

Sublingual immunotherapy for allergic conjunctivitis: Cochrane systematic review and meta-analysis

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Clinical & Experimental Allergy

Summary

Background Allergic conjunctivitis (AC) is a common manifestation and represents an important co-morbidity of allergic rhinitis (AR). Sublingual immunotherapy (SLIT) is an effective and safe treatment for nasal symptoms of AR; its effectiveness is however less well established for ocular symptoms.

Objectives To evaluate the effectiveness of SLIT in reducing ocular symptoms, the need for ocular treatments and the threshold exposure for conjunctival immediate allergen sensitivity (CIAS).

Methods We searched eight databases up to January 2010. We included only randomized controlled trials (RCT), double-blind and placebo-controlled evaluating the efficacy of SLIT in patients with symptoms of allergic rhinoconjunctivitis (ARC) or AC. Primary outcome measures were total ocular symptom scores, individual ocular symptoms scores (itchy eyes, eye redness, watery eyes, swelling eyes), eye drops use and CIAS. Meta-analysis was undertaken using RevMan 5 software.

Results From 811 abstracts that were screened, 109 studies were reviewed in their full text version. Forty two trials including 3958 participants ($n = 2011$ SLIT and $n = 1947$ placebo) had data suitable for inclusion in the meta-analysis. SLIT induced a significant reduction on both total ocular symptom scores (SMD: -0.41 ; 95%CI: -0.53 to -0.28 ; I^2 : 59%) and individual ocular symptoms scores [red (-0.33 ; -0.45 to -0.22), itchy (-0.31 ; -0.42 to -0.20) and watery eyes (-0.23 ; -0.34 to -0.11)] compared with placebo. Participants in the SLIT group showed an increase in the threshold dose for the CIAS (SMD: 0.35 ; 0.00 – 0.69). No significant reduction was observed on eye drops use (SMD: -0.10 ; -0.22 to 0.03).

Conclusions and Clinical Relevance SLIT is effective in reducing total and individual ocular symptom scores in subjects with ARC or conjunctivitis. No significant reduction was observed in ocular eye drops use.

Keywords allergic, conjunctivitis, eye, immunotherapy, meta-analysis, ocular, rhinitis, sublingual, symptoms

Submitted 28 April 2011; revised 10 May 2011; accepted 10 May 2011.

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Cite this as: M. A. Calderon, M. Penagos, A. Sheikh, G. W. Canonica and S. R. Durham, *Clinical & Experimental Allergy*, 2011 (41) 1263–1272.

This article is based on a Cochrane Review published in the Cochrane Database of Systemic Reviews (CDSR) 2011, issue 7, Art.No: CD007685. DOI:10.1002/14651858.CD007685.pub2 (see www.thecochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and the CDSR should be consulted for the most recent version of the review.

Background

Allergic conjunctivitis (AC) is strongly associated with allergic rhinitis (AR); approximately 90% of patients with AR experience at least 1 day of ocular symptoms per week [1–3]. The prevalence of ocular allergies in the general population is estimated at over 20% in the United States and 18% in the United Kingdom [4]. Seasonal allergic

conjunctivitis (SAC) is mainly due to the direct exposure of the ocular mucosal surfaces to environmental allergens (e.g. pollens from trees, grasses and weeds) interacting with the pollen-specific IgE found on the mast cells of the eye [5]. Perennial allergic conjunctivitis (PAC) is more frequently associated with perennial household allergens (e.g. dust mites, moulds and animal dander). The most common conjunctival symptoms are itching, redness, tearing and swelling [4, 6]. Major visual impairment is uncommon; temporary blurring of vision is the most common corneal symptom [7].

Randomized controlled trials (RCTs) evaluating sublingual immunotherapy (SLIT) for AR have demonstrated that this intervention is clinically effective, safe and provides an antigen-specific protective immune effect [8, 9]. Recent RCTs have begun to investigate the effectiveness of SLIT on ocular symptoms in patients treated for AR [10, 11]. Despite these encouraging initial observations, it is unclear whether these effects are observed consistently across studies. A critical evaluation of the effectiveness of this potential treatment option in people with AC is therefore warranted. The objective of this systematic review was to evaluate the effectiveness of SLIT, compared with placebo, in reducing ocular symptoms, use of topical ocular treatments and the threshold dose to induce conjunctival immediate allergen sensitivity (CIAS).

Materials and methods

Criteria for considering studies for this review

We included double-blind, placebo RCTs using SLIT for children and adults presenting with allergic rhinoconjunctivitis (ARC) or AC. Studies on patients with either seasonal or perennial forms of the disease were eligible for inclusion. We included studies using SLIT administered either by drops or tablets compared with placebo. The primary outcome of interest was the total ocular symptom scores (TOSS); secondary outcomes included: (i) Individual ocular symptom scores (itchy eyes, watery eyes, eye redness, swelling eyes); (ii) combined symptom-medication scores; (iii) eye drops use; and (iv) CIAS. We evaluated the effect of interventions on primary and secondary outcomes after at least one pollen season for seasonal allergens and for at least 6 consecutive months for perennial allergens.

Search methods for identification of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) in The Cochrane Library, MEDLINE, EMBASE, Latin American and Caribbean Literature on Health Sciences (LILACS), Web of Science, Biosis Previews, UK Clinical Trials Gateway and Scopus

up to January 2010 (Cochrane Library 2010/2011) for published work. We in addition searched for unpublished and in-progress work by: (i) constructing a database of and searching for first and last authors of potentially eligible studies and The Science Citation Index Expanded (SCI-EXPANDED); (ii) database of international experts in SLIT; (iii) scrutinizing the bibliographies of identified studies; (iv) contacting relevant product manufacturers; (v) searching websites listing ongoing trials, i.e. <http://clinicaltrials.gov/> [12] and <http://www.actr.org.au/> [13] and the UK Clinical Trials Gateway on the Current Controlled Trials website (<http://www.controlled-trials.com>) [14]. There was no language restrictions used in any of our searches.

Data collection and analysis

Selection of studies. Two authors (M. C. and M. P.) independently reviewed titles and abstracts from literature searches for relevant trials for full review. The full text versions of all potentially eligible studies were obtained and subjected to independent review. At this stage, any study rejected was documented in the 'Characteristics of excluded studies table' (Cochrane Library 2010/2011). The percentage agreement between the investigators for the assessment of inclusion was reported. We resolved disagreement by discussion between both of the authors; in the case of consensus not being reached, a third author (S. R. D.) was involved and, if necessary, arbitrated [15, 16].

Data extraction and management. Two authors (M. P. and M. C.) independently extracted data using a suitably adapted version of the data extraction form developed by the Cochrane Eyes and Vision Group. We resolved disagreements by discussion between both of the authors; in case of consensus not being reached, a third author (S. R. D.) was involved and, if necessary, arbitrated.

Assessment of risk of bias in included studies. Two authors (M. C. and M. P.) working independently assessed the included studies for sources of systematic bias in trials according to the guidelines in *Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions* [17]. The agreement of authors on risk of bias assessment was measured [15, 16]; disagreements were resolved by discussion and, if necessary, with the involvement of a third author (S. R. D. or A. S.). We considered the following domains for assessing risk of bias (The Cochrane Collaboration's tool) [17]: (i) sequence generation; (ii) allocation concealment; (iii) blinding; (iv) incomplete outcome data; (v) selective outcome reporting and (vi) other sources of bias.

Measures of treatment effect. We used the Review Manager 5.0 software [18] for data analysis and data synthesis. For continuous data (TOSS and individual symptom scores, ocular medication scores and CIAS), we calculated individual and, if appropriate, pooled statistics as mean differences (MD) and/or standardized means differences with 95% confidence interval (CI). Quantitative analyses of outcomes were wherever possible, on an intention-to-treat basis.

Dealing with missing data. We contacted authors for details about study design or descriptive statistics for outcomes that were not presented in the paper (mean $\pm$ SD). If the authors did not respond within a reasonable time (6–8 weeks), we proceeded with analysis using available data.

Assessment of heterogeneity. We gave consideration to the appropriateness of meta-analysis in the presence of significant clinical or statistical heterogeneity. We tested for inconsistency using the I^2 statistic and substantial heterogeneity was assumed if I^2 is $> 50\%$ (i.e. more than 50% of the variability in outcome between trials could not be explained by sampling variation).[19–22]

Assessment of reporting biases. We looked for evidence of publication bias graphically using funnel plots and statistically by means of the Begg's and the Egger's tests, if a sufficient number of trials was identified for the primary outcome [17, 23–25].

Data synthesis. If there was a significant heterogeneity ($I^2 < 40\%$), a random-effects model was chosen, otherwise a fixed-effect model was used.

Subgroup analysis and investigation of heterogeneity. We investigated using subgroup analyses. Our subgroups of interest were: (i) seasonal or perennial conjunctivitis; (ii) treatment duration; (iii) allergen dose (daily dose in μg , if this was available) and (iv) participant's age group (children < 18 or adults).

Sensitivity analysis. Sensitivity analysis was performed by: (i) determining the impact of exclusion of studies with lower methodological quality and (ii) by using different statistical methods (fixed-effect and random-effects models).

Results

Description of studies

Results of the search. Our search strategy identified 811 citations. After reading title and abstracts 693 were excluded; 109 papers were identified as potentially relevant and were evaluated in detail (Fig. 1). Fifty-two

studies were excluded from this review upon detailed reading. Reasons for exclusion were: outcomes of interest not evaluated ($n = 12$), studies not controlled with placebo ($n = 12$), study design differences ($n = 8$), outcomes reported in other studies ($n = 8$), not double-blind ($n = 6$), trials designed to evaluate safety ($n = 2$), reviews ($n = 2$), studies that were non-randomized ($n = 1$) and other inclusion criteria ($n = 1$). From the original search, 57 studies (8.6%) met the inclusion criteria. Of these, 15 studies did not have extractable data and therefore were not included in the meta-analysis [26]. Forty-two studies (5.1%) had available data to evaluate the efficacy of SLIT on AC and were included in the analysis [8, 9, 27–65].

Included studies

Eleven studies were published between 1994 and 1999, 13 from 2000 to 2005 and 18 from 2006 up to the last search. Thirty-five (88%) of the included studies evaluated the efficacy of seasonal allergens and seven (12%) trials focussed on those with perennial disease. Nineteen (45%) used grass pollen extracts, 10 (24%) trials evaluated tree pollen extracts, six (14.5%) mites, six (14.5%) weeds and one (2%) was a study assessed the efficacy of a standardized cat extract. All of these trials compared SLIT with placebo using a double-blind design. Thirty-one (74%) studies administered the extracts as sublingual drops, nine (21%) as tablets and two (5%) both drops during the build-up phase and subsequently tablets for maintenance. A total of 3958 participants with a median age of 29.7 years were treated for a median duration of 12 months (range 3–36). SLIT was given to 2011 (50.8%) participants and placebo to 1947 (49.2%). Two studies [58, 65] were included in the systematic review, but not in the pooled analyses; due to authors provided us with raw data, which did not allow us to perform calculations of arithmetic means and standard deviations.

Imputation of missing variance data

No imputation of data was performed in the case of missing outcomes; all the authors were contacted, if the information was not available, the study was excluded from the meta-analysis but included in the systematic review.

Risk of bias in included studies

Allocation. Thirty-one studies described the methods used to generate the allocation sequence (50%) and 12 trials described the methods used to conceal the allocation sequence (29%).

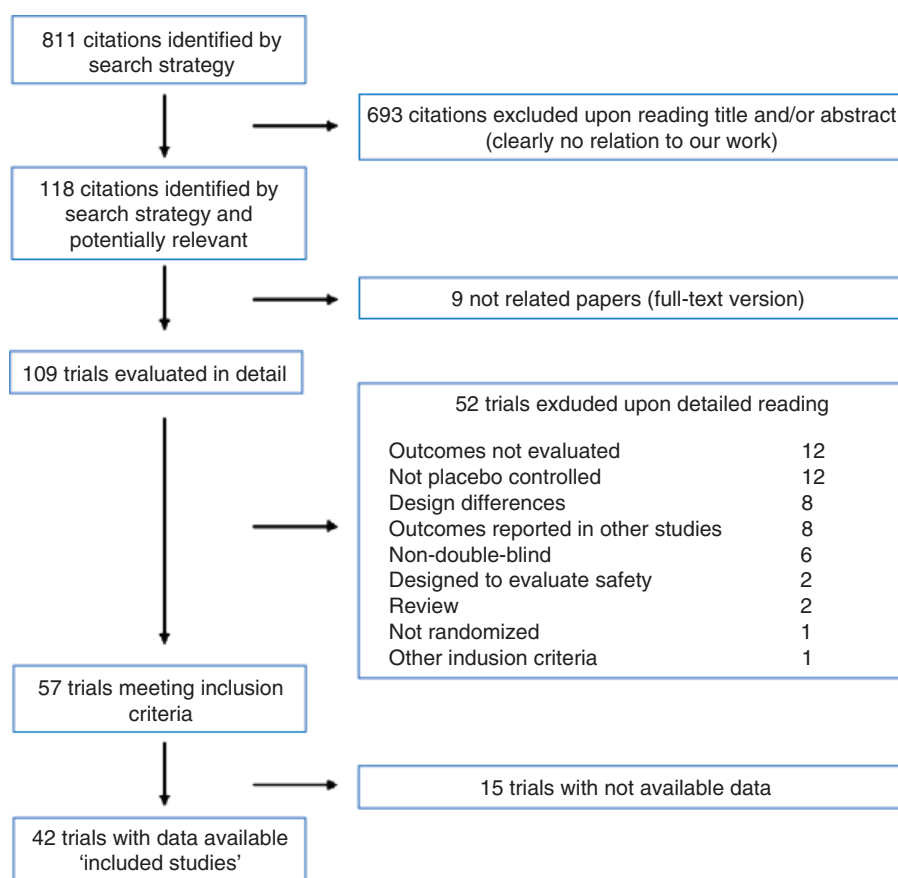


Fig. 1. Flowchart showing selection of studies for inclusion in meta-analysis.

Blinding. Thirty-eight studies (91%) described the measures used to blind study participants and personnel from knowledge of which intervention a participant received.

Incomplete outcome data. Forty studies (95%) described the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis.

Selective reporting. Forty studies (95%) stated how the possibility of selective outcome reporting was examined by the review authors, and what was found.

Other potential sources of bias. Thirty-three studies (79%) stated any important concerns about bias not addressed in the other domains in the tool (Cochrane Library 2011).

Effectiveness of sublingual immunotherapy

Effects of sublingual immunotherapy on total ocular symptom scores

TOSS was evaluated in 36 studies ($n = 1725$ SLIT and $n = 1674$ placebo). SLIT induced a significant reduction on TOSS compared with placebo (SMD, -0.41 ; 95%CI,

-0.53 to -0.28). There was evidence of heterogeneity between studies ($I^2 = 59\%$) (Fig. 2). Assessment according to the allergen type for those studies using SLIT with seasonal allergens ($n = 30$) showed a significant reduction on total ocular symptom scores compared with placebo (SMD, -0.38 ; 95%CI, -0.50 to -0.25 ; $I^2 = 58\%$), but not perennial allergens ($n = 6$) (SMD, -0.52 ; 95%CI, -1.05 to 0.01 ; $I^2 = 70\%$).

TOSS in adults was evaluated in 27 studies ($n = 1304$ SLIT and $n = 1238$ placebo). There was a significant reduction in the subjects treated with SLIT (SMD -0.48 ; 95%CI, -0.63 to -0.32 ; $I^2 = 64\%$). TOSS in children was assessed in nine studies ($n = 421$ SLIT and $n = 436$ placebo) showed a significant reduction on total ocular symptom scores (SMD -0.27 ; 95%CI, -0.46 to -0.07 ; $I^2 = 39\%$).

The impact of the duration of treatment was evaluated. Twenty-six studies gave treatment up to 12 months ($n = 1468$ SLIT and $n = 1420$ placebo); these studies found a significant reduction on TOSS in the SLIT group compared with placebo (SMD -0.40 ; 95%CI, -0.53 to -0.27 ; $I^2 = 58\%$). Ten trials gave treatment for 13 months or more ($n = 257$ SLIT and $n = 254$ placebo) and showed a significant reduction on TOSS (SMD -0.43 ; 95%CI, -0.76 to -0.10 ; $I^2 = 68\%$).

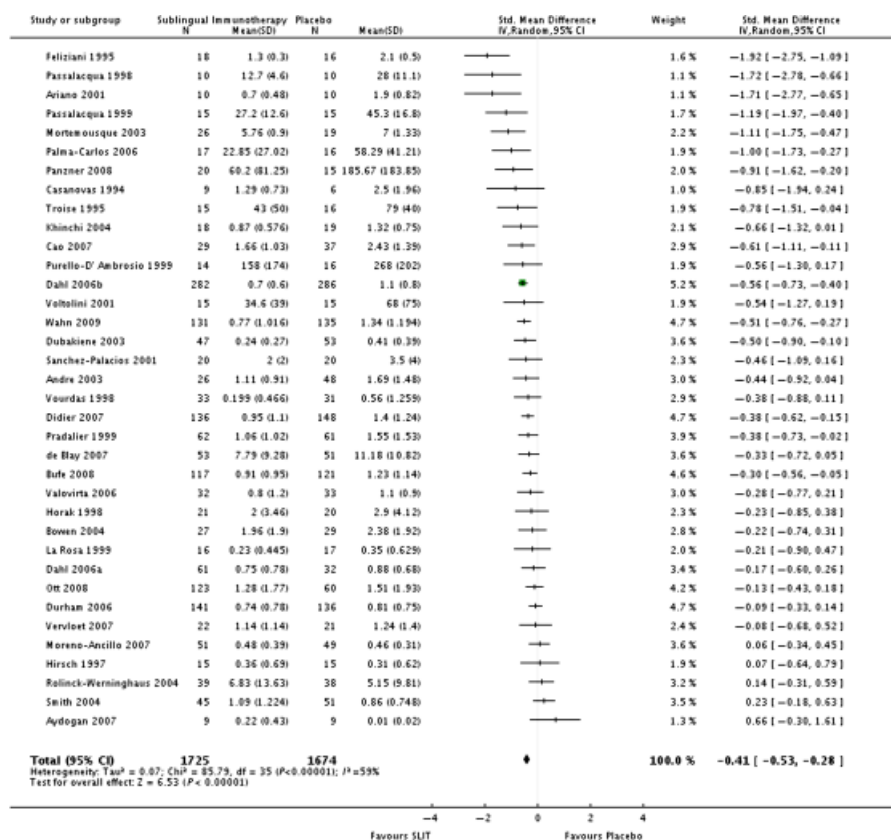


Fig. 2. Sublingual immunotherapy compared with placebo. Outcome: Total ocular symptom scores.

Effects of sublingual immunotherapy on individual ocular symptom scores

Itchy-gritty eyes was evaluated in 28 studies ($n = 1540$ SLIT and $n = 1480$ placebo). There was a significant reduction on eye itchiness in the subjects treated with SLIT (SMD: -0.31 ; 95%CI, -0.42 to -0.20). No significant inter-study heterogeneity was found ($I^2 = 46\%$). For two studies, this was the primary ocular outcome and data for total ocular symptom scores were not reported.[50, 55]

Watery eyes was assessed in 21 studies ($n = 1344$ SLIT and $n = 1297$ placebo). There was a significant reduction in watery eyes in those subjects who received SLIT compared with placebo (SMD: -0.23 ; 95%CI, -0.34 to -0.11 ; $I^2 = 42\%$).

Red eyes was reported in 20 studies ($n = 624$ SLIT and $n = 587$ placebo). The overall effect across these trials showed a significant reduction on the scores of the participants treated with SLIT (SMD: -0.33 ; 95%CI, -0.45 to -0.22). No significant inter-study heterogeneity was found ($I^2 = 27\%$).

Ocular swelling was reported only in two studies ($n = 66$ SLIT and $n = 66$ placebo). No effect was observed between both treatments (SMD: -0.23 ; 95%CI, -1.19 to 0.72). Inter-study heterogeneity was significant ($I^2 = 83\%$).

Effects of sublingual immunotherapy on combined symptom-medication scores

Three studies reported combined symptom-medication scores as outcome ($n = 176$ SLIT and $n = 175$ placebo). There was a marginally non-significant reduction in the combined scores in those patients receiving SLIT (SMD: -0.21 ; 95%CI, -0.55 to 0.13). Heterogeneity among studies was significant ($I^2 = 59\%$). In two studies, this was the primary ocular outcome and total ocular symptom scores were not reported [31, 51].

Effects of sublingual immunotherapy on ocular medication scores

Thirteen studies reported the use of eye drops ($n = 560$ SLIT and $n = 478$ placebo). There were not significant differences between the interventions (SMD: -0.10 ; 95%CI, -0.22 to 0.03) No significant inter-study heterogeneity was found ($I^2 = 34\%$).

Effects of sublingual immunotherapy on the conjunctival immediate allergen sensitivity

Four trials evaluated this outcome ($n = 130$ SLIT and $n = 120$ placebo). Those subjects in the active treatment showed an increase in the threshold dose for the

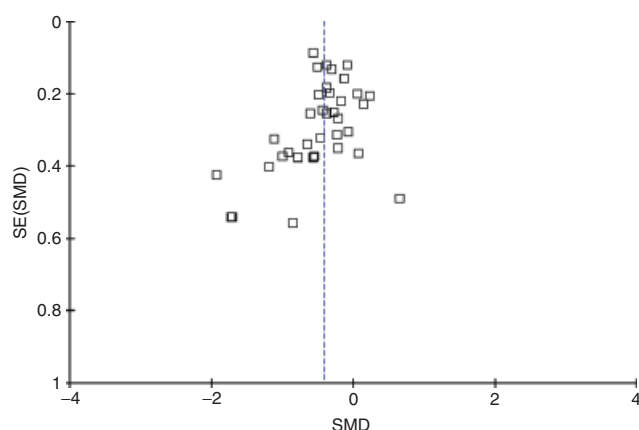


Fig. 3. Funnel plot for publication bias detection for total ocular symptoms score.

conjunctival allergen provocation test (SMD: 0.35; 95%CI, 0.00–0.69). No substantial inter-study heterogeneity was found ($I^2 = 43\%$).

Analysis of publication bias

Funnel plots. Funnel plots for TOSS were reasonably symmetrical and there did not appear to be a paucity of smaller trials with small or absent symptoms reduction effect (Fig. 3).

Egger's and Begg's tests. The analysis of small study bias for TOSS using the Egger's test was not statistically significant ($P = 0.144$); however, the Begg's test showed a significant publication bias ($P = 0.007$). Both tests were not significant in other analyses. Tertile analysis based on publication year: A *post hoc* tertile analysis for TOSS was carried out to determine the effect of the year of publication of trials on SLIT reported efficacy. The SMD of the latest tertile (2006–2009) was compared with that of the earliest tertile (1994–1999); there was no significant difference for total symptom scores between them.

Sensitivity analyses

Sensitivity analyses were performed to assess the robustness of the results, which were unchanged whether the fixed-effect model or random-effects model were used.

Discussion

This systematic review and meta-analysis of double-blind, placebo-controlled RCTs confirms that SLIT reduces significantly both the total and individual ocular symptoms scores (redness, itchiness and watery eyes) in patients with AC with or without rhinitis. Participants in all included trials were selected based on objective confirmation of

their atopic status and the clinical manifestation of the allergic disease. Most of the studies reported adequately on the age and sex of the patients, allergen causing disease and disease severity. Therefore patients were broadly representative of patients with AC, which enhances the generalizability of our findings.

Although early trials assessing the effects of SLIT did not particularly focus on symptoms of conjunctivitis, more recent studies have tended to refer to the improvement in ocular symptoms when these have been evaluated as a separate outcome. The effect sizes of SLIT over placebo observed in the present analysis, compare favourably with those found in recent large double-blind, placebo-controlled RCTs [8, 9]. For example, similar effect sizes were seen in a RCT enrolling 644 adults with ARC who were treated with a sublingual grass allergen tablet ($n = 316$) or placebo ($n = 318$) given for at least 16 weeks before and continuing during the grass pollen season [8, 10]. For eye symptoms, the score for the actively treated group was reduced in 36% as compared with placebo ($P = 0.0001$). The analysis of individual symptoms also showed consistently lower scores in the immunotherapy group. The percentage reductions relative to placebo were 32% for gritty eyes ($P < 0.0001$) and 44% for watery eyes ($P < 0.0001$). [10] Similarly, in another study with 628 adults using a grass pollen tablet for SAR symptoms of watery and itchy eyes were significantly reduced after pre-seasonal and co-seasonal treatment ($P = 0.0016$ and $P = 0.0012$, respectively) [9].

In our review, we found that reductions were evident in the studies assessing seasonal allergens ($P < 0.00001$), but not perennial ($P = 0.05$). These differences could be explained by the paucity of studies evaluating perennial allergens ($n = 6$) (SMD -0.52 , 95%CI -1.05 to 0.01) and for the small numbers of participants analysed for this outcome (SLIT 109 vs. placebo 110).

SLIT in children induced a significant reduction in TOSS after pooling the nine studies including exclusively participants aged 4–17 years old ($P = 0.007$). This has been confirmed in recent studies in children, including large populations [32, 64]. Similar reductions were observed for TOSS in adults ($P < 0.00001$).

Interestingly, increasing the duration of treatment beyond 12 months did not appear to affect the treatment effect. However, we consider that this sub-analysis is difficult to assess due to the fact that most of the studies evaluated diverse schedules of treatment, different types of allergens and the timing of treatment was variable with respect to pollen seasons. Other factors such as the frequency of administration of the SLIT and the continuity of the treatment out-seasons may also affect outcomes.

Reduction of medications scores in subjects receiving SLIT has been shown in previous meta-analyses.[66–71] The participants in large studies also used significantly less rescue medication as compared with placebo (reduction of

total symptom score 38%, $P < 0.0001$) [8, 9]. However, in the current review, we did not find a significant effect of SLIT in the reduction of eye drops use ($P = 0.14$). This lack of effect could be explained by the fact that participants generally are instructed to use intranasal steroids and take systemic anti-histamines as rescue medications. These medications are easy to be taken and both have demonstrated to be effective to reduce ocular symptoms in patients with ARC.

The effect of standard medications in ocular symptoms has been evaluated. In recent retrospective analyses of RCTs using topical nasal corticosteroids compared with placebo, ocular symptom scores have been reduced.[72, 73] The mechanism by which an intranasal corticosteroid reduces ocular allergic symptoms has been under investigation, some effects on both the reflex neural activity and the local inflammation facilitating the nasolacrimal drainage have been proposed.[4, 72, 74] Additionally, second generation antihistamines have shown reductions in individual ocular symptoms following allergen conjunctival challenges or continuous treatment for AR, respectively.[3, 75] No studies have been conducted to evaluate the effect of SLIT vs. standard medications.

Regarding the allergen dose, available evidence particularly derived from large comparisons evaluating diverse dosages of pollen extracts, has demonstrated that the efficacy is related with the daily amount of allergen administered [8, 9, 38, 60]. Meta-analyses are not the best methods to determine the effect of the allergen dose on the clinical outcomes. This is due to the diversity of allergen preparations used, variable daily and cumulative doses and, the lack of information in some studies regarding the dose of the major allergen expressed in a common unit (mcg). Other statistical methods are available to assess this relationship such as the meta-regression. However, the ideal way of looking at the effect of dose would be to have randomized trials comparing the doses (head-to-head comparisons) [16, 76–78].

We identified some studies with design limitations, lack of sample size calculation and poor measures to prevent bias. These studies, basically published earlier, did not follow the Consolidated Standards of Reporting Trials (CONSORT) statement for the publication of randomized controlled trials [79]. This made the identification of key information regarding randomization methods and concealment of allocation difficult. On the other hand, publication bias is an important drawback of systematic reviews and is difficult to avoid. The analyses of publication bias for TOSS using the funnel plot analysis and the Egger's test did not show a statistical significant bias. However, a significant bias was detected using the Begg's test. We conclude that small study bias (including publication) is possible in our review, but this should not affect the statistical significance of our findings. Authors have been encouraged to publish 'negative results studies' to allow researchers to avoid publication bias [78].

We identified some possible bias sources in the present meta-analysis, such as some outcomes presented a degree of inter-study inconsistency (heterogeneity); studies with low statistical power were included and some outcomes included few numbers of studies [16]. Heterogeneity among studies (I^2) was around 50% or below for all end-points. This applies for all outcomes except for swelling eyes ($I^2 = 83\%$); however, this outcome was assessed in only two studies. Moderate heterogeneity was found when TOSS was analysed ($I^2 = 59\%$). Subgroup analysis for TOSS did not decrease statistical heterogeneity, therefore, we cannot rule out that this is due to a true variability of effects in the studies, or due to methodological variability (e.g. measurement tools used to obtain the total symptom score). A key methodological limitation is the small sample size of most of the studies (56%, less than 30 participants per arm). In this review, only 17% included more than 100 participants in each arm, 8% up to 50 and 19% up to 30. Some trials did not adequately describe their method of randomization or allocation concealment thus precluding formal assessment of the likelihood of selection bias.

This review has several strengths, such as the restrictive inclusion criteria for the studies, the fulfilment of the AMSTAR criteria [80], the statistically significant effect size found according to Cohen's criteria, the robust statistical methods to control both inter and intra study variability and the quantitative approach carried out. Moreover, most of the analysed data were provided by the authors.

We need more well-designed and powered studies assessing the impact on quality of life, cost-effectiveness and head-to-head studies with other treatment regimens. At the time of this review, we identified in an international clinical trials registry (<http://clinicaltrials.gov/>) [12] 14 randomized, parallel-group, double-blind and placebo-controlled clinical trials which are currently in progress. Their data were not available for inclusion in this review. A better understanding of the long-term effectiveness of SLIT in inducing tolerance is also required.

In conclusion, SLIT has effects on multiple allergic symptoms, including ocular symptoms, and is effective in the treatment of rhinoconjunctivitis.

Acknowledgements

We thank Anupa Shah, Review Group Co-ordinator for Cochrane Eyes Vision Group (CEVG). We acknowledge CEVG Trials Search Co-ordinator Iris Gordon for devising and running the electronic searches. We thank the Co-ordinating Editor, Richard Wormald for his assistance and comments. We are grateful to Giovanni Virgili from the University of Florence, Italy for his statistical support and advice in this review.

Declarations of interest: Dr Calderon has received lectures fees from ALK-Abello Denmark, manufactures of allergen extracts. Dr Martin Penagos has nothing to

declare. Professor Canonica has received research grants from ALK-Abello, Lofarma and Stallergènes – manufacturers of allergen extracts. Professor Durham has received consultancy fees from ALK-Abello Denmark, Circassia UK

and Greer Laboratories USA, manufacturers of allergen extracts and research grants from ALK-Abello via Imperial College London.

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