 S10 (MM "Quantitative Studies")
 S9 (MM "Placebos")
 S8 TX placebo*
 S7 TX random* allocat*

S6 (MM "Random Assignment")

S5 TX randomi* control* trial*

S4 TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))

S3 TX clinic* n1 trial*

S2 PT Clinical trial

S1 (MH "Clinical Trials+")

The search filter for trials at the beginning of the CINAHL strategy was developed by the Scottish Intercollegiate Guidelines Network ([SIGN 2010](#)).

Appendix 6. OpenGrey search strategy

Keratoconjunctivitis or conjunctivitis AND cyclosporin* or ciclosporin*

Appendix 7. metaRegister of Controlled Trials search strategy

keratoconjunctivitis and cyclosporine

Appendix 8. ClinicalTrials.gov search strategy

(Keratoconjunctivitis OR Conjunctivitis) AND (Closporin OR Ciclosporin)

Appendix 9. ICTRP search strategy

condition keratoconjunctivitis or conjunctivitis and intervention cyclosporin or ciclosporin

Appendix 10. IFPMA Clinical Trials Portal

keratoconjunctivitis and cyclosporine

Appendix 11. Web of Science CPCI-S search strategy

5 #3 AND #4

4 TS=(cyclosporin* or ciclosporin*)

3 #1 OR #2

2 TS=conjunctivitis

1 TS=keratoconjunctivitis

Appendix 12. Methods for future updates of this review

Assessment of reporting biases

We will look for evidence of publication bias for each outcome and assess publication bias in two different ways:

- graphically, by visual assessment of funnel plots (Table 1); and
- statistically, provided there are at least 10 studies in the meta-analysis. We will follow the guide provided by Sterne 2011 for statistical testing for funnel plot asymmetry.

Results from tests for funnel plot asymmetry will be interpreted cautiously. If there is evidence of 'small-study effects' (Table 1), we will consider publication bias as only one of a number of possible explanations (Sterne 2011).

Data synthesis

We will try to combine the outcome measures from the individual trials in a meta-analysis to provide a pooled effect estimate for each outcome only if the studies are clinically and methodologically comparable.

If the number of trials for each outcome measure is greater than three and no heterogeneity in their results is detected statistically or by observation, we will use a random-effects model to pool data. If the number of trials is three or less, we will use the fixed-effect model, provided that heterogeneity has not been detected either statistically or by observation (Deeks 2011). We will assess the influence of the statistical model in the effects being evaluated (Appendix 14). We will use the generic inverse variance to meta-analyse trials that have used paired data with trials that have not.

If heterogeneity is detected, it may be inappropriate to combine results to produce a single summary measure. In this case, we will not combine results but undertake a narrative analysis of studies, providing a descriptive presentation of the results, with supporting tables. We will perform the analyses using the RevMan (RevMan 2011) statistical package provided by The Cochrane Collaboration and we will present the results with 95% confidence intervals (95% CI).

Sensitivity analysis

If there are sufficient studies, we will undertake the following sensitivity analyses:

- we will assess the effect of excluding trials in which one eye was treated with topical CsA and compared to the other eye (we will also include these trials in the meta-analysis);
- we will explore the effect of the risk of bias in the meta-analysis by excluding studies with any domain assessed as 'high risk of bias' or 'unclear risk of bias';
- we will explore the impact of the assumptions taken in the 'available case analysis' by performing a sensitivity analysis with imputation of missing data:
 - for dichotomous outcomes, we will consider the 'best-case' and 'worst-case' scenarios (Gamble 2005). We will define the 'best-case' scenario as all participants with missing outcomes in the experimental intervention group having good outcomes, and all those with missing outcomes in the control intervention group having poor outcomes; the 'worst-case' scenario will be the converse (Higgins 2011b);
 - for continuous data, we will conduct a sensitivity analysis assuming a fixed difference between the actual mean for the missing data and the mean assumed by the analysis (Higgins 2011b);
- we will assess the effect of the statistical model chosen for meta-analysis: we will use a fixed-effect model for those meta-analyses performed with a random-effects model, and perform a random-effects model for meta-analyses based on a fixed-effect model in the first place.

HISTORY

Protocol first published: Issue 4, 2011

Review first published: Issue 9, 2012

CONTRIBUTIONS OF AUTHORS

Conceiving the review: JJGL

Designing the review: JJGL, JLA

Co-ordinating the review: JJGL, JLA

Data collection for the review

- Designing search strategies: CEVG Trials Search Co-ordinator, JJGL, JLA

- Undertaking manual searches: JJGL, RML

- Screening search results: JJGL, RML

- Organising retrieval of papers: JJGL

- Screening retrieved papers against inclusion criteria: JJGL, RML

- Appraising quality of papers: JJGL, JLA, RML

- Abstracting data from papers: JJGL, JLA

- Writing to authors of papers for additional information: JJGL

- Providing additional data about papers: JJGL

- Obtaining and screening data on unpublished studies: JJGL, RML

- Data management for the review: JJGL, JLA

- Entering data into RevMan: JJGL, JLA

Analysis of data: JJGL, JLA

Interpretation of data

- Providing a methodological perspective: JJGL, JLA

- Providing a clinical perspective: JJGL, RML, RFB, GRF

- Providing a policy perspective: JLA, GRF

Writing the review: JJGL, JLA, RFB

Performing previous work that was the foundation of current study: JJGL

Guarantor for the review: JJGL

DECLARATIONS OF INTEREST

None of the authors declare any potential conflict of interest relevant to this review.

SOURCES OF SUPPORT

Internal sources

- Department of Ophthalmology, Hospital Universitario Ramón y Cajal, Madrid, Spain.
- Health Technology Assessment Unit, Agency Laín Entralgo (Cochrane Collaborating Centre), Madrid, Spain.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the published protocol, we were planning to document the inter-rater reliability in the 'Risk of bias' assessment using the kappa statistic ([Higgins 2003](#)). However, we believe that the kappa statistic is not appropriate in these circumstances.

The 'Risk of bias' tool was changed during preparation of the review to reflect the changes suggested in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* version 5.1.0 ([Higgins 2011a](#)).