Cochrane Library

Cochrane Database of Systematic Reviews

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

Kim SE, Quartilho A, Larkin F, Hingorani M, Tuft S, Dahlmann-Noor A

Kim SE, Quartilho A, Larkin F, Hingorani M, Tuft S, Dahlmann-Noor A.
Systemic interventions for severe atopic and vernal keratoconjunctivitis in children and young people up to the age of 16 years.
Cochrane Database of Systematic Reviews 2019, Issue 4. Art. No.: CD013298.
DOI: 10.1002/14651858.CD013298.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

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

Soyang Ella Kim[1], Ana Quartilho[2], Frank Larkin[3], Melanie Hingorani[3], Stephen Tuft[3], Annegret Dahlmann-Noor[2]

[1]Royal Free London NHS Foundation Trust, London, UK. [2]NIHR Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK. [3]Moorfields Eye Hospital NHS Foundation Trust, London, UK

Contact address: Annegret Dahlmann-Noor, NIHR Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, EC1V 2PD, UK. annegret.dahlmann-noor@moorfields.nhs.uk.

Editorial group: Cochrane Eyes and Vision Group.
Publication status and date: New, published in Issue 4, 2019.

Citation: Kim SE, Quartilho A, Larkin F, Hingorani M, Tuft S, Dahlmann-Noor A. Systemic interventions for severe atopic and vernal keratoconjunctivitis in children and young people up to the age of 16 years. *Cochrane Database of Systematic Reviews* 2019, Issue 4. Art. No.: CD013298. DOI: 10.1002/14651858.CD013298.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

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.

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, and 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 (cyclosporin A), montelukast and monoclonal anti-IgE antibodies (omalizumab). This review will 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 from 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 drops 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 would 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 plan to include randomised controlled trials of systemic interventions for AKC and VKC in this review.

Types of participants

We will include studies which 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 keratits which 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 will include trials which enrolled both adults and children if data on children are reported as a subgroup, or can be made available to us. This review will 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 will include trials which 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 will not be 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 will be defined by the included studies.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist will search the following electronic databases for randomised controlled trials and controlled clinical trials. There will be no language or publication year restrictions.

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

Searching other resources

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

Data collection and analysis

Selection of studies

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

We will obtain full-text copies of potentially relevant trials. We will 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 will obtain English translations of abstracts and full-text articles before making a final decision. We will take care to identify multiple reports of the same study.

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

Data extraction and management

Two review authors will independently extract data using an online data extraction form which will be piloted before use. Where data are unclear or inadequate, we will contact the study investigator for missing data or clarification. We will import data directly into Review Manager 5 (RevMan 5) (Review Manager 2014); and the review authors will cross-check for any errors.

Study characteristics

We will 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 including registration number if available.

Outcome data

For continuous outcomes, we will 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 will collect data on the number of events and number of people followed up in each group.

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

We will seek clarification from trial investigators as needed.

Assessment of risk of bias in included studies

Two review authors will 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 2017).

We plan to grade each parameter of trial quality as 'low risk', 'high risk' or 'unclear risk' of bias. We will resolve disagreements by discussion, and if necessary consult a third person. For parameters graded as 'unclear risk', we will contact trial investigators for clarification.

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

1. Selection bias

We will grade studies as either 'high risk', 'low risk', or 'unclear risk' based on the method 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. Lack of allocation concealment would classify as 'high risk', and studies where the details of allocation schedule are not published would be classed as 'unclear risk'. If we make an assessment of 'unclear risk', we plan to ask the study authors to provide further information to enable us to make a more detailed risk 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 will therefore 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 plan to classify attrition bias as 'high risk' if the study authors have not taken missing data into consideration. Other reasons for classifying as high risk would be: if the missing outcome data is 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

Where a study protocol is available, we will compare the protocol with the final outcomes to assess the risk of selective outcome reporting.

6. Other bias

We intend to judge whether the design of each study was subject to any risk of other bias not detailed above.
We will seek clarification from trial investigators as needed.

Measures of treatment effect

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

Unit of analysis issues

Eyes and people

We will not include cross-over studies, and we do 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 included in this review will randomise people, not eyes, to the intervention and comparator, but some outcomes will be reported for eyes, not people.
Our primary outcome (increase in health- or vision-related quality of life) is reported 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 participant.
For those of our outcomes which are reported for people, not eyes, there will not be a unit of analysis issue. If people are randomly allocated to treatment but both eyes are included and reported, we will analyse as 'clustered data' i.e. adjust for within-person correlation. We may have to contact the trial investigators for further information to do this.

Dealing with missing data

If possible, we will conduct an intention-to-treat (ITT) analysis. We will use imputed data if computed by the trial investigators using an appropriate method, but will not impute missing data ourselves.
If ITT data are not available, we will do an available case analysis. This assumes that data are missing at random. We will 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 will 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 are similar enough to make pooling study results sensible.
We will look at the forest plots of study results to see how consistent the results of the studies are, in particular looking at the size and direction of effects.
We will 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 will consider I^2 values over 50% to indicate substantial inconsistency but will also consider Chi^2 P value. As this may have low power when the number of studies are few we will consider P less than 0.1 to indicate statistical significance of the Chi^2 test.

Assessment of reporting biases

We will use the risk of bias assessment tool to look for selective or incomplete reporting. See Assessment of risk of bias in included studies.
If there are 10 trials or more included in a meta-analysis, we will construct funnel plots and consider tests for asymmetry for assessment of publication bias, according to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017).

Data synthesis

We will 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 will describe the results of individual trials narratively.
We will pool data using a random-effects model in RevMan 5. If there are fewer than three trials in a comparison we will use a fixed-effect model.
If there is inconsistency between individual study results such that a pooled result may not be a good summary of the individual trial results - for example, the effects are in different directions or I^2 is

greater than 50% and P is less than 0.1 - we will not pool the data but will describe the pattern of the individual study results.
If there is statistical heterogeneity but all the effect estimates are in the same direction, such that a pooled estimate would seem to provide a good summary of the individual trial results, we may pool the data.

Subgroup analysis and investigation of heterogeneity

We do not plan to carry out subgroup analyses.

Sensitivity analysis

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

Summary of findings

We will prepare a 'Summary of findings' table presenting relative and absolute risks. Two authors will grade independently the overall quality of the evidence for each outcome using the GRADE classification (GRADEpro 2015). We will include our primary and five secondary outcomes in the 'Summary of findings' table, as well as the proportion of participants experiencing adverse effects.

ACKNOWLEDGEMENTS

The methods section of this protocol is based on a standard template prepared by Cochrane Eyes and Vision (CEV). CEV created and will execute the electronic search strategies. We thank Louise Allen and Catey Bunce for peer review comments on this protocol. We thank Anupa Shah and Jennifer Evans for their assistance during the preparation of this protocol.

REFERENCES

Additional references

Akpek 2004
Akpek EK, Dart JK, Watson S, Christen W, Dursun D, Yoo S, et al. A randomized trial of topical cyclosporin 0.05% in topical steroid-resistant atopic keratoconjunctivitis. *Ophthalmology* 2004;**111**(3):476–82.

Anderson 2009
Anderson R, Theron AJ, Gravett CM, Steel HC, Tintinger GR, Feldman C. Montelukast inhibits neutrophil pro-inflammatory activity by a cyclic AMP-dependent mechanism. *British Journal of Pharmacology* 2009;**156**(1): 105–15.

Anzaar 2008
Anzaar F, Gallagher MJ, Bhat P, Arif M, Farooqui S, Foster CS. Use of systemic T-lymphocyte signal transduction inhibitors in the treatment of atopic keratoconjunctivitis. *Cornea* 2008;**27**(8):884–8.

Babu 2013
Babu KS, Polosa R, Morjaria JB. Anti-IgE--emerging opportunities for Omalizumab. *Expert Opinion on Biological Therapy* 2013;**13**(5):765–77.

Bacon 1993
Bacon AS, Tuft SJ, Metz DM, McGill JI, Buckley RJ, Baddeley S, et al. The origin of keratopathy in chronic allergic eye disease: a histopathological study. *Eye* 1993;**7** (Pt 3 Suppl):21–5.

Baschant 2010
Baschant U, Tuckermann J. The role of the glucocorticoid receptor in inflammation and immunity. *Journal of Steroid Biochemistry and Molecular Biology* 2010;**120**(2-3):69–75.

BenEzra 1986
BenEzra D, Pe'er J, Brodsky M, Cohen E. Cyclosporine eyedrops for the treatment of severe vernal keratoconjunctivitis. *American Journal of Ophthalmology* 1986;**101**(3):278–82.

BenEzra 1988
BenEzra D, Matamoros N, Cohen E. Treatment of severe vernal keratoconjunctivitis with cyclosporine A eyedrops. *Transplant Proceedings* 1988;**20**(2 Suppl 2):644–9.

Bleik 1991
Bleik JH, Tabbara KF. Topical cyclosporine in vernal keratoconjunctivitis. *Ophthalmology* 1991;**98**(11):1679–84.

Bonini 2000
Bonini S, Bonini S, Lambiase A, Marchi S, Pasqualetti P, Zuccaro O, et al. Vernal keratoconjunctivitis revisited: a case series of 195 patients with long-term followup. *Ophthalmology* 2000;**107**(6):1157–63.

Bonini 2004
Bonini S, Coassin M, Aronni S, Lambiase A. Vernal keratoconjunctivitis. *Eye* 2004;**18**(4):345–51.

Bonini 2007
Bonini S, Sacchetti M, Mantelli F, Lambiase A. Clinical grading of vernal keratoconjunctivitis. *Current Opinion in Allergy and Clinical Immunology* 2007;**7**(5):436–41.

Bremond-Gignac 2008
Bremond-Gignac D, Donadieu J, Leonardi A, Pouliquen P, Doan S, Chiambarretta F, et al. Prevalence of vernal keratoconjunctivitis: a rare disease?. *British Journal of Ophthalmology* 2008;**92**(8):1097–102.

Buhl 2005
Buhl R. Anti-IgE antibodies for the treatment of asthma. *Current Opinion in Pulmonary Medicine* 2005;**11**(1):27–34.

Cameron 1995a
Cameron JA. Shield ulcers and plaques of the cornea in vernal keratoconjunctivitis. *Ophthalmology* 1995;**102**(6): 985–93.

Cameron 1995b
Cameron JA, Antonios SR, Badr IA. Excimer laser phototherapeutic keratectomy for shield ulcers and corneal plaques in vernal keratoconjunctivitis. *Journal of Refractive Surgery* 1995;**11**(1):31–5.

Covidence [Computer program]
Veritas Health Innovation. Covidence. Version accessed 16 January 2019. Melbourne, Australia: Veritas Health Innovation.

Dahan 1983
Dahan E, Appel R. Vernal keratoconjunctivitis in the black child and its response to therapy. *British Journal of Ophthalmology* 1983;**67**(10):688–92.

Daniell 2006
Daniell M, Constantinou M, Vu HT, Taylor HR. Randomised controlled trial of topical ciclosporin A in steroid dependent allergic conjunctivitis. *British Journal of Ophthalmology* 2006;**90**(4):461–4.

De Smedt 2012
De Smedt S, Nkurikiye J, Fonteyne Y, Tuft S, De Bacquer D, Gilbert C, et al. Topical ciclosporin in the treatment of vernal keratoconjunctivitis in Rwanda, Central Africa: a prospective, randomised, double-masked, controlled clinical trial. *British Journal of Ophthalmology* 2012;**96**(3):323–8.

Doan 2017
Doan S, Amat F, Gabison E, Saf S, Cochereau I, Just J. Omalizumab in severe refractory vernal keratoconjunctivitis in children: case series and review of the literature. *Ophthalmology and Therapy* 2017;**6**(1):195–206.

Ebihara 2009
Ebihara N, Ohashi Y, Uchio E, Okamoto S, Kumagai N, Shoji J, et al. A large prospective observational study of novel cyclosporine 0.1% aqueous ophthalmic solution in the treatment of severe allergic conjunctivitis. *Journal of Ocular Pharmacology and Therapeutics* 2009;**25**(4):365–72.

el-Asrar 1996
el-Asrar AM, Tabbara KF, Geboes K, Missotten L, Desmet V. An immunohistochemical study of topical cyclosporine in vernal keratoconjunctivitis. *American Journal of Ophthalmology* 1996;**121**(2):156–61.

Glanville 2006
Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. *Journal of the Medical Library Association* 2006; **94**(2):130–6.

GRADEpro 2015 [Computer program]
McMaster University (developed by Evidence Prime). GRADEpro GDT. Version accessed prior to 9 January 2019. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Greaves 1976
Greaves MW. Anti-inflammatory action of corticosteroids. *Postgraduate Medical Journal* 1976;**52**(612):631–3.

Guglielmetti 2010
Guglielmetti S, Dart JK, Calder V. Atopic keratoconjunctivitis and atopic dermatitis. *Current Opinion in Allergy and Clinical Immunology* 2010;**10**(5):478–85.

Heffler 2016
Heffler E, Picardi G, Liuzzo MT, Pistorio MP, Crimi N. Omalizumab treatment of vernal keratoconjunctivitis. *JAMA Ophthalmology* 2016;**134**(4):461–3.

Higgins 2002
Higgins J, Thompson S, Deeks J, Altman D. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. *Journal of Health Services Research and Policy* 2002;**7**(1):51–61.

Higgins 2017
Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors), Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017), Cochrane, 2017. Available from www.training.cochrane.org/handbook.

Hingorani 1998
Hingorani M, Moodaley L, Calder VL, Buckley RJ, Lightman S. A randomized, placebo-controlled trial of topical cyclosporin A in steroid-dependent atopic keratoconjunctivitis. *Ophthalmology* 1998;**105**(9):1715–20.

Kim 2010
Kim SJ, Flach AJ, Jampol LM. Nonsteroidal anti-inflammatory drugs in ophthalmology. *Survey of Ophthalmology* 2010;**55**(2):108–33.

Kumar 2009
Kumar S. Vernal keratoconjunctivitis: a major review. *Acta Ophthalmologica* 2009;**87**(2):133–47.

Leonardi 2000
Leonardi A, Borghesan F, Faggian D, Depaoli M, Secchi AG, Plebani M. Tear and serum soluble leukocyte activation markers in conjunctival allergic diseases. *American Journal of Ophthalmology* 2000;**129**(2):151–8.

Leonardi 2006a
Leonardi A, Busca F, Motterle L, Cavarzeran F, Fregona IA, Plebani M, et al. Case series of 406 vernal keratoconjunctivitis patients: a demographic and epidemiological study. *Acta Ophthalmologica Scandinavica* 2006;**84**(3):406–10.

Leonardi 2006b
Leonardi A, Curnow SJ, Zhan H, Calder VL. Multiple cytokines in human tear specimens in seasonal and chronic allergic eye disease and in conjunctival fibroblast cultures. *Clinical and Experimental Allergy* 2006;**36**(6):777–84.

MacGlashan 1997
MacGlashan DW Jr, Bochner BS, Adelman DC, Jardieu PM, Togias A, Lichtenstein LM. Serum IgE level drives basophil and mast cell IgE receptor display. *International Archives of Allergy and Immunology* 1997;**113**(1-3):45–7.

Miyake 2002
Miyake K, Ibaraki N. Prostaglandins and cystoid macular edema. *Survey of Ophthalmology* 2002;**47 Suppl 1**:S203–18.

Pattnaik 2015
Pattnaik L, Acharya L. A comprehensive review on vernal keratoconjunctivitis with emphasis on proteomics. *Life Sciences* 2015;**128**:47–54.

Power 1998
Power WJ, Tugal-Tutkun I, Foster CS. Long-term follow-up of patients with atopic keratoconjunctivitis. *Ophthalmology* 1998;**105**(4):637–42.

Pucci 2002
Pucci N, Novembre E, Cianferoni A, Lombardi E, Bernardini R, Caputo R, et al. Efficacy and safety of cyclosporine eyedrops in vernal keratoconjunctivitis. *Annals of Allergy, Asthma & Immunology* 2002;**89**(3):298–303.

Pucci 2015
Pucci N, Caputo R, di Grande L, de Libero C, Mori F, Barni S, et al. Tacrolimus vs cyclosporine eyedrops in severe cyclosporine-resistant vernal keratoconjunctivitis: A randomized, comparative, double-blind, crossover study. *Pediatric Allergy and Immunology* 2015;**26**(3):256–61.

Review Manager 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Robinson 2008
Robinson AJ, Kashanin D, O'Dowd F, Williams V, Walsh GM. Montelukast inhibition of resting and GM-CSF-stimulated eosinophil adhesion to VCAM-1 under flow conditions appears independent of cysLT(1)R antagonism. *Journal of Leukocyte Biology* 2008;**83**(6):1522–9.

Ruzicka 1997
Ruzicka T, Bieber T, Schopf E, Rubins A, Dobozy A, Bos JD, et al. A short-term trial of tacrolimus ointment for atopic dermatitis. European Tacrolimus Multicenter Atopic Dermatitis Study Group. *New England Journal of Medicine* 1997;**337**(12):816–21.

Sacchetti 2007
Sacchetti M, Baiardini I, Lambiase A, Aronni S, Fassio O, Gramiccioni C, et al. Development and testing of the quality of life in children with vernal keratoconjunctivitis questionnaire. *American Journal of Ophthalmology* 2007; **144**(4):557–63.

Sacchetti 2010
Sacchetti M, Lambiase A, Mantelli F, Deligianni V, Leonardi A, Bonini S. Tailored approach to the treatment of vernal keratoconjunctivitis. *Ophthalmology* 2010;**117**(7):1294–9.

Scadding 2010
Scadding GW, Scadding GK. Recent advances in antileukotriene therapy. *Current Opinion in Allergy and Clinical Immunology* 2010;**10**(4):370–6.

Secchi 1990
Secchi AG, Tognon MS, Leonardi A. Topical use of cyclosporine in the treatment of vernal keratoconjunctivitis. *American Journal of Ophthalmology* 1990;**110**(6):641–5.

Shaker 2016
Shaker M, Salcone E. An update on ocular allergy. *Current Opinion in Allergy and Clinical Immunology* 2016;**16**(5): 505–10.

Shiraki 2016
Shiraki Y, Shoji J, Inada N. Clinical usefulness of monitoring expression levels of CCL24 (Eotaxin-2) mRNA on the ocular surface in patients with vernal keratoconjunctivitis and atopic keratoconjunctivitis. dx.doi.org/10.1155/2016/3573142 (accessed prior to 23 January 2019); Vol. Journal of Ophthalmology 2016. DOI: dx.doi.org/10.1155/2016/3573142

Tabbara 1999
Tabbara KF. Ocular complications of vernal keratoconjunctivitis. *Canadian Journal of Ophthalmology. Journal Canadien d'Ophtalmologie* 1999;**34**(2):88–92.

Tahan 2008
Tahan F, Jazrawi E, Moodley T, Rovati GE, Adcock IM. Montelukast inhibits tumour necrosis factor-alpha-mediated interleukin-8 expression through inhibition of nuclear factor-kappaB p65-associated histone acetyltransferase activity. *Clinical and Experimental Allergy* 2008;**38**(5): 805–11.

Taillé 2010
Taillé C, Doan S, Neukirch C, et al. Omalizumab for severe atopic keratoconjunctivitis. *Case Reports* 2010;**2010**: bcr0420102919.

Tintinger 2010
Tintinger GR, Feldman C, Theron AJ, Anderson R. Montelukast: more than a cysteinyl leukotriene receptor antagonist?. *Scientific World Journal* 2010;**10**:2403–13. DOI: 10.1100/tsw.2010.229

Tuft 1991
Tuft SJ, Kemeny DM, Dart JK, Buckley RJ. Clinical features of atopic keratoconjunctivitis. *Ophthalmology* 1991;**98**(2):150–8.

Uchio 2008
Uchio E, Kimura R, Migita H, Kozawa M, Kadonosono K. Demographic aspects of allergic ocular diseases and evaluation of new criteria for clinical assessment of ocular allergy. *Graefe's Archive for Clinical and Experimental Ophthalmology* 2008;**246**(2):291–6.

Ukponmwan 2003
Ukponmwan CU. Vernal keratoconjunctivitis in Nigerians: 109 consecutive cases. *Tropical Doctor* 2003;**33**(4):242–5.

Varni 2001
Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Medical Care* 2001;**39**(8):800–12.

Vichyanond 2013
Vichyanond P, Kosrirukvongs P. Use of cyclosporine A and tacrolimus in treatment of vernal keratoconjunctivitis. *Current Allergy and Asthma Reports* 2013;**13**(3):308–14.

* *Indicates the major publication for the study*

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* Reported power calculation (Y/N*), if yes, sample size and power* Unusual study design/issues
Unit of randomisation/unit of analysis	**Unit of analysis participants:** quality of life, symptom score, proportion of patients experiencing systemic adverse events, proportion of patients 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 re-	

(*Continued*)

	ported, we will analyse as 'clustered data' i. e. adjust for within-person correlation. We may have to contact the trial investigators for further information to do this	
Participants		
Country		Setting Ethnic group Equivalence of baseline characteristics (Y/
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.*	
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)* Reported subgroup analyses (Y/N) Were trial investigators contacted?
Sources of funding		
Declaration of interest ***See MECIR 69***		

CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

The authors of this proposed review have no known conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- Moorfields Eye Charity, UK.

External sources

- National Institute for Health Research (NIHR), UK.
- Richard Wormald, Co-ordinating Editor for Cochrane Eyes and Vision (CEV) acknowledges financial support for his CEV research sessions from the Department of Health through the award made by the National Institute for Health Research to Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology for a Specialist Biomedical Research Centre for Ophthalmology.
- This protocol was supported by the NIHR, via Cochrane Infrastructure funding to the CEV UK editorial base.

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.