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REVIEW ARTICLE

Ragweed sublingual immunotherapy (SLIT) tablets in allergic rhinoconjunctivitis: a systematic review and meta-analysis

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Abstract

Purpose Ragweed allergen causes Allergic rhinoconjunctivitis and sublingual immunotherapy is one of the treatment modalities to desensitize allergic individuals. This systematic review assesses the effectiveness and safety of sublingual immunotherapy for allergic rhinoconjunctivitis caused due to Ragweed.

Methods The databases search was done through December 2020. English-language randomized controlled trials were included if they compared sublingual immunotherapy with placebo, pharmacotherapy, or other sublingual immunotherapy regimens, and reported clinical outcomes. The strength of the evidence for each comparison and outcome was graded based on the risk of bias, consistency, magnitude of effect, and the directness of the evidence.

Results The searches performed according to the protocol identified 134 abstracts of which 67 were duplicates. A total of 37 full papers were therefore reviewed of which 5 were included for the final study. Participants' ages ranged from 4 to 58 years. The risk of bias was low in most studies. The review suggests that sublingual immunotherapy improves rhinoconjunctivitis symptoms, with 4 of 4 studies reporting efficacy showed improvement in the symptom score of SLIT groups compared to placebo. Local reactions were frequent, but anaphylaxis was not reported in any of the studies. Serious adverse events were very few in all the studies.

Conclusions The overall evidence showed the effectiveness of sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis with or without asthma, but high-quality studies are still needed to answer questions regarding optimal dosing strategies.

Keywords Allergic rhinoconjunctivitis · Sublingual immunotherapy · Ragweed allergy

Abbreviations

ARC	Allergic rhinoconjunctivitis
AR/C	Allergic rhinitis, with or without conjunctivitis
SLIT	Sublingual immunotherapy
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROSPERO	Prospective register of systematic review
RCT	Randomized controlled trials
TCS	Total combined symptom and medication score
DSS	Daily symptom score
DMS	Daily medication score
AE	Adverse effects

Introduction

Allergic rhinoconjunctivitis (ARC) is an allergic disorder of the nose and eyes, resulting in a chronic, mostly eosinophilic, inflammation of the nasal mucosa and conjunctiva [1, 2]. The disease is triggered by exposure to seasonal and/or perennial allergens and, depending on the nature of the allergenic trigger(s) and patterns of exposure, symptoms may be intermittent, persistent or persistent with intermittent exacerbations [3]. Allergic rhinitis, with or without conjunctivitis (AR/C), is one of the most prevalent allergic diseases affecting around a fifth of the general population [1, 4]. Allergic rhinitis is typically characterized by symptoms of nasal obstruction, a watery nasal discharge, sneezing, and itching, and there is often (but

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not invariably) involvement of the conjunctiva (allergic conjunctivitis), which manifests with itching, injection, and tearing. Furthermore, allergic rhinitis is a risk factor for the development of asthma [5].

Ragweed (*Ambrosia artemisiifolia*) is a weed that belongs to the Asteraceae family. It is a small annual weed with a peculiar bloom. More than 30 species exist worldwide. *A. artemisiifolia* is a weed that originates from North America and also effects parts of Europe [6]. From a clinical point of view, ragweed pollen can cause allergic rhinoconjunctivitis. Approximately 25% to 40% of patients with ragweed pollen-induced allergic rhinitis with or without conjunctivitis (AR/C) have comorbid asthma, [7, 8] and a direct link between asthma exacerbations and peak ragweed pollen levels has been made in some regions of the United States [9, 10].

Allergy immunotherapy is a treatment option for ARC that has long-lasting disease-modifying and preventive effects [11]. Sublingual immunotherapy (SLIT) represents a mode of treatment that is safe, convenient, and effective treatment modality for the management of allergic respiratory disease [12]. SLIT tablets allows for daily at-home administration. The convenience of at-home administration and the avoidance of repeat injections may make SLIT tablets an appealing alternative to subcutaneous immunotherapy, particularly for children [13]. Sublingual immunotherapy involves placement of the allergen under the tongue for local absorption to desensitize the allergic individual over an extended treatment period to diminish allergic symptoms [14]. Hence, this study was done with the following objectives:

- To determine the efficacy of ragweed Sublingual immunotherapy (SLIT) tablets for the treatment of allergic rhinoconjunctivitis.
- To determine the safety of ragweed Sublingual immunotherapy (SLIT) tablets in the treatment of allergic rhinoconjunctivitis.

Materials and methods

Design and registration

This was a systematic review and meta-analysis of experimental studies. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for reporting systematic reviews incorporating meta-analyses for reporting our review [16]. The study protocol was registered on *"prospective register of systematic review (PROSPERO)"*. PROSPERO (Registration Number: CRD42021228544).

Eligibility criteria

Type of participants/population

Study population included persons of any age or sex with a history of allergic rhinoconjunctivitis with/without asthma caused due to the Ragweed allergen. Trials dealing with asthma alone were excluded. Individuals had to have no other clinically relevant allergen sensitivities.

Intervention

Sublingual immunotherapy (SLIT) tablets or immunotherapy delivered by the sublingual route at all doses and all durations of treatment.

Control

Comparator group included placebo treatment or any other alternative intervention.

Types of study included

The review included all types of experimental studies, including randomized controlled trials (RCTs) and controlled clinical trials, mainly phase II and above.

Outcome measures

The primary end point was symptom scores recorded.

- The average total combined symptom and medication score (TCS), which is the sum of the average rhinoconjunctivitis daily symptom score (DSS) and average rhinoconjunctivitis daily medication score (DMS)

Additional outcome(s)

Adverse events.

Other inclusion criteria

1. Only those studies published in English language, academic peer-reviewed journals were included in the review.
2. The studies with good supporting evidence, such as details of databases searched, sound methodological background with qualitative assessment of the included study were included in our systematic review.

3. Only with full-text availability.

Other exclusion criteria

1. Studies with no comparison group, but only single group were excluded from the study.
2. Secondary analyses or pooled analysis, narrative reviews, scoping reviews, any discussions of literature, and systematic review without good theoretical or methodological background were excluded.

Searches

Only those studies published in the English language, academic peer-reviewed journals published were included in the review. A systematic literature search was performed in PubMed, Embase, Cochrane Library, and clinical trial.gov through March 2021 in the English language. A literature search was carried out by two independent authors using a structured search strategy (Table 1). In the first step, free text searching of the keywords and their synonyms was done using appropriate truncations, wildcards, and proximity searching. Search also was conducted for key concepts using corresponding subject headings in each database. The final search was carried out by combining the individual search results using appropriate Boolean operators. The searches were complemented by screening the references of selected articles to find those that did not appear in the search databases. Additional references were obtained from a simple Google search.

Data extraction (selection and coding)

All the citations along with the title and abstract retrieved using the search strategy were imported to a specified endnote library and final list of studies were screened for inclusion in the study and were prepared by removing the duplicates. Two researchers carefully screened the title and abstracts to shortlist the studies which were likely to satisfy the inclusion criteria of the review. Any disagreement between them over the eligibility of particular studies was resolved through discussion with a third researcher. Attempts were made to obtain full-text articles for all these shortlisted studies, and thorough assessment was done for the satisfaction of inclusion and exclusion criteria. Studies not satisfying inclusion criteria were excluded further. The list of excluded studies and the reasons for exclusion were presented in the "characteristics of excluded studies" table. "PRISMA flow chart" was used to clearly represent the screening and selection process. Data were extracted from included studies manually on to a structured data extraction form, which was developed and pilot tested using the "Cochrane Consumers and Communication Review Group" Data Extraction Template. Attempts were made to obtain all the relevant missing data by contacting the primary authors.

Risk-of-bias (quality) assessment

Methodological quality of included studies was assessed for all individual elements of RCTs, including randomization, allocation concealment, blinding, selective outcome reporting, and completeness of the data. Attempt was made to evaluate the possibility of reporting bias by comparing the final study with the study protocol. Fixed- and random-effects estimate was compared to assess the role of small sample bias and random-effects estimate was presented in the presence of it. If a sufficient number of studies are available, funnel plots were made to explore the role of reporting bias further.

Strategy for data synthesis

We assessed the included studies for methodological heterogenicity with respect to PICOST components of the study. The demographic composition and severity of the disease condition was considered as important population characteristics. The dosage and schedule of primary intervention, nature, dosage, and duration of the supportive interventions was considered. The outcomes and methods used for their assessment, timing of their assessment, and study design features were evaluated.

The results were summarized by meta-analysis in the absence of substantial methodological heterogenicity; else, a qualitative synthesis was performed. Each outcome was combined and calculated using the statistical software R according to the statistical guidelines referenced in the current version of the Cochrane Handbook for Systematic Reviews of Interventions. Chi-square test with 0.1 significance level and I^2 statistic was used to assess the statistical heterogenicity. Attempts were made to explain the source heterogenicity by subgroup analysis or sensitivity analysis. Fixed- or random-effects model was chosen based on the level of heterogenicity.

Treatment effect was summarized by pooled relative risk (RR) with 95% CI for dichotomous outcomes. For continuous outcomes, weighted mean differences (with 95% CI) or standardized mean differences (95% CI) if different measurement scales were used. Skewed data and non-quantitative data were presented descriptively. All the studies were assessed for consistency with respect to unit of randomization and unit of analysis.

Results

The searches performed according to the protocol identified 134 abstracts (PUBMED = 26, EMBASE = 72, COCHRANE = 32, CLINICALTRIAL.GOV = 6), of

Table 1 Search strategy

Sl no	PubMed
1	**#1:** ("Ambrosia"[Mesh]) OR "ragweed pollen" [Supplementary Concept] **883** **#2:** ((((("ragweed"[Title/Abstract]) OR ("ragweed allergy"[Title/Abstract])) OR ("ragweeds"[Title/Abstract])) OR ("ambrosia"[Title/Abstract])) OR ("ambrosia allergen"[Title/Abstract]) **3,238** **#3:** "Sublingual Immunotherapy"[Mesh] **516** **#4:** ((("sublingual immunotherapy"[Title/Abstract]) OR ("sublingual immunotherapies"[Title/Abstract])) OR ("slit"[Title/Abstract])) **19,711** **#5:** (immunotherap* OR desensiti*ation) AND (sublingual) **2,171** **#6**: "rhinoconjunctivitis"[Title/Abstract] **2,544** **#7:** (((immunotherap* OR desensiti*ation) AND (sublingual)) OR ((((("sublingual immunotherapy"[Title/Abstract]) OR ("sublingual immunotherapies"[Title/Abstract])) OR ("slit"[Title/Abstract])))) OR ("Sublingual Immunotherapy"[Mesh]) **20,137** **#8:** (((((("ragweed"[Title/Abstract]) OR ("ragweed allergy"[Title/Abstract])) OR ("ragweeds"[Title/Abstract])) OR ("ambrosia"[Title/Abstract])) OR ("ambrosia allergen"[Title/Abstract])) OR (("Ambrosia"[Mesh]) OR "ragweed pollen" [Supplementary Concept]) **3,306** **#9:** (((((((("ragweed"[Title/Abstract]) OR ("ragweed allergy"[Title/Abstract])) OR ("ragweeds"[Title/Abstract])) OR ("ambrosia"[Title/Abstract])) OR ("ambrosia allergen"[Title/Abstract])) OR (("Ambrosia"[Mesh]) OR "ragweed pollen" [Supplementary Concept])) AND ((((immunotherap* OR desensiti*ation) AND (sublingual)) OR ((((("sublingual immunotherapy"[Title/Abstract]) OR ("sublingual immunotherapies"[Title/Abstract])) OR ("slit"[Title/Abstract])))) OR ("Sublingual Immunotherapy"[Mesh]))) AND ("rhinoconjunctivitis"[Title/Abstract]) **26**
2	Embase **#1 'ragweed allergy'**/exp OR **'ragweed allergy'**/de OR **'ragweed pollen'**/exp OR **'ragweed pollen'**/de OR **'ragweed'**/exp OR **'ragweed'**/de **3,037** **#2: ragweed**:ti,ab,kw **3,667** **#3:'ragweed allergy'**:ti,ab,kw **172** **#4: ambrosia**:ti,ab,kw **1,338** **#5: #1** OR **#2** OR **#3** OR # **44,973** **#6: 'sublingual immunotherapy'**:ti,ab,kw **2,788** **#7: slit** AND **tablets** **352** **#8:**(**immunotherap*** OR **desensiti*ation**) AND **sublingual** **4,644** **#9: #6** OR **#7** OR # **84,704** **#10: 'rhinoconjunctivitis'**/exp OR **'rhinoconjunctivitis'**/de **4,519** **#11: 'rhinoconjunctivitis'**:ti,ab **4,225** **#12: rhino** AND **conjunctivitis** **532** **#13: #10** OR **#11** OR **#12** **6,251** **#14**: **#5** AND **#9** AND **#13** **70** Cochrane

Table 1 (continued)

Sl no	PubMed
	#1MeSH descriptor: [Ambrosia] explode all trees48 #2("Ambrosia"):ti,ab,kw81 #3(ragweed allergy):ti,ab,kw195 #4(ragweed):ti,ab,kw577 #5(ragweed pollen):ti,ab,kw322 #6#1 OR #2 OR #3 OR #4 OR #5591 #7MeSH descriptor: [Sublingual Immunotherapy] explode all trees100 #8(sublingual immunotherapy):ti,ab,kw1119 #9(SLIT tablets):ti,ab,kw171 #10#7 OR #8 OR #91,148 #11(rhinoconjunctivitis):ti,ab,kw1626 #12#6 AND #10 AND #1132
	Clinical trial.gov
	Sublingual Immunotherapy | Ragweed Allergy **6 studies**

which 67 were duplicates. Out of the 86 articles, 49 s were immediately considered unsuitable for inclusion (review articles, descriptive studies, and other routes of allergen administration). A total of 37 full papers were therefore reviewed of which 5 were included for the final study (Fig. 1).

Description of studies

Five studies were therefore included in this analysis. The methods, participants, interventions, dose, and duration of the included studies are listed in the table of characteristics of included studies. One study was done both in adults and children [14]. Three studies were conducted in adults [12, 15, 16]. and one in children [13]. Two studies administered the drug as tablets and 3 others as droplets (Table 2). It was earlier determined that we would conduct a meta-analysis. However, the study population, mode of administration of drug, drug dosage, and also the duration of treatment given differed in all the studies. Hence, only narrative review was done. Moreover, Nayak A. S et al. [16] conducted only safety analysis.

Methodological quality of included studies

All included studies were double-blind placebo-controlled trials of parallel group design. Concealment of treatment allocation was considered adequate in almost all studies—based on statements made by the original authors. Blinding of study subjects and investigators was almost universally maintained by use of identical placebo preparations. It should, however, be noted that most investigators reported high levels of minor oral side effects (tingling, itching, and swelling beneath the tongue) in actively treated subjects (Table 3).

Symptom scores

All of the included studies reported daily symptom scores (DSS), recorded in patient diaries, as a primary outcome measure. A few studies also reported daily medication score (DMS) and total combined score (TCS). Data obtained in this way were expressed in terms of mean and SD. One study by Nayak A. S. et al. [16] conducted only safety analysis and was therefore excluded from the analysis. All the studies reported the symptoms throughout the year, whereas Bowen T. et al. [17] reported the symptoms only in peak season (Table 4).

Safety

The safety data were reported in all studies and are summarized in Table 5. Most adverse events were mild-to-moderate in nature. The severe events in the included studies were very less. The most common AEs were localized pruritus, nasal irritation, throat irritation, and oronasal adverse events. Nausea was observed more frequently in the treatment group. Only Nolte H. et al. [13] reported hypersensitivity in two patients. However, anaphylaxis was not observed in any of the studies.

Discussion

The effectiveness of SLIT on allergic rhinitis, allergic rhinoconjunctivitis, and asthma has been evaluated previously in a number of systematic reviews [5, 14, 18–20]. These systematic reviews demonstrate its effectiveness for grass mix, tree mix, pollen, house dust mite, or multiple allergens driven allergens. There are also some data that suggest that SLIT may prevent the development of asthma [21, 22]. SLIT has been shown to be a safe treatment in many clinical trials and post-marketing surveys both in adults and in children,

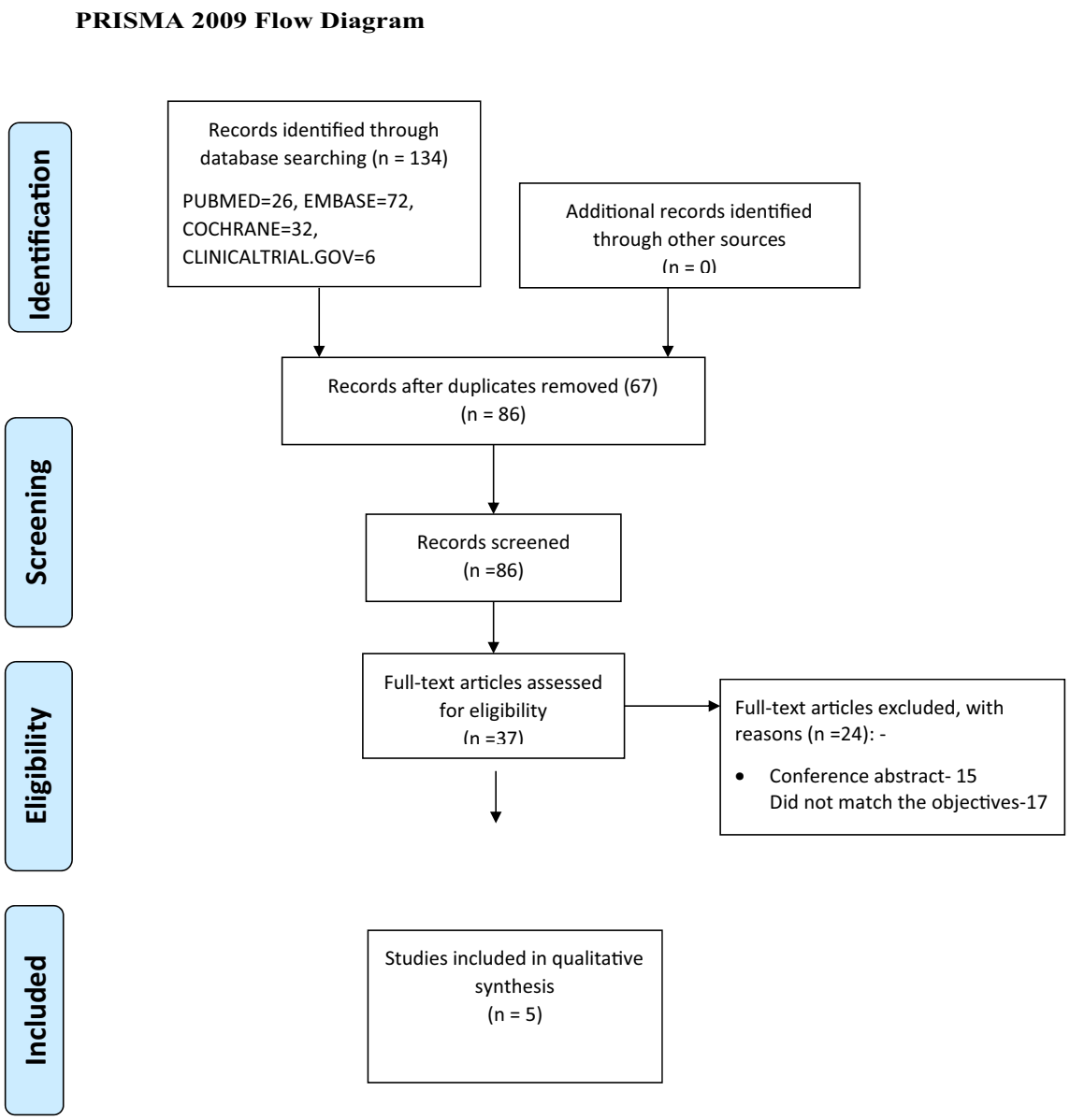

Fig. 1 PRISMA 2009 Flow Diagram

as well as in pre-school aged children [23–25]. Hence, we wanted to determine if SLIT is sufficient for controlling ragweed allergy alone in allergic rhinoconjunctivitis with or without asthma.

A total of 5 studies were included in this systematic review. Four of the five studies determined the efficacy of the ragweed SLIT tablets. Most studies had a low risk of bias, and a few studies had limited information on the randomization and blinding. However, on the overall, the studies had a low risk of bias with good study design. The meta-analyses could not be performed due to heterogenicity in the study population, mode of administration of drug, drug dosage, and also the duration of treatment. Bowen et al. [17] had the highest dosage administered from 116 µg of Amb a 1, with the objective of reaching 314 µg of Amb a 1 daily maintenance therapy, both in children and adults. In adults, the dosing by Skoner D. et al. [15] ranged from 4.8 to 48 µg Amb a 1/d and 18 µg Amb a 1 to 50 µg Amb a 1 by Creticos P. S. et al. [12] in children the dose of 12 µg Amb a 1 was maintained by Nolte H. et al. [13]; hence, the dosage ranged from 4.8 µg Amb a 1 to 314 µg Amb a 1/day. However, it was seen that the direction of all the study results was in favour of the intervention. Additionally, two studies found an increase in efficacy of the drugs with an increase in dosage. However, the dose–response relationship must be further studied and discussed.

Table 2 Characteristics of included studies

Sl no	Author/date	Experimental N(M/F)	Placebo N(M/F)	Study population	Asthma diagnosis, no. (%)	Dose received	Duration	Mode of administration
1	Bowen T. et al. [17] (2004)	37(23/14)	39(22/17)	Pediatric and adult patients (6–58 years)	Placebo: 6 (15.4) Experimental: 9 (24.3)	Daily dose of 0.5 to 300 IR (index of reactivity dosage) i.e. 10-, 100-, and 300-IR/mL concentration	17 days	Drops
2	Skoner D. et al. [15] (2010)	Medium dose 39(10/29) High dose 36(12/24)	40(19/21)	Adults 18–50	Placebo: 3 (7.5) Experimental: 3 (7.7)	medium-dose extract (4.8 µg Amb a 1/d; n 5 39), or high-dose extract (48 µg Amb a 1/d; n 5 36)	17 ± 3 weeks	Drops
3	Nayak A. S. et al. [16] (2012)	40(19/21)	13(7/6)	Adults 18–50 years	Placebo: 2 (15) Experimental:5(13)	Six dose groups were planned: 3, 6, 12, 24, 50, and 100 µg Amba1	28 days	Tablets
4	Creticos P. S. et al. [12] (2014)	218(91/127)	211(94/117)	Adults 18–55 years	Placebo: 19 (9.0) Experimental: 17 (7.8)	18 µg Amb a 1 or approximately 50 µg Amb a 1)	8–16 weeks	Liquid extract
5	Nolte H. et al. [13](2020)	512(324/188)	510(319/191)	Children 4–17 years	Placebo: 217 (42.5) Experimental: 219 (42.8)	12 Amb a 1-Unit dose	28 weeks	Tablets

Table 3 Risk of assessment of bias

	Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data assessments	Selective reporting	Other bias
1	Bowen T. et al. [17] (2004)	Low	Unknown	Low	Unknown	Unknown	Low	Low
2	Skoner D. et al. [15] (2010)	Low	Low	Low	Unknown	Low	Low	Low
3	Nayak A. S. et al. [16] (2012)	Low	Low	Low	Unclear	Low	Low	Low
4	Creticos P. S. et al. [12] (2014)	Low	Low	Low	Unclear	Low	Low	Low
5	Nolte H. et al. [13] (2020)	Low	Low	Low	Unclear	Low	Low	Low

The duration of the studies ranged from 17 days to 28 weeks. Currently, the EMA currently recommends an experimental, randomized, controlled design involving 3 years of therapy with a 2 year follow-up period off treatment [1]. All included studies evaluated the efficacy of SLIT follow participants for less than 1 year on therapy. A few studies have demonstrated benefit with SLIT-tablet grass pollen therapy for more than 3 years. [26, 27] It is recommended to conduct a long-term study with respect to ragweed immunotherapy to determine the efficacy of the SLIT tablet to control ragweed allergy.

Table 4 Effect of SLIT in allergic rhinoconjunctivitis

S no	Author/date	Season	Daily symptom score	Daily medication score	Combined score (Mean ± SD)
1	Bowen T. et al. [17] (2004)	Peak season	Total rhinitis score Placebo group: 5.03 ± 2.54 Treatment group: 3.95 ± 2.45 Total conjunctivitis score Placebo group: 2.38 ± 1.92 Treatment group: 1.96 ± 1.90	Placebo group: 1.26 ± 1.24 Treatment group: 1.05 ± 1.60	
2	Skoner D. et al. [15] (2010)	Peak season	Placebo group: 1.24 ± 2.88 Medium dose: 0.74 ± 1.95 High dose: 0.53 ± 1.35	Placebo group: 1.01 ± 2.07 Medium dose: 0.40 ± 1.35 High dose: 0.28 ± 0.70	Placebo group: 2.25 ± 4.25 Medium dose: 1.14 ± 3.03 High dose: 0.81 ± 1.74
		Entire pollen season	Placebo group: 1.00 ± 2.30 Medium dose: 0.46 ± 1.40 High dose: 0.19 ± 1.16	Placebo group: 0.63 ± 1.06 Medium dose: 0.16 ± 0.92 High dose: 0.0003 ± 1.64	Placebo group: 1.63 ± 2.99 Medium dose: 0.63 ± 2.02 High dose: 0.19 ± 2.32
3	Creticos P. S. et al. [12] (2014)	Peak season	Placebo group: 2.02 ± 3.20 Treatment group: 1.17 ± 2.10		Placebo group: 1.90 ± 3.01 Treatment group: 1.12 ± 1.99
		Entire pollen season	Placebo group: 1.44 ± 2.40 Treatment group: 0.82 ± 1.64		Placebo group: 1.37 ± 2.29 Treatment group: 0.79 ± 1.56
4	Nolte H. et al. [13] (2020)	Peak season	Placebo group: 3.95 (3.63–4.26) Treatment group: 2.55 (2.24–2.86)	Placebo group: 3.85 (3.14–4.57) Treatment group: 2.01 (1.57–2.46)	Placebo group: 7.12 (6.57–7.67) Treatment group: 4.39 (3.85–4.94)
		Entire pollen season	Placebo group: 3.26 (3.00–3.52) Treatment group: 2.27 (2.01–2.53)	Placebo group: 2.48 (2.22–2.73) Treatment group: 1.61 (1.36–1.86)	Placebo group: 5.75 (5.30–6.20) Treatment group: 3.88 (3.44–4.33)

No serious intraoperative or postoperative complications were observed in any of the studies. The known side effects were mild in nature. The safety outcomes were however not consistent throughout the included studies. SLIT has been shown to be a safe treatment in many clinical trials and post-marketing survey both in adults and in children, as well as in pre-school aged children, in children with allergic rhinitis or controlled asthma. [23, 28, 29] Mild local adverse reactions were commonly reported in all the studies. They disappear within a few days of treatment. The well-known adverse events of SLIT mainly consist of oral itching or swelling, lip edema, throat pruritus, and nausea. They are easily contained by transitorily diminishing the dose or antihistamine premedication for several weeks. Systemic reactions and asthma exacerbations were very uncommon, while anaphylaxis had not been reported in any of the studies.

In the present study, co-existing asthma was seen in all the studies. Co-existing asthma has no impact on the efficacy of SLIT for ARC and may also lead to improvement in asthma. Relative reductions in asthma symptom score, SABA use, and nocturnal awakenings due to asthma symptoms were observed with ragweed SLIT-tablet treatment compared with placebo in the study by Nolte H. et al. [13]; also, in the same study, the safety profile in children with asthma was comparable to that in children without asthma. None of the other included study studied the effect of SLIT tablets on asthma patients. SLIT has been found to be generally effective in treatment of patients with house dust mite and grass pollen allergies, but studies are lacking for other allergens [30]. However, the uncontrolled or severe asthma was definitely considered to be an absolute contraindication to AIT in the previous literature [31–34].

Limitations

1. The key limitation of the review is that the studies conducted on Ragweed allergy SLIT tablets is very limited compared to the other allergen.
2. There is a huge heterogenicity in the baseline characteristics of the intervention and control groups in the included studies.
3. The sample size determination has not been mentioned in any of the studies. Moreover, a few studies had small number of subjects and short duration of treatment,

Table 5 Sublingual immunotherapy safety summary of studies reporting adverse events (continued)

	Overall AEs	Severe AEs	Nasopharyngitis	Sinus/nasal congestion	Oromucosal (edema/pain pruritus)	Throat irritation	Ear pruritus	Skin pruritis	Eye pruritis
Bowen T. et al.									
Placebo	16 (40%)	0							
Experimental	30 (70%)	0							
Skoner D. et al.									
Placebo	29 (73%)	3			0				
Medium dose	25 (64%)	1			13%				
High dose	20 (56%)	8			11%				
Nayak A. S. et al.									
Placebo	7 (54%)	0		1 (8)	0	0	1 (8)	0	8 (20)
Experimental	34 (85%)	3 (8)		4 (10)	25 (63)	4 (10)	11 (28)	2 (5)	1 (8)
Creticos P. S. et al.									
Placebo	105 (44%)	6 (3)	9 (4)	10 (5)	5 (2)		1 (0.5)	8 (4)	
Experimental	93 (48) %	2 (1)	12 (6)	4 (2)	22 (10)		4 (2)	10 (5)	
Nolte H. et al.									
Placebo	338 (65.9%)		8 (1.6)		75 (14.7)	92 (18.1)	32 (6.3)		
Experimental	160 (31.4%)		56 (10.9)		304 (59.3)	249 (48.5)	174 (33.9		

which make it difficult for rare AEs or problems associated with long-term use to be detected.

4. The greater incidence of AEs with active treatment may have caused some subjects and investigators to guess treatment assignment despite double blinding, thus possibly influencing perceived tolerability.
5. Another potential limitation of the trial was that the number of ragweed pollens in the particular region and the presence of other pollens or allergens could have impacted the results or the randomization at done at the baseline.

Despite these limitations and the fact that the data could not be pooled to arrive at an overall estimate, it could be said that the direction of the effect was favoring the intervention group compared to placebo. It could be summarized that the findings of the current study indicate that short ragweed pollen allergenic extract administered by sublingual swallow is safe and shows potential as an effective therapy in adults with rhinoconjunctivitis caused by ragweed pollen.

The overall evidence.

Conclusions

Based on the results of this systematic review, it can be concluded that there is evidence in the literature showing the effectiveness of sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis with or without asthma, but high-quality studies are still needed to answer questions regarding optimal dosing strategies.

Recommendations

1. Large-scale, scientifically designed Randomized Controlled Trails are needed to generate better quality evidence regarding the efficacy of SLIT tablets on ragweed allergic rhinoconjunctivitis.
2. Considering the limited availability of studies from selected countries of Europe and USA, with wide cultural variations, there is a need to undertake interven-

tional studies in these settings, to identify region-specific outcomes.
3. More importance must be given to the dose–response relationship in children as well as adults.
4. The long-term effect of ragweed allergies must be studied.

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Declarations

Conflict of interest The authors declare no conflicts of interest.

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