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Systemic interventions for severe atopic and vernal keratoconjunctivitis in children and young people up to the age of 16 years (Review)

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TABLE OF CONTENTS

[Intervention Review]

Systemic interventions for severe atopic and vernal keratoconjunctivitis in children and young people up to the age of 16 years

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ABSTRACT

Background

Atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC) are severe and potentially sight-threatening allergic eye diseases characterised by chronic inflammation of the ocular surface. Both topical and systemic treatments are used. This Cochrane Review focuses on systemic treatments.

Objectives

To assess the effects of systemic treatments (including corticosteroids, NSAIDS, immunomodulators, and monoclonal antibodies), alone or in combination, compared to placebo or other systemic or topical treatment, for severe AKC and VKC in children and young people up to the age of 16 years.

Search methods

We searched CENTRAL, Ovid MEDLINE, Ovid Embase, the ISRCTN registry, ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). There were no restrictions to language or year of publication. We last searched the electronic databases on 17 February 2020.

Selection criteria

We searched for randomised controlled trials (RCTs) that involved systemic treatments in children aged up to 16 years with a clinical diagnosis of AKC or VKC. We planned to include studies that evaluated a single systemic medication versus placebo, and studies that compared two or multiple active treatments.

Data collection and analysis

We used standard methods expected by Cochrane.

Main results

No trial met the inclusion criteria of this Cochrane Review. No RCTs have been carried out on this topic.

Authors' conclusions

There is currently no evidence from randomised controlled trials regarding the safety and efficacy of systemic treatments for VKC and AKC. Trials are required to test efficacy and safety of current and future treatments. Outcome measures need to be developed which can capture both objective clinical and patient-reported aspects of the condition and treatments.

PLAIN LANGUAGE SUMMARY

What medicines, taken by mouth or given as an injection, work best to treat severe allergic eye disease in children and young people under 16 years old?

What is allergic eye disease?
An immune response is how the body recognises and defends itself against substances that appear harmful, usually by producing specific blood proteins (antibodies) against them. An allergy is a reaction by the body's immune system to a particular substance (an allergen) that is usually harmless, such as grass or tree pollens in the air. Different allergens affect different tissues, and their effects can be mild or serious.

In the eye, allergic reactions can cause conjunctivitis: the conjunctiva (the tissue covering the white of the eye and lining the inside of the eyelids) becomes swollen and sore. Severe allergic eye disease may also affect the cornea (the clear, front part of the eye), causing keratoconjunctivitis.

Vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC) are rare types of severe allergic eye disease. VKC usually develops in children and is more common in boys; AKC can affect children and adults. These conditions usually affect both eyes and make them red, itchy, sore, watery and sensitive to light. Both conditions can damage the cornea, which can affect eyesight and lead to blindness. Treatment is essential to save eyesight.

Treatments for severe allergic eye disease
Both conditions are treated with medicines that try to block the allergic reaction and reduce swelling. Symptoms may get better with medicines given as eye drops, but if these don't work, other medicines may be taken by mouth or given as an injection (systemic medicines). Systemic medicines that are often used to treat severe allergic eye disease include ones that target or suppress the immune response, such as `anti-inflammatory` medicines and antibodies.

Why we did this Cochrane Review
We wanted to find out which systemic treatments work best for severe allergic eye disease in children and young people.

What did we do?
We searched for studies that looked at systemic medicines to treat severe allergic eye disease in children and young people under 16 years of age. We wanted to find studies that compared a single medicine with a placebo (dummy) medicine, or studies that compared two or more medicines against each other.

We looked for randomised controlled studies, in which the treatments people received were decided at random, because these studies usually give the most reliable evidence about the effects of a treatment.

Search date: We searched for evidence published up to 17 February 2020.

What we found
We found no randomised controlled studies in children and young people with severe allergic eye disease treated by systemic medicines.

Conclusions

There is no evidence from randomised controlled studies about how well systemic medicines work for severe allergic eye disease in children and young people aged under 16 years.

Research is needed to investigate how well systemic medicines work to treat severe allergic eye disease in children and young people, and to learn about any unwanted effects these medicines might cause.

BACKGROUND

Atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC) are severe and potentially sight-threatening allergic eye diseases characterised by chronic inflammation of the ocular surface. Milder forms of allergic conjunctivitis (that are not the subject of this review) are seasonal allergic conjunctivitis and perennial allergic conjunctivitis (Bonini 2004). There is no agreed consensus to distinguish the phenotypes of VKC and AKC in children. Due to an increasing overlap between the two conditions, with VKC now often persisting into adulthood, and children with atopy presenting with features classically typical for VKC, the terms have been used interchangeably. Management of chronic allergic conjunctivitis (AKC and VKC) can be difficult and may require chronic use of topical anti-inflammatory eye drops and intermittent use of systemic medication.

Description of the condition

Allergic ocular surface inflammation is mediated by mast cells and symptoms in the acute phase include itching, tearing, redness, photophobia, lid swelling, and conjunctival chemosis.

In VKC, there are characteristic proliferative conjunctival changes, including giant papillary proliferation of the tarsal conjunctiva and gelatinous papillae with cell infiltration of the limbal conjunctiva (Shiraki 2016). VKC can be complicated by corneal epithelial breakdown, corneal ulceration and secondary corneal vascularisation, which can affect vision. Visual loss is more common in individuals with palpebral disease. AKC typically presents in older individuals who have a prior history of severe atopic dermatitis. AKC can present with similar signs and the release of allergic mediators onto the ocular surface and tear film can cause similar corneal complications such as ulceration, stromal vascularisation, and sub-epithelial plaque formation. Both conditions are associated with keratoconus (Bacon 1993).

VKC commonly affects young and adolescent males (Bonini 2000; Leonardi 2006a; Leonardi 2006b), and has a wide geographical distribution, with high prevalence in warm, dry areas such as Central Africa, India, South America and Mediterranean regions (Pattnaik 2015). Its prevalence is reported to be between 3.2/10,000 population in Western Europe to 400/10,000 in Central Africa (Bremond-Gignac 2008). VKC-related inflammation is often exacerbated in the spring season, though 23% of patients may have a perennial form with recurrences all year round (Kumar 2009; Ukponmwan 2003).

AKC affects both children and adults and is commonly associated with severe atopic dermatitis of the face, and the symptoms are usually perennial.

Allergic eye diseases are classic immunoglobulin E-mediated conditions. First-line treatments include allergen avoidance, oral antihistamines, topical dual-acting antihistamine/mast cell stabilising agents, and treatment of tear film dysfunction. Other treatment options include immunotherapy, and topical ester-based corticosteroids (Shaker 2016). However, although topical corticosteroids can usually control the inflammatory process, they may themselves contribute to complications such as glaucoma, cataract, and infections. In refractory cases of severe allergic keratoconjunctivitis, systemic therapy may be used. This includes systemic steroids (Doan 2017), and systemic immunomodulators such as tacrolimus, cyclosporine A, or omalizumab.

Although the majority of patients with VKC and AKC have a good prognosis, early intervention is important for preventing potentially sight-threatening corneal changes (BenEzra 1986; Cameron 1995a; Cameron 1995b; Dahan 1983; Guglielmetti 2010; Leonardi 2000; Power 1998; Tabbara 1999; Tuft 1991).

The diagnosis of both AKC and VKC is based on clinical signs and symptoms. At least five severity-grading systems have been developed and used in observational studies and clinical trials, usually as composite scoring systems (BenEzra 1986; Bleik 1991; Bonini 2007; Hingorani 1998; Uchio 2008). Symptom scales grade itching, eye watering/tearing, photophobia, mucous discharge and foreign body sensation/discomfort on a scale from 0 (no symptoms) to 3, 4 or 5 (severe symptoms preventing normal activities of daily living), whilst scales for clinical signs grade conjunctival, limbal and corneal signs, such as bulbar conjunctival hyperaemia, upper tarsal conjunctival papillae, punctate keratitis, corneal neovascularisation, cicatrising conjunctivitis and blepharitis, also from 0 (no inflammatory changes) to 3, 4 or 5 (severe changes) (Akpek 2004; BenEzra 1986; Bleik 1991; Bonini 2007; Daniell 2006; De Smedt 2012; Doan 2017; Ebihara 2009; Hingorani 1998; Pucci 2002; Pucci 2015; Sacchetti 2010). Some authors have modified previous scales to include particular features of VKC such as limbal inflammation (De Smedt 2012). Only one tool has been developed to assess the impact of VKC on quality of life in children, though this questionnaire focuses on activities of daily living in children in Mediterranean countries and is of limited use in other settings (Sacchetti 2007). A second tool has been used in one study only, and has not been validated (Pucci 2015).

Description of the intervention

Systemic treatments for VKC and AKC include corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), immunomodulators (cyclosporine A), montelukast and monoclonal anti-IgE antibodies (omalizumab). This review does not include periocular (including subtarsal) injections.

How the intervention might work

Corticosteroids

Corticosteroids are potent immunosuppressive agents with complex actions on immune cells inhibiting cytokine release, inhibiting migration, and inducing apoptosis, amongst other features (Baschant 2010). They inhibit release of arachidonic acid, and therefore control the release of inflammatory mediators such as prostaglandins and leukotrienes (Greaves 1976).

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are inhibitors of cyclooxygenase (COX), which are a group of enzymes that catalyse biosynthesis of eicosanoids from arachidonic acid to produce pro-inflammatory prostaglandins and thromboxanes. Prostaglandins cause vasodilation, increased vascular permeability with the disruption of blood-ocular barrier, and leukocyte migration (Miyake 2002). By inhibiting COX enzymes, NSAIDs reduce synthesis of prostaglandins. The main classes of NSAIDs include salicylates, acetic acids, propionic acids, enolic acid derivatives, fenamates, and COX-2 specific NSAIDs (Kim 2010).

Cyclosporine

Cyclosporine decreases the signs and symptoms of severe allergic eye disease (BenEzra 1986; Vichyanond 2013), which may be a result of its immunomodulating effect on components of cell-mediated and humoral immune response (el-Asrar 1996). Cyclosporine inhibits the calcium-dependent intracellular signalling protein calcineurin by binding to its receptor cyclophilin. This results in inhibition of cytokines and chemokines such as IL-4 and IL-5 from effector cells including Th2 lymphocytes, which in turn reduces histamine (BenEzra 1988; Secchi 1990; Vichyanond 2013).

Tacrolimus

Tacrolimus is a macrolide lactone compound that has immunosuppressant effects via inhibition of T cell activation. Tacrolimus binds to immunophilin FK-binding protein (FKBP-12), which inhibits calcineurin. It also inhibits histamine release and production of inflammatory mediators (Anzaar 2008; Ruzicka 1997)

Montelukast

Montelukast is a leukotriene receptor antagonist; other drugs in this category include zafirlukast and pranlukast.

Leukotriene receptor antagonists such as montelukast, zarfirlukast, and pranlukast inhibit proinflammatory actions of cysteinyl-leukotrienes. Leukotrienes are inflammatory mediators synthesised from arachidonic acid, and are produced by a variety of inflammatory cells such as mast cells, eosinophils, and basophils (Scadding 2010; Tintinger 2010). Activation of cysteinyl-leukotriene receptors results in activation and recruitment of inflammatory cells, and increase in vascular permeability. In addition to antagonising leukotriene receptors, there is evidence that montelukast also has other anti-inflammatory properties including inhibition of enzymes 5-lipoxygenase, histone acetyltransferase, and adenosine 3',5'-cyclic monophosphate (cAMP) phosphodiesterase (Anderson 2009; Robinson 2008; Tahan 2008).

Omalizumab

Omalizumab is a recombinant humanised monoclonal chimeric antibody that binds to the Ce3 receptor binding domain of free circulating IgE. The binding is specific to free IgE and therefore clears IgE immune complexes from the plasma (Babu 2013; Buhl 2005). It can reduce circulating free IgE by up to 99%, thus suppressing the activation of mast cells (MacGlashan 1997).

Why it is important to do this review

Treatment of severe allergic ocular surface inflammation with eyedrops requires frequent administration over prolonged periods of time. This may be a significant burden on the child and the family, as well as posing logistic difficulties when drops need to be applied during school hours. Systemic treatments which may only need to be administered daily or even periodically may significantly reduce this burden, provided they have a low risk of systemic adverse events and high ocular efficacy. At the same time the high prevalence of severe allergic eye disease in warm or hot climates in countries with limited resources to support the provision of healthcare make it important to identify effective, feasible and low-cost interventions.

OBJECTIVES

To assess the effects of systemic treatments (including corticosteroids, NSAIDS, immunomodulators, and monoclonal antibodies), alone or in combination, compared to placebo or other systemic or topical treatment, for severe atopic and vernal keratoconjunctivitis (AKC and VKC) in children and young people up to the age of 16 years.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include randomised controlled trials (RCTs) of systemic interventions for AKC and VKC in this review.

Types of participants

We planned to include studies that enrolled children up to the age of 16 years with a diagnosis of severe AKC or VKC, defined as corneal inflammation (keratitis) not responsive to two weeks of high-frequency treatment with topical antihistamines, mast cell stabilisers, cyclosporine A and corticosteroids; or keratitis that can no longer be treated with these medications because ocular or systemic adverse events have developed, which preclude their use (Bonini 2007; Doan 2017; Heffler 2016; Taillé 2010). We planned to include trials that enrolled both adults and children if data on children were reported as a subgroup, or could be made available to us. This review planned to focus on paediatric trials, as this is the age group in whom the condition first manifests; the group in which the inflammation tends to be most severe and complications may affect visual development, education and life chances; and the group in which the burden of treatment is of particular importance, as it affects the young person's family as well as the person suffering from the condition.

Types of interventions

We planned to include trials that compared two or more systemic interventions, or an active systemic intervention with systemic placebo.

Systemic interventions

- Subcutaneous omalizumab or other monoclonal antibody treatments.
- Oral cyclosporine A.
- Oral tacrolimus.
- Oral leukotriene receptor antagonists such as montelukast, zafirlukast and pranlukast.
- Oral corticosteroids, such as betamethasone, deflazacort, dexamethasone, hydrocortisone, methylprednisolone and prednisolone.
- Oral non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, ibuprofen, ketotifen, ketoprofen, sulindac, naproxen, diclofenac, etodolac, fenoprofen, flurbiprofen, ketorolac, piroxicam, indomethacin, mefenamic acid, meloxicam, nabumetone, oxaprozin, famotidine, meclofenamate, tolmetin, salsalate.
- Oral antihistamines, such as brompheniramine, cetirizine, chlorpheniramine, clemastine, diphenhydramine, fexofenadine, levocabastine, loratadine.

- Oral immunotherapy.
- Oral cyclophosphamide.
- Oral methotrexate.
- Oral 5-lipoxygenase inhibitors such as zileuton.

Types of outcome measures

The outcomes of interest are listed below. These outcomes were not used as criteria for including studies.

Primary outcomes

- Proportion of participants with an increase in health- or vision-related quality of life score between baseline (before treatment) and 4 months ± 2 months later, using validated health-related quality of life scales (Varni 2001), or VKC-related quality of life scales for children (Pucci 2015; Sacchetti 2007).

Secondary outcomes

- Proportion of participants who report a symptom score of zero (full control of symptoms), using any validated symptom scale.
- Proportion of participants with a 'clinical signs of active inflammation score' of zero (full control of signs of inflammation), using any validated clinical signs grading scale.
- Proportion of participants requiring topical steroids (rescue medication).
- Mean change in health-related quality of life score between baseline (before treatment) and 4 months ± 2 months later, using validated health-related quality of life scales for children (Varni 2001).
- Mean change in vision-related quality of life score between baseline (before treatment) and 4 months ± 2 months later, using validated VKC-related quality of life scales for children (Pucci 2015; Sacchetti 2007).

Timing of outcome assessment

4 months ± 2 months after start of treatment.

Adverse effects

- Proportion of participants experiencing systemic adverse events. Adverse events were defined by the included studies.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist searched the following electronic databases for randomised controlled trials and controlled clinical trials. There were no restrictions to language or year of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2020; Issue 2) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 17 February 2020) (Appendix 1).
- MEDLINE Ovid (1946 to 17 February 2020) (Appendix 2).
- Embase Ovid (1980 to 17 February 2020) (Appendix 3).
- International Standard Research Clinical Trial Number (ISRCTN) registry (www.isrctn.com/editAdvancedSearch; searched 17 February 2020) (Appendix 4).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 17 February 2020) (Appendix 5).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp; searched 17 February 2020) (Appendix 6).

Searching other resources

We scrutinised the reference lists of the studies included in the review. We planned to use the Science Citation Index to find studies that have cited individual trials included in this review. We planned to contact relevant pharmaceutical companies for any clinical trials information that was not released for publication. We did not handsearch conference proceedings or journals specifically for the review.

Data collection and analysis

Selection of studies

Two review authors independently carried out the study selection from the results of searches (titles and abstracts) to identify relevant studies using Covidence. We intended to divide studies into 'definitely include', 'definitely exclude', and 'possibly include' categories and to resolve disagreements by discussion, followed by consultation with a third review author if discussion did not lead to agreement. In general, all citations considered not relevant at this stage were not documented in the review, other than to note the number of these in a flow chart.

We planned to obtain full-text copies of potentially relevant trials. We planned to make a final judgement regarding the inclusion or exclusion of studies in the 'possibly include' category after obtaining the full text of each of these articles. Where necessary, we planned to obtain English translations of abstracts and full-text articles before making a final decision. We intended to take care to identify multiple reports of the same study.

Review authors were not masked with respect to study authors, institution or journal, and we intended to correspond with study authors to clarify study eligibility, as appropriate.

Data extraction and management

Two review authors (ADN and VN) independently extracted data using an online data extraction form, which was piloted before use. Where data were unclear or inadequate, we intended to contact the study investigator for missing data or clarification. We planned to import data directly into Review Manager 5 (RevMan 5) (Review Manager 2014); and for review authors to cross-check for any errors.

Study characteristics

We intended to collect the following information on study characteristics, and summarise these in a table (Appendix 7).

- Study design: parallel group RCT, with either one or both eyes of each participant reported.
- Participants: country, total number of participants, age, sex, inclusion and exclusion criteria.
- Intervention and comparator details, including number of people (eyes) randomised to each group.
- Adherence to treatment.

- Primary and secondary outcomes as measured and reported in the trials, and adverse events.
- Length of follow-up.
- Date study conducted.
- Funding and conflicts of interest.
- Included on trials registry (Y/N); registration number, if available.

Outcome data

For continuous outcomes, we planned to extract the following data from each included study for our predefined outcomes separately for intervention and comparator groups: mean, standard deviation, and number of participants followed up. For dichotomous outcomes, we planned to collect data on the number of events and number of people followed up in each group.

For multi-arm studies, we planned to use data relevant to our intervention and comparator groups. If two groups contain relevant data, we intended to combine groups, using the calculator within RevMan 5.

We intended to seek clarification from trial investigators as needed.

Assessment of risk of bias in included studies

Two review authors intended to independently assess the risk of bias in included studies using Cochrane's 'Risk of bias' assessment tool, as detailed in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

In each trial, we planned to classify each domain of bias risk as 'high, 'low' or 'unclear' risk of bias. We intended to resolve disagreements by discussion, and if necessary consult a third person. For domains classified as 'unclear' risk of bias, we planned to contact trial investigators for clarification.

We planned to consider and report on the six main domains of the Cochrane 'Risk of bias' tool, as follows.

1. Selection bias

We planned to classify studies as being at 'high,' 'low,' or 'unclear' risk of bias based on the methods of randomisation (sequence generation) and allocation concealment. Examples of 'low' risk would include using computer-generated sequences or random number tables, central allocation of treatments, and concealment of allocation. Studies with lack of allocation concealment would be classified as 'high' risk, and studies where the details of allocation schedule were not published would be classed as being at 'unclear' risk of bias. If we had made an assessment of 'unclear' risk of bias, we planned to ask the study authors to provide further information, to enable us to make a more detailed risk of bias assessment.

2. Performance bias

Performance bias can occur if study participants, carers, or investigators know the assigned intervention.

3. Detection bias

Detection bias can occur if outcome assessors know the treatment assignment of the study participants. We therefore planned to judge studies on their use of masking strategies.

4. Attrition bias

Withdrawal of study participants or loss from follow-up can cause attrition bias. We planned to classify attrition bias as 'high' risk if the study authors did not take missing data into consideration. Other reasons for classifying studies as having high risk of attrition bias would be: if the missing outcome data were likely to be related to the true outcome; if the proportion of missing outcomes compared with observed events may have induced clinically relevant bias in the effect size of the intervention; if plausible effect size (difference in means or standardised difference in means) among missing outcomes might have induced clinically relevant bias in observed effect size; if the study authors analysed data 'as treated' with substantial departure of the intervention received from the initially allocated group; and if there was inappropriate application of simple imputation.

5. Reporting bias

If a study protocol were available, we planned to compare the protocol with the final outcomes, to assess the risk of selective outcome reporting.

6. Other bias

We intended to judge whether the design of each study were subject to any risk of other bias not detailed above.

We planned to seek clarification from trial investigators as needed.

Measures of treatment effect

Our primary outcome is dichotomous, as are some of the secondary outcomes. We planned to compute the risk ratio (RR) with 95% confidence intervals (CI) as the measure of treatment effect for dichotomous outcomes. For continuous (approximately) normally distributed secondary outcomes, we planned to compute the mean differences (MD) with their 95% CIs. We planned to note whether or not study authors assessed the symmetry of their data. We planned to compute odds ratios (OR) with 95% CIs for adverse events, as these are relatively good approximations when risks are rare (less than 10%). However, if the included studies had reported a variety of adverse events and only one trial reported each type, we planned to simply collate this information.

Unit of analysis issues

Eyes and people

We planned not to include cross-over studies, and we did not anticipate cluster-randomised trials, as the intervention is delivered to the individual. VKC and AKC affect both eyes, but systemic treatment is given to a person, not their eyes, and will therefore have an effect on both eyes. Trials we planned to include in this review would randomise people, not eyes, to the intervention and comparator, but we planned to report some outcomes for eyes, not people.

We planned to report our primary outcome (increase in health- or vision-related quality of life) for a person, not for an individual eye.

Five of our secondary outcomes (symptom score, clinical signs/ inflammation score, change in best corrected visual acuity, change in health-related quality of life score, change in vision-related quality of life score) are usually reported for a participant's 'worse

eye.' The sixth secondary outcome (proportion of patients requiring topical steroids) can be reported either per eye or per person.

Our safety outcome (proportion of patients experiencing systemic adverse events) is reported per participant.

For those of our outcomes that are reported for people, not eyes, we anticipated there would not be a unit of analysis issue. If people were randomly allocated to treatment but both eyes are included and reported, we planned to analyse as 'clustered data,' i.e. to adjust for within-person correlation. To do this, we planned to consider contacting the trial investigators for further information.

Dealing with missing data

If possible, we planned to conduct an intention-to-treat (ITT) analysis. We planned to use imputed data if computed by the trial investigators using an appropriate method, but did not plan to impute missing data ourselves.

If ITT data were not available, we planned to do an available-case analysis. This assumes that data are missing at random. We planned to assess whether this assumption is reasonable by collecting data from each included trial on the number of participants excluded or lost to follow-up and reasons for loss to follow-up by treatment group, if reported.

Assessment of heterogeneity

We planned to examine the overall characteristics of the studies, in particular the type of participants and types of interventions, to assess the extent to which the studies might have been similar enough for sensible pooling of study results.

We planned to examine the forest plots of study results to determine their consistency or inconsistency. In particular, we would have looked at the size and direction of effects.

We planned to calculate the I^2 statistic, which is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) (Higgins 2002). We planned to consider I^2 values over 50% to indicate substantial inconsistency, but would also have considered Chi^2 P value. As this may have low power when the number of studies are few, we planned to consider P less than 0.1 to indicate statistical significance of the Chi^2 test.

Assessment of reporting biases

We intended to use the risk of bias assessment tool to look for selective or incomplete reporting. See Assessment of risk of bias in included studies.

If we had included 10 trials or more in a meta-analysis, we planned to construct funnel plots and consider tests for asymmetry for assessment of publication bias, as advised in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

Data synthesis

We planned to meta-analyse the primary and all secondary outcomes, as well as the adverse effects, and summarise the results in the 'Summary of findings' table. For outcomes for which it is not appropriate to carry out a meta-analysis we planned to describe the results of individual trials narratively.

We planned to pool data using a random-effects model in RevMan 5. If there had been fewer than three trials in a comparison we planned to use a fixed-effect model.

If there had been inconsistency between individual study results such that a pooled result may not have been a good summary of the individual trial results – for example, if the effects had been in different directions, or I^2 had been greater than 50% and P were less than 0.1 – we intended not to pool the data, but instead to describe the pattern of the individual study results.

If there had been statistical heterogeneity but all the effect estimates were in the same direction, such that a pooled estimate would seem to provide a good summary of the individual trial results, we planned to consider pooling the data.

Subgroup analysis and investigation of heterogeneity

We did not plan to carry out subgroup analyses.

Sensitivity analysis

We planned to carry out one sensitivity analysis to assess the role of the risk of bias, and to repeat the analysis, excluding trials at high risk of bias in one or more domains.

Summary of findings and assessment of the certainty of the evidence

For future updates of this review, we plan to prepare a 'Summary of findings' table (Table 1) presenting relative and absolute risks. Two authors will grade independently the overall quality of the evidence for each outcome using the GRADE methodology (GRADEpro). We intend to include our primary and five secondary outcomes in the 'Summary of findings' table, as well as the proportion of participants experiencing adverse effects.

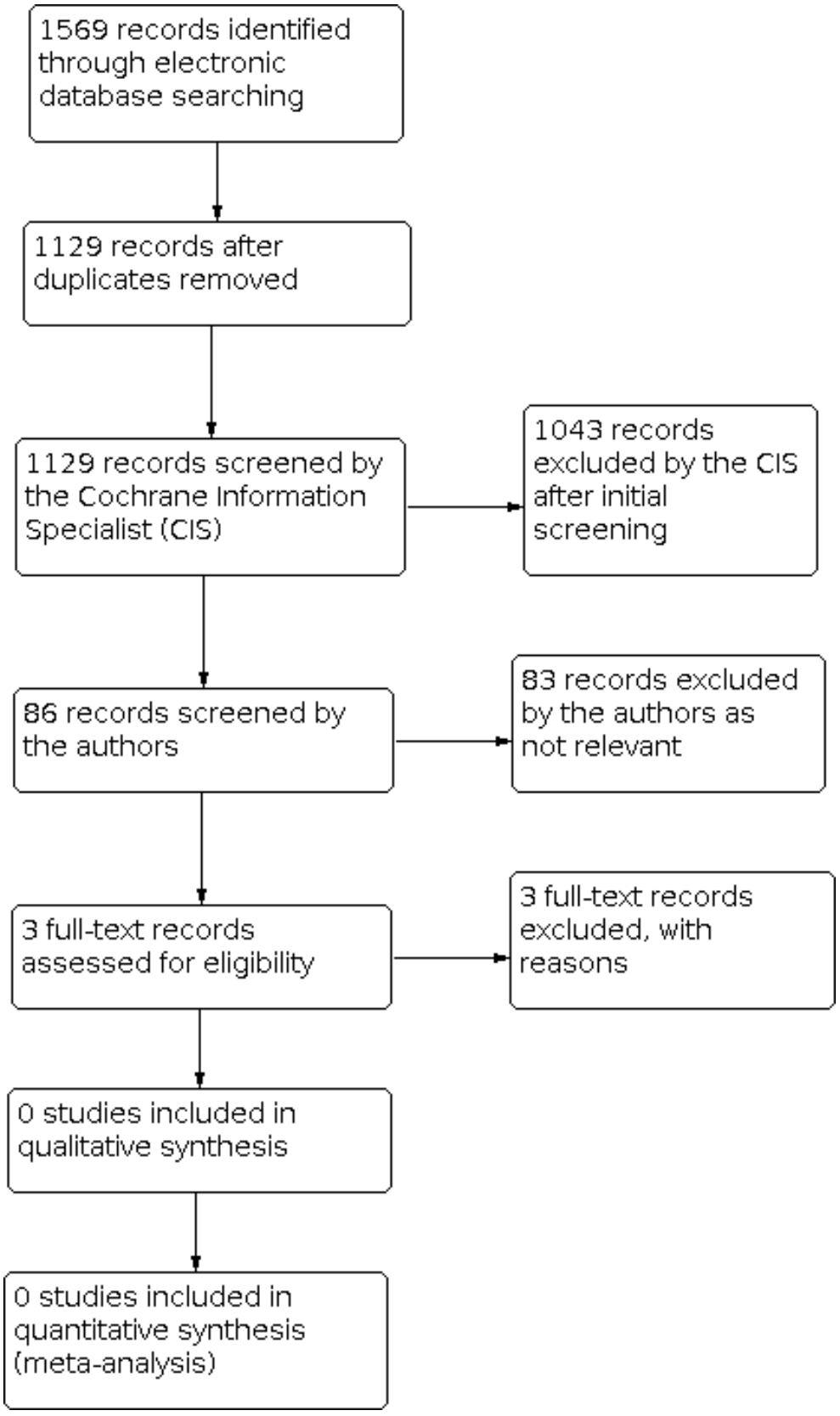
RESULTS

Description of studies

Results of the search

The electronic searches yielded a total of 1569 references (Figure 1). After 440 duplicate records were removed, the Cochrane Information Specialist (CIS) screened the remaining 1129 records and removed 1043 records which were not relevant to the scope of the review. Two review authors (ADN and VAN) independently screened the remaining 86 records and obtained full-text reports of three studies for further investigation. After assessment, the three studies were excluded. See Characteristics of excluded studies for details.

Figure 1. Study flow diagram.



Included studies

No study met the eligibility criteria.

Excluded studies

We reviewed three studies in full and excluded them (NCT00445120; Srinivas 1989; Syrbopoulos 1986). See the Characteristics of excluded studies table or further information.

Risk of bias in included studies

No study met the eligibility criteria.

Effects of interventions

No study met the eligibility criteria.

DISCUSSION

Summary of main results

No study met the inclusion criteria of this Cochrane Review. This means that there is no high-quality evidence of the safety and efficacy of systemic treatments for VKC and atopic keratoconjunctivitis AKC.

Overall completeness and applicability of evidence

As we could not include any studies, we were unable to address the objectives of this review.

Quality of the evidence

The current body of evidence does not include any RCTs.

Potential biases in the review process

Our search methods for this Cochrane Review were comprehensive, and would have captured all eligible reports. It is unlikely that we have overlooked any relevant studies.

Agreements and disagreements with other studies or reviews

We are unaware of any other systematic review of high-quality evidence on this topic. Existing reviews are narrative expert opinion summaries about VKC and its treatment, and did not grade the certainty of the evidence.

AUTHORS' CONCLUSIONS

Implications for practice

In the absence of high-quality evidence about efficacy and safety of different treatment regimes, there is uncertainty about indications and effectiveness of systemic treatment of atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC) .

Implications for research

Clinical trials are required to test efficacy and safety of current and any future treatments. Pre-trial work-up including patient and public involvement to explore acceptability to patients, their families and patients' treating clinicians is required. A clinician practice survey to investigate current national and international practice as part of a service evaluation would be helpful in determining which systemic treatments to compare. A feasibility study would be useful to gather preliminary data on numbers presenting to individual units to inform a decision about whether a multi-site study would be preferable. A set of outcome measures should be agreed, ideally as part of the International Consortium on Health Outcomes Measurement. It would be important to have expert input from a Clinical Trials Unit with experience of paediatric studies to assist with study design with adequate funding to support running such a non-commercial trial.

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CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
NCT00445120	The study is investigating Lactobacillus Rhamnosus GG, a probiotic that is not an intervention considered in this review
Srinivas 1989	Wrong study design
Syrbopoulos 1986	Wrong route of administration

ADDITIONAL TABLES

Table 1. Summary of findings table template

Systemic interventions compared with placebo or oral corticosteroids for severe VKC / AKC in children

Patient or population: children under the age of 16 years with severe VKC / AKC

Settings: [setting]

Intervention: REPLICATE THIS TABLE FOR EVERY SYSTEMIC INTERVENTION

Comparison: INDICATE HERE: PLACEBO or SYSTEMIC CORTICOSTEROIDS

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	[control]	[experimental]				
Proportion of participants with an increase in health- or vision-related quality of life score between baseline (before treatment) and 4 +/- 2 months later	The mean [outcome] ranged across control groups from [value][measure]	The mean [outcome] in the intervention groups was **[value] [lower/higher]** [(value to value lower/higher)]		[value] ([value])	[Delete as appropriate] ⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**	
Proportion of participants who report a symptom score of zero (full control of symptoms)						

Table 1. Summary of findings table template *(Continued)*

Proportion of participants with a clinical signs of active inflammation score of zero (full control of signs of inflammation)				
Proportion of participants requiring topical steroids (rescue medication)				
Mean change in health-related quality of life score between baseline (before treatment) and 4 +/- 2 months later				
Mean change in vision-related quality of life score between baseline (before treatment) and 4 +/- 2 months later				
Proportion of participants experiencing systemic adverse events				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; [other abbreviations, eg. OR, etc]

GRADE Working Group grades of evidence
High-quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate-quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-quality: We are very uncertain about the estimate.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Keratoconjunctivitis] this term only
#2 MeSH descriptor: [Conjunctivitis, Allergic] this term only
#3 (vernal or atopic) near/2 keratoconjunctiv*
#4 VKC or AKC
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Antibodies, Monoclonal, Humanized] this term only
#7 omalizumab*
#8 MeSH descriptor: [Cyclosporine] this term only
#9 c?closporin*
#10 MeSH descriptor: [Tacrolimus] this term only
#11tacrolimus$ or FK506*
#12 #6 or #7 or #8 or #9 or #10 or #11
#13 oral* or systemic
#14 #12 and #13
#15 MeSH descriptor: [Leukotriene Antagonists] this term only
#16 leukotri* near/2 (receptor* or antagonist*)
#17 montelukast* or zarfirlukast* or pranlukast*
#18 MeSH descriptor: [Arachidonate 5-Lipoxygenase] this term only
#195 lipoxygenase or zileuton*
#20 #15 or #16 or #17 or #18 or #19
#21 MeSH descriptor: [Hydrocortisone] this term only

#22 Hydrocortisone*
#23 MeSH descriptor: [Betamethasone] this term only
#24 betamethasone*
#25 MeSH descriptor: [Dexamethasone] this term only
#26 dexamethasone*
#27 MeSH descriptor: [Dexamethasone Isonicotinate] this term only
#28 MeSH descriptor: [Methylprednisolone] this term only
#29 methylprednisolone*
#30 MeSH descriptor: [Prednisolone] this term only
#31 prednisolone*
#32 deflazacort*
#33 #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32
#34 #13 and #33
#35 MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees
#36 nsaid*
#37 nonsteroidal anti-inflammator*
#38 non-steroidal anti-inflammator*
#39#35 or #36 or #37 or #38
#40 #13 and #39
#41 MeSH descriptor: [Aspirin] this term only
#42 aspirin*
#43 MeSH descriptor: [Diclofenac] this term only
#44 diclofenac*
#45 MeSH descriptor: [Ibuprofen] this term only
#46 ibuprofen*
#47 MeSH descriptor: [Fenoprofen] this term only
#48 fenoprofen*
#49 MeSH descriptor: [Flurbiprofen] this term only
#50 flurbiprofen*
#51 MeSH descriptor: [Indomethacin] this term only
#52 indometacin* or ketorolac*
#53 MeSH descriptor: [Ketoprofen] this term only
#54 ketoprofen*
#55 MeSH descriptor: [Ketotifen] explode all trees
#56 ketotifen*
#57 MeSH descriptor: [Piroxicam] this term only
#58 piroxicam* or meloxicam*
#59 MeSH descriptor: [Naproxen] this term only
#60 naproxen*
#61 nabumetone*
#62 MeSH descriptor: [Mefenamic Acid] this term only
#63 mefenamic*
#64 MeSH descriptor: [Meclofenamic Acid] this term only
#65 meclofenamic*
#66 MeSH descriptor: [Etodolac] this term only
#67 etodolac*
#68 MeSH descriptor: [Sulindac] explode all trees
#69 sulindac*
#70 MeSH descriptor: [Tolmetin] this term only
#71 tolmetin* or tolectin*
#72salsalate*
#73 #41 or #42 or #43 or 6 or #45 or #47 or #48 or #52 or #53 or #54 or #55 or #56 or 6 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72
#74 MeSH descriptor: [Brompheniramine] this term only
#75 brompheniramine*
#76 MeSH descriptor: [Chlorpheniramine] this term only
#77 chlorpheniramine*
#78 MeSH descriptor: [Diphenhydramine] this term only
#79 diphenhydramine*
#80 MeSH descriptor: [Clemastine] this term only
#81 clemastine*
#82 fexofenadine* or levocabastine*

#83 MeSH descriptor: [Loratadine] this term only
#84 loratadine*
#85 MeSH descriptor: [Cetirizine] this term only
#86 cetirizine*
#87 #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86
#88 MeSH descriptor: [Administration, Sublingual] this term only
#89 sublingual* or SLIT
#90 oral* near/3 immunotherap*
#91 MeSH descriptor: [Cyclophosphamide] this term only
#92 cyclophosphamide*
#93 MeSH descriptor: [Methotrexate] this term only
#94 methotrexa*
#95 #88 or #89 or #90 or #91 or #92 or #93 or #94
#96 #14 or #20 or #34 or #40 or #73 or #87 or #95
#97 #5 and #96

Appendix 2. MEDLINE Ovid 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. ((vernal or atopic) adj2 keratoconjunctiv$).tw.
16. (VKC or AKC).tw.
17. or/13-16
18. Antibodies, Monoclonal, Humanized/
19. omalizumab$.tw.
20. Cyclosporine/
21. c?closporin$.tw.
22. Tacrolimus/
23. (tacrolimus$ or FK506$).tw.
24. or/18-23
25. (oral$ or systemic).tw.
26. 24 and 25
27. Leukotriene Antagonists/
28. (leukotri$ adj2 (receptor$ or antagonist$)).tw.
29. (montelukast$ or zarfirlukast$ or pranlukast$).tw.
30. Arachidonate 5-Lipoxygenase/
31. (5 lipoxygenase or zileuton$).tw.
32. or/27-31
33. hydrocortisone/
34. hydrocortisone$.tw.
35. betamethasone/
36. betamethasone$.tw.
37. dexamethasone/
38. dexamethasone isonicotinate/
39. dexamethasone$.tw.
40. methylprednisolone/
41. methylprednisolone$.tw.
42. prednisolone/
43. prednisolone$.tw.
44. deflazacort$.tw.

45. or/33-44
46. (oral$ or systemic).tw.
47. 45 and 46
48. exp nonsteroidal antiinflammatory agent/
49. nsaid$.tw.
50. nonsteroidal anti-inflammator$.tw.
51. non-steroidal anti-inflammator$.tw.
52. or/48-51
53. 52 and 46
54. Aspirin/
55. aspirin$.tw.
56. diclofenac/
57. diclofenac$.tw.
58. ibuprofen/
59. ibuprofen$.tw.
60. fenoprofen/
61. fenoprofen$.tw.
62. flurbiprofen/
63. flurbiprofen$.tw.
64. exp indometacin/
65. (indometacin$ or ketorolac$).tw.
66. ketoprofen/
67. ketoprofen$.tw.
68. ketotifen/
69. ketotifen$.tw.
70. piroxicam/
71. (piroxicam$ or meloxicam$).tw.
72. naproxen/
73. naproxen$.tw.
74. nabumetone/
75. nabumetone$.tw.
76. mefenamic acid/
77. mefenamic$.tw.
78. meclofenamic acid/
79. meclofenamic$.tw.
80. etodolac/
81. etodolac$.tw.
82. sulindac/
83. sulindac$.tw.
84. tolmetin/
85. (tolmetin$ or tolectin$).tw.
86. salsalate$.tw.
87. or/54-86
88. brompheniramine/
89. brompheniramine$.tw.
90. chlorpheniramine/
91. chlorpheniramine$.tw.
92. diphenhydramine/
93. diphenhydramine$.tw.
94. clemastine/
95. clemastine$.tw.
96. fexofenadine$.tw.
97. levocabastine$.tw.
98. Loratadine/
99. loratadine$.tw.
100. Cetirizine/
101. cetirizine$.tw.
102. or/88-101
103. exp administration, sublingual/
104. sublingual$.tw.
105. SLIT.tw.
106. (oral$ adj3 immunotherap$).tw.

107. cyclophosphamide/
108. cyclophosphamide$.tw.
109. methotrexate/
110. methotrexate$.tw.
111. or/103-110
112. 26 or 32 or 47 or 53 or 87 or 102 or 111
113. 17 and 112
114. 12 and 113

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville 2006.

Appendix 3. Embase Ovid 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$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. keratoconjunctivitis/
34. atopic keratoconjunctivitis/
35. allergic conjunctivitis/
36. (vernal adj2 keratoconjunctiv$).tw.
37. VKC.tw.
38. or/33-37
39. omalizumab/
40. omalizumab$.tw.
41. Cyclosporine/
42. c?closporin$.tw.
43. Tacrolimus/
44. (tacrolimus$ or FK506$).tw.
45. or/41-44
46. (oral$ or systemic).tw.
47. 45 and 46
48. Montelukast/
49. (montelukast$ or zarfirlukast$ or pranlukast$).tw.

50. leukotriene receptor blocking agent/
51. (leukotri$ adj2 (receptor$ or antagonist$)).tw.
52. arachidonate 5 lipoxygenase/
53. (5 lipoxygenase or zileuton$).tw.
54. or/48-53
55. hydrocortisone/
56. hydrocortisone$.tw.
57. betamethasone/
58. betamethasone$.tw.
59. dexamethasone/
60. dexamethasone isonicotinate/
61. dexamethasone$.tw.
62. methylprednisolone/
63. methylprednisolone$.tw.
64. prednisolone/
65. prednisolone$.tw.
66. deflazacort$.tw.
67. or/55-66
68. (oral$ or systemic).tw.
69. 67 and 68
70. nonsteroid antiinflammatory agent/
71. nsaid$.tw.
72. nonsteroidal anti-inflammator$.tw.
73. non-steroidal anti-inflammator$.tw.
74. or/70-73
75. 68 and 74
76. Aspirin/
77. aspirin$.tw.
78. diclofenac/
79. diclofenac$.tw.
80. ibuprofen/
81. ibuprofen$.tw.
82. fenoprofen/
83. fenoprofen$.tw.
84. flurbiprofen/
85. flurbiprofen$.tw.
86. exp indometacin/
87. (indometacin$ or ketorolac$).tw.
88. ketoprofen/
89. ketoprofen$.tw.
90. ketotifen/
91. ketotifen$.tw.
92. piroxicam/
93. (piroxicam$ or meloxicam$).tw.
94. naproxen/
95. naproxen$.tw.
96. nabumetone/
97. nabumetone$.tw.
98. mefenamic acid/
99. mefenamic$.tw.
100. meclofenamic acid/
101. meclofenamic$.tw.
102. etodolac/
103. etodolac$.tw.
104. sulindac/
105. sulindac$.tw.
106. tolmetin/
107. (tolmetin$ or tolectin$).tw.
108. salsalate$.tw.
109. or/76-108
110. brompheniramine/
111. brompheniramine$.tw.

112. chlorpheniramine/
113. chlorpheniramine$.tw.
114. diphenhydramine/
115. diphenhydramine$.tw.
116. clemastine/
117. clemastine$.tw.
118. fexofenadine$.tw.
119. levocabastine$.tw.
120. Loratadine/
121. loratadine$.tw.
122. Cetirizine/
123. cetirizine$.tw.
124. or/110-123
125. sublingual drug administration/
126. oral immunotherapy/
127. sublingual$.tw.
128. SLIT.tw.
129. (oral$ adj3 immunotherap$).tw.
130. cyclophosphamide/
131. cyclophosphamide$.tw.
132. methotrexate/
133. methotrexate$.tw.
134. or/125-133
135. 47 or 54 or 69 or 75 or 109 or 124 or 134
136. 38 and 135
137. 32 and 136

Appendix 4. ISRCTN search strategy

vernal keratoconjunctivitis OR atopic keratoconjunctivitis

Appendix 5. ClinicalTrials.gov search strategy

vernal keratoconjunctivitis OR atopic keratoconjunctivitis

Appendix 6. WHO ICTRP search strategy

vernal keratoconjunctivitis

atopic keratoconjunctivitis

Appendix 7. Data on study characteristics

Mandatory items		**Optional items**
Methods		
Study design	**Parallel group RCT**	Exclusions after randomisation Losses to follow-up Number randomised/analysed How were missing data handled? *e.g. available case analysis, imputation methods*
Unit of randomisation/unit of analysis	**Unit of analysis participants:** quality of life, symptom score, proportion of participants experiencing systemic adverse events, proportion of participants requiring topical steroids **Unit of analysis one eye of each participant:** clinical signs score, change in best corrected visual acuity, proportion of eyes requiring topical steroids. If people are randomly allocated to treatment but both eyes are included and reported, we will analyse as 'clustered data' i.e. adjust for with-	

(Continued)

	in-person correlation. We may have to contact the trial investigators for further information to do this.	Reported power calculation (Y/N*), if yes, sample size and power* Unusual study design/issues
Participants		
Country		Setting
Total number of participants	*This information should be collected for total study population recruited into the study. If these data are reported for the people who were followed up only, please indicate.*	Ethnic group Equivalence of baseline characteristics (Y/N)
Number (%) of men and women		
Average age and age range		
Inclusion criteria		
Exclusion criteria		
Interventions		
Intervention (n =) Comparator (n =) ***See MECIR 65 and 70***	· Number of people randomised to this group · Drug (or intervention) name · Dose · Frequency · Route of administration	
Outcomes		
Primary and secondary outcomes *as defined in study reports* ***See MECIR R70***	List outcomes Adverse events reported (Y/N) Length of follow up and intervals at which outcomes assessed	Planned/actual length of follow up
Notes		
Date conducted	Specify dates of recruitment of participants mm/yr to mm/yr	Full study name: *(if applicable)*
Sources of funding		Reported subgroup analyses (Y/N)
Declaration of interest ***See MECIR 69***		Were trial investigators contacted?
Included on trials registry	Y/N; including registration number if available	

HISTORY

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Review first published: Issue 10, 2020

CONTRIBUTIONS OF AUTHORS

SEK and ADN developed the protocol. VN prepared the review. FL, MH, and ST critically reviewed the clinical sections. AQ reviewed the statistical section.

DECLARATIONS OF INTEREST

SEK, VN, AQ, FL, MH and ST have no known conflicts of interest to declare.
ADN has received a consulting fee/honorarium/payment from Aerie and Santen to support protocol development for trials, and to review emerging information about treatments for VKC, and to speak at a VKC webinar in 2020. These activities are relevant to the topic of this review (VKC), but as emerging treatments are administered topically, and this review is on systemic treatments, there is no immediate conflict of interest.

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  The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

New co-author, Victoria Nowak taken on for the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [therapeutic use]; Anti-Inflammatory Agents, Non-Steroidal [therapeutic use]; Antibodies, Monoclonal [therapeutic use]; Conjunctivitis, Allergic [*drug therapy]; Immunologic Factors [therapeutic use]; Keratoconjunctivitis [*drug therapy]

MeSH check words

Adolescent; Child; Humans