

Role of sublingual immunotherapy in the treatment of asthma: An updated systematic review

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Background: The purpose of the systematic review is to evaluate the efficacy and safety of sublingual immunotherapy (SLIT) for the treatment of allergic asthma.

Methods: PubMed, Embase, and CENTRAL databases were searched, updating an earlier review (January 1, 2005 through May 8, 2017). Randomized, controlled studies (RCTs) were included, which reported one of the prespecified outcomes: asthma symptoms measured by control composite scores; quality of life; medication use; pulmonary physiology; and health-care utilization. For safety outcomes, RCTs and observational studies were included. Two independent reviewers extracted data, assessed risk of bias, and graded strength of evidence (SOE) for each outcome.

Results: Fourteen RCTs (n = 2585) assessed the efficacy of SLIT for asthma. The RCTs utilized house dust mite (HDM), birch, or grass allergen. SLIT improved asthma symptoms (high SOE), decreased use of long-term control medication, and improved forced expiratory volume in 1 second (FEV₁) (moderate SOE). SLIT may decrease quick-relief medication use, and improve disease-specific quality of life (low SOE). For safety, 20 RCTs and 10 observational studies

(n = 3621) were identified. Local (risk differences ranged from −0.03 to +0.765) and systemic allergic reactions (risk differences ranged from −0.03 to +0.06) were a common occurrence in SLIT and control groups. Life-threatening reactions were uncommon, with 3 cases of anaphylaxis and no deaths reported.

Conclusion: There is moderate-to-high strength evidence that SLIT improves allergic asthma symptoms, reduces long-term control medication use, and improves FEV₁ based on studies of HDM, birch, and grass. SLIT rarely is associated with life-threatening adverse events. © 2018 ARS-AAOA, LLC.

Key Words:

allergy immunotherapy; asthma; sublingual immunotherapy; allergens

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Asthma is a chronic inflammatory disorder of the airways, characterized by varying degrees of airflow obstruction. Globally, asthma ranks 14th based on the burden of disease, as measured by disability adjusted life-years.¹ Allergic asthma is triggered by inhaling airborne allergens, which trigger an immunoglobulin E (IgE)-mediated

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hypersensitivity reaction that eventually results in airway inflammation and swelling. In the United States, 78% of asthmatic children and 75% of middle-aged adult asthmatics are allergic to 1 or more inhalant allergens, as evidenced by allergy skin testing.²

There are currently 3 treatment options for patients with allergic asthma: allergen avoidance; pharmacotherapy, including biologics; and allergen immunotherapy (AIT). AIT consists of the repeated administration of 1 or multiple allergens to which the patient is sensitized, which leads to increased tolerance to the allergen and decreased symptoms. It offers the advantage of modulating the immune system, reducing IgE-mediated hypersensitivity, and therefore could have long-lasting effects on the control of allergic asthma.

Sublingual immunotherapy (SLIT) is a form of AIT that may be dosed at home, and consists of exposure to the allergen via an aqueous solution or tablet formulation placed under the tongue. The rationale for this route of therapy is based on its perceived improved safety margin in comparison to subcutaneous immunotherapy (SCIT) (reduced risk of anaphylaxis) and its simple and convenient oral dosing regimen (avoiding the discomfort of injections and the inconvenience of office visits required for allergy shots). Currently, in the US, there are 2 forms of SLIT: tablet and “off-label” aqueous solution (which involves the use of those allergens approved for SCIT in an “off-label” form of administration, as there are no aqueous products specifically approved by the Food & Drug Administration [FDA] for sublingual use). Four tablet formulations of SLIT are available in the US for clinical use: dust mite; ragweed; Timothy grass; and grass mix. Typical regimens for SLIT include daily home administration, with dosing regimens such as year-round or pre-/co-seasonal for several years.

In 2013, the Johns Hopkins University Evidence-based Practice Center (JHU EPC) completed a review of AIT for the treatment of allergic rhinoconjunctivitis and/or asthma.³ The report was limited to aqueous formulations of SLIT only. The previous evidence report found high strength of evidence that SLIT in the aqueous form reduces asthma symptoms. However, in the interim, since publication of the 2013 report, the number of well-designed randomized, controlled trials (RCTs) of SLIT and asthma has continually increased. The purpose of the current systematic review is to assess the efficacy and safety of SLIT (tablet and aqueous) in patients with allergic asthma by expanding the scope of the review and updating the evidence from the previous 2013 report.

Materials and methods

We report here a subset of results from a larger review that assessed SLIT and subcutaneous immunotherapy.³ The current systematic review assesses the efficacy and safety of SLIT for allergic asthma by expanding the scope and updating the evidence from the previous 2013 report. Our protocol for the full review was developed with

guidance from a technical expert panel, and from representatives of both the Agency for Health Care Research and Quality (AHRQ) and the National Heart, Lung, and Blood Institute (NHLBI). The protocol was registered in PROSPERO (<http://www.crd.york.ac.uk/PROSPERO/>), registration number CRD42016047749, and posted on the AHRQ website (<https://effectivehealthcare.ahrq.gov/ehc/products/644/2311/asthma-immunotherapy-protocol-160913.pdf/>).

Data sources and searches

We rescreened all of the included studies in our previous systematic review³ to confirm eligibility for this review. We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 1, 2005 through May 8, 2017 (see Appendix Table S1 in the Supplementary Material online for detailed search strategy). We requested Scientific Information Packages from industry representatives, but no information was provided. We also hand-searched previous reviews and guidelines,^{4–7} searched ClinicalTrials.gov, and reviewed the FDA Adverse Event Reporting System (FAERS).

We included studies of patients of any age with diagnosis of allergic asthma. Subjects of included articles had allergic rhinitis, positive allergy testing, and asthma. Studies had to report on prespecified outcomes, which included: asthma symptoms as reported by asthma control composite scores; quality of life; medication use; health-care utilization; and pulmonary physiology (ie, forced expiratory volume in 1 second [FEV₁]). Safety outcomes included anaphylaxis, local effects (adverse reactions as the site of administration), systemic effects, and deaths. Studies were required to have an intervention arm receiving SLIT (tablet or aqueous). We excluded studies on food allergies, if aeroallergens were not related to asthma, or if the type of allergen was not specified. We excluded studies on allergic conditions that did not report results separately for patients with asthma. Study inclusion was not restricted by language of publication. We included only RCTs for efficacy. For adverse events, we included RCTs, and observational studies (cohort, case-control, case series, and case reports).

Study selection

Abstracts and full-text articles were screened independently by 2 reviewers. Any disagreements regarding inclusion were resolved through discussion, and unresolved conflicts were adjudicated during team meetings.

Data extraction and quality assessment

Two reviewers sequentially extracted data and assessed risk of bias of included studies. Efficacy outcomes that were specified in our protocol included: asthma symptoms as reported by asthma control composite scores; quality of life; medication use; health-care utilization; and pulmonary physiology (FEV₁). Safety outcomes included anaphylaxis, local effects (adverse reactions as the site

of administration), systemic effects, and deaths. Details regarding SLIT, including allergen, formulation, dose, and treatment duration, were extracted.

For RCTs, the risk of bias was assessed using the Cochrane tool.⁸ Overall risk of bias was graded as low, moderate, or high. We used the ROBINS-I (Risk Of Bias In Non-randomized Studies-of Interventions) tool to assess observational studies.⁹ Overall risk of bias was graded as low, medium, or high. For case reports and case series, we used the World Health Organization (WHO) criteria to judge the likelihood that the intervention was causally related (dose- and time-related) to the observed adverse event.¹⁰ Following this guidance, we reported causality from case reports and case series as certain/probable, likely/possible, unlikely/conditional, unclassified/unassessable, or unclassifiable.

Data synthesis and analysis

We completed a qualitative synthesis for all questions. We considered meta-analyses but determined that the studies were not sufficiently homogeneous, with variability in patient characteristics, allergen and dose used, study duration, and outcome definitions.

We graded the strength of evidence (SOE) for each outcome using the scheme recommended in the Evidence-based Practice Center Methods Guide.^{11,12} Five domains were considered when grading the SOE for an outcome: study limitations (called risk of bias in this review); directness; consistency; precision; and reporting bias.¹¹ SOE was classified into 1 of 4 grades: (1) “high” grade (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect); (2) “moderate” grade (indicating moderate confidence that the evidence reflects the true effect but further research could change our confidence in the estimate of the effect and may change the estimate); (3) “low” grade (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and (4) “insufficient” grade (indicating evidence is unavailable or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion). We graded RCT and non-RCT evidence separately; we did not grade case reports/case series.

Role of funding source

Protocol development was conducted with input from representatives of the NHLBI and from AHRQ.

Results

The new search identified 2771 citations, and 142 articles were screened from the previous review (Fig. 1). We included 32 studies, with 22 RCTs and 10 observational studies (see Appendix Table S2 online).

Efficacy outcomes

We identified 14 RCTs regarding the efficacy of SLIT for asthma encompassing 2585 patients. The RCTs utilized house dust mite (HDM), birch, or grass allergen. Appendix Table S1 provides the details of each study. The articles were published between 2001 and 2016, with 75% of the articles originating from Europe. The majority of studies treated HDM allergy; the next most commonly treated allergies in these studies were birch and grass. No efficacy study used multiple allergen immunotherapy.

Asthma symptoms

Asthma symptom control outcomes were reported in 4 RCTs,^{13–16} which included a total of 1193 patients (see Appendix Tables S3 online). Clinically and statistically significant improvement in scores were reported in 2 of 4 studies.^{14–16} Three studies had low risk of bias, and the fourth had medium risk of bias. Two studies used tablets,^{13,14} and 2 used aqueous drops.^{15,17}

Three studies used HDM in comparison to placebo and utilized the Asthma Control Questionnaire (ACQ), a standardized questionnaire for evaluation of asthma symptoms.^{13–15} The treatment duration for all 3 HDM studies was 1 year. One of the 3 HDM studies was performed in patients with mild to moderate persistent asthma and demonstrated statistically significant improvement in asthma symptoms with SLIT.¹⁵ This study compared the percentage of patients with an ACQ score of <0.75 at the end of the study based on treatment vs placebo; raw data were not reported by the authors, so it could not be determined whether they achieved the minimal clinically important difference (MCID).¹⁷ However, a subgroup analysis of 180 moderate persistent asthmatics found statistically significant improvement in their ACQ (percentage improvement 56% vs 40%, $p < 0.039$); this effect was not found in the mild asthmatics.¹⁵ The second RCT found a decrease of 0.41 in ACQ score in the 6 Standardized Quality House Dust Mite (SQ-HDM) treatment group ($p > 0.05$), compared with no change in score in the control group that was not statistically significant.¹⁴ This decrease in ACQ is not considered clinically important. The third HDM study was performed in patients with moderate to severe asthma and did not demonstrate statistically significant improvement ($p = 0.22$).¹³

The fourth study of asthma symptoms used aqueous birch allergen for 3 years plus daily inhaled budesonide 400 $\mu\text{g}/\text{d}$ and the Asthma Control Test (ACT), a standardized questionnaire, to assess asthma symptoms.¹⁶ The comparator group was treated with inhaled budesonide (800 $\mu\text{g}/\text{d}$, 1600 $\mu\text{g}/\text{d}$, or 400 μg inhaled budesonide plus montelukast 10 mg/d).

Treatment with birch allergen resulted in a statistically significant improvement of ACT scores ($p < 0.05$); the improvement exceeded the MCID for the ACT.¹⁷

Based on a body of evidence that is consistent in the direction of change (all studies demonstrating improvement in

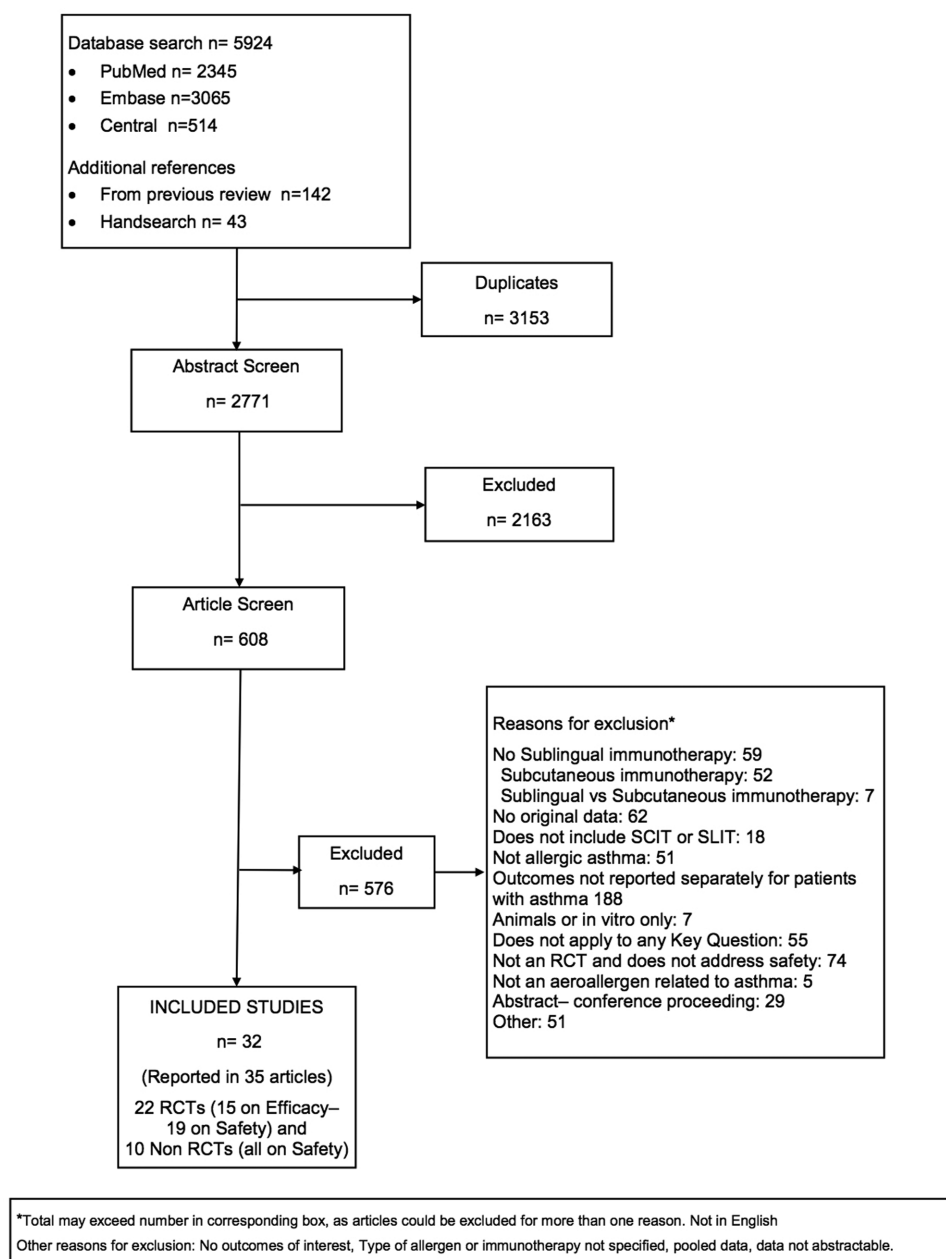


FIGURE 1. Search Flow Diagram.

comparison to placebo), precise, direct, and with an overall low risk of bias, there is high strength of evidence that SLIT improves asthma symptoms (Table 1).

Quality of life

Three RCTs, all of HDM allergen with a total of 1120 patients, examined the impact of SLIT on disease-specific quality of life using the Asthma Quality of Life Questionnaire (AQLQ).^{13–15} Two studies were low risk of bias, and 1 study was medium risk of bias. Two of the 3 RCTs used tablets,^{13,14} and 1 used aqueous drops.¹⁵ All studies utilized treatment for 1 year (Appendix Tables S3 online).

The largest study ($n = 877$) reported that scores improved in both the SLIT groups and placebo group, but there was no statistically significant difference between SLIT and placebo.¹³ The RCT that reported statistically significant changes in AQLQ in the treatment group pretreatment vs posttreatment used a 6 SQ-HDM tablet, but no significant differences were reported when the treatment group was compared with controls.¹⁴ The third study reported no significant improvement at the end of treatment comparing the SLIT group with placebo.¹⁵

Each RCT reported improvement in AQLQ in both the SLIT and placebo groups, but only 1 study indicated statistically significant improvement. The use of SLIT may improve disease-specific quality of life with asthma, based

TABLE 1. Efficacy data presented for each graded outcome

Outcome	Number of studies/number of participants	Allergen; asthma severity; presentation (n)	Comparators (number of studies)	Summary of grading data	Findings	Strength of evidence
Asthma symptom control	4/1193	Dust mite (3), birch (1); mild and moderate (5), moderate and severe (1), mild (1); tablet (3), aqueous (1)	SLIT vs placebo (3) vs pharmacotherapy (1)	3 studies with low RoB, 1 with medium. Overall, the evidence was consistent in the direction of change, precise, and direct.	Three studies demonstrated clinical and statistical significant improvement in the SLIT group. One study did not show significant improvement.	High
Quality of life	3/1120	Dust mite (3); mild and moderate (2); moderate and severe (1); tablet (2), aqueous (1)	SLIT vs placebo (3)	2 studies with low RoB, 1 with medium. Overall, the evidence was consistent in the direction of change, precise, and direct.	All studies showed improvement in QOL in the SLIT group, but no significant change when compared with placebo.	Low
Quick relief medication use	5/298	Dust mite (2), birch (2), grass mix (1); mild and moderate (2), mild (2), moderate (1); tablet (1), aqueous (4)	SLIT vs placebo (2) vs pharmacotherapy (3)	One study with low RoB, 2 with medium and 2 with high. Overall, the evidence was consistent in the direction of change, imprecise, and direct.	Three studies showed reduction in the use of quick-relief medication (SABA) when compared with pharmacotherapy and 1 study when compared with placebo. One study with dust mite found no significant change when compared with placebo.	Low
Long-term control medication use	4/1308	Dust mite (4); mild and moderate (3), mild (1); tablet (2), aqueous (2)	SLIT vs placebo (4)	Two studies with low RoB and 2 were medium. Overall, the evidence was consistent in the direction of change, precise, and direct.	Two studies showed reduction in the use of long-term control medication when compared with placebo. Two smaller studies found no significant difference.	Moderate
Systemic corticosteroids	1/110	Dust mite (1); mild (1); aqueous (1)	SLIT vs placebo (1)	One study with low RoB.	One study showed significant reduction in medication consumption in the SLIT group when compared with placebo.	Insufficient
Health-care utilization	0					Insufficient
Pulmonary physiology—FEV ₁	11/1694	Dust mite (7), grass (3), birch (1); mild and moderate (7), mild (3), excluded severe (1); tablet (5), aqueous (7)	SLIT vs placebo (9) vs pharmacotherapy (2)	Five studies with low RoB and 5 were medium and 1 high. Overall, the evidence was consistent in the direction of change, precise, and direct.	Four studies showed significant improvement on FEV ₁ in the SLIT when compared to placebo. Three studies showed significant changes on the SLIT arm but not when compared with placebo. All the other studies showed nonsignificant changes.	Moderate

FEV₁ = forced expiratory volume in 1 second; QOL = quality of life; RoB = risk of bias; SLIT = sublingual immunotherapy.

on a body of evidence that is consistent in the direction of change, precise, direct, and with an overall low risk of bias (low SOE).

Medication use

Quick-relief medications. Five RCTs of 298 people included data on quick-relief medication (SABA) outcomes (see Appendix Tables S3 online).^{16,18–21} Four RCTs reported quick-relief medication outcomes in doses of SABA over 3 months, with 3 of the 4 studies demonstrating a statistically significant decrease in the need for SABA.^{16,18,19} The fifth RCT reported reduction in doses of SABA used over a 6-month period.²¹ The studies were performed in patients with mild to moderate asthma (see Appendix Tables S3). The risk of bias was low for 1 study, medium for 2 studies, and high for the remaining study. The high risk of bias was due to lack of allocation concealment and blinding.¹⁹

Two studies were performed with birch allergen, with 5 years of continuous treatment or 3 years of pre/co-seasonal treatment.^{16,18} The first birch SLIT study measured SABA use in doses during 3-month pollen seasons annually over 5 years. There were 4 randomized arms in this study: SLIT plus budesonide 400 μ d; budesonide 800 μ d; budesonide 1600 μ d; or budesonide 400 μ g/d plus daily montelukast. The study also found significant improvement ($p < 0.01$) in the comparison of all arms vs control. The SLIT group decreased SABA intake, on average, by 16.1 doses, compared with the control group treated with montelukast, which had a decrease, on average, of 3.6 doses ($p = 0.019$).¹⁸ The second birch SLIT study measured SABA use during the 3-month pollen season annually for 3 years; it was found that the SLIT group decreased SABA intake, on average, by 10.1 doses, when compared with the control groups treated with inhaled budesonide ($p < 0.001$).¹⁶

The third study was a grass mix study that measured doses of SABA over 3-month pollen seasons annually for 5 years and identified an average decrease of 17.9 doses in the SLIT group, compared with an average decrease of 9.4 doses in the control group treated with inhaled budesonide ($p = 0.01$).¹⁹

The fourth and fifth studies were both of HDM. The fourth study did not indicate a significant change in measured puffs of SABA per day compared with placebo ($p = 0.951$).²⁰ The fifth study was performed in adults, and measured the reduction in SABA doses over the pollen season. The study found a 50% reduction in the treatment group, compared with a 21% reduction in the placebo group ($p < 0.03$).²¹

Based on a body of evidence that is consistent, imprecise, direct, and with an overall medium risk of bias, SLIT may decrease the use of quick-relief medications (low SOE).

Long-term control medications. Four RCTs of SLIT reported long-term control medication use and included a total of 1308 patients. All RCTs treated mild to moderate persistent asthmatics with HDM and evaluated the use of

inhaled corticosteroids (ICS) compared with placebo (see Appendix Tables A3 online).^{14,15,20,22} Two studies were low risk of bias and 2 were medium risk of bias. Treatment duration ranged from 6 to 24 months. In the first study, which used a 300-Index of Reactivity (IR) dose of HDM, the authors measured absolute decrease in daily inhaled budesonide dose in micrograms, with the SLIT group decreasing by 218.5 μ g, on average, compared with the placebo group, which decreased by 126.5 μ g, on average ($p = 0.004$).¹⁵ The second study, which utilized the highest SLIT dosing as 6 SQ-HDM, reported the difference between placebo and SLIT in change from baseline in daily ICS use of 327 μ g ($p < 0.0001$).¹⁴ The third RCT reported no statistically significant differences in ICS use between SLIT and control.²² The fourth RCT similarly found no statistically significant decrease in ICS use measured in puffs per day when comparing SLIT with placebo ($p = 0.215$).²⁰

Four studies with low to medium risk of bias included 2 large studies with statistically significant improvement comparing SLIT with controls. We found moderate SOE that SLIT decreases the use of long-term control medications (ICS). The strength of evidence was based on a body of evidence that is consistent in the direction of change, precise, direct, and with an overall medium risk of bias.

Systemic corticosteroids. One RCT at medium risk of bias reported on the effects of SLIT on systemic corticosteroid use.²⁰ This trial of HDM SLIT vs placebo in 110 patients with mild to moderate persistent asthma reported on the use of oral systemic corticosteroids after a 24-week intervention²⁰ and found no difference in the use within or between groups. Overall evidence is insufficient to determine the effect of SLIT on oral corticosteroid use.

Health-care utilization. There were no studies of the effect of SLIT on health-care utilization.

Pulmonary physiology. FEV₁ was reported in 11 RCTs.^{14–16,19–26} The total number of patients in these studies was 1694 and all had mild to moderate asthma (see Appendix Tables S3 online). Seven studies were of HDM, 2 of grass mix, 1 of birch, and 1 of Timothy grass.

Three of 4 RCTs of pollen allergen identified statistically significant improvements in FEV₁. One trial of grass mix SLIT vs control (treated with montelukast alone) for 5 years reported an increase from an average of 78.5% to 96.2% of percent predicted FEV₁ in the SLIT group, compared with a change in the control group of 76.4% to 81.2% ($p < 0.0001$).¹⁹ The second RCT, of birch allergen, was performed with pre/co-seasonal dosing (1000-AU tablets 5 days/wk) for 3 years. This study found that mean FEV₁ improved from 85.2% to 103.3% in the SLIT group compared with the 3 control groups treated with budesonide alone, which improved from 88.3% to 90.3%, 87.0% to 92.4%, and 86.2% to 96.5%, respectively ($p < 0.05$ for SLIT compared with any of the control groups).¹⁶ The third pollen trial, of grass mix over 2 years (maintenance dose of 43,800 IR 3 times per week), reported that FEV₁ in the treatment group improved from 92.9% to 100.4%,

compared with the placebo group, which improved from 87.9% to 88.2% ($p = 0.005$).²⁶

Regarding HDM, 1 trial reported statistically significant improvement in FEV₁, with treatment group improvement statistically significant compared with the placebo group ($p < 0.03$).²¹ Three other HDM trials each noted a statistically significant improvement in FEV₁ in the SLIT arm, but there was no statistically significant difference between arms.^{20,23,24} The 3 remaining HDM studies demonstrated improvement in those treated with SLIT, but the improvements were not found to be statistically significant.

The risk of bias was medium in 5 RCTs, low in 5, and high in 1. There is moderate SOE that SLIT improves FEV₁, based on evidence that is precise, direct, consistent, and with a medium overall risk of bias.

Safety outcomes

Our search identified a total of 33 articles on 30 unique studies/populations reporting safety data, encompassing a total of 3621 patients. Of the included studies, 20 were RCTs,^{13–16,20–38} whereas 10 were either cohort, case-control, or case reports.^{39–48} Details regarding these studies are presented in Appendix Table S2 online.

Local reactions to SLIT were common (some reactions occurring in up to 80% of patients in RCTs); however, reactions also commonly occurred with placebo (risk differences ranged from -0.03 to 0.765). Systemic allergic reactions to SLIT were frequent (some reactions occurring in up to 22% of patients in RCTs), with only a few reports of anaphylaxis and no reports of death (risk differences ranged from -0.03 to 0.06). Although the rates of anaphylaxis with SLIT compared with no treatment could not be determined (no cases reported in RCTs, insufficient evidence), 3 case reports suggested that, in rare cases, anaphylaxis may occur with SLIT treatment.^{39,40,42} Two of 3 reports of anaphylaxis secondary to SLIT were in patients who received multiple-allergen therapy.^{39,40} No deaths secondary to SLIT therapy were reported (moderate SOE). Table 2 presents a summary of safety outcomes.

Discussion

Our systematic review identified 15 RCTs that assessed the efficacy of SLIT for allergic asthma. The patients in these studies generally had mild to moderate asthma; however, the diagnosis of asthma and asthma control before treatment was not clearly stated in several studies. We found high strength of evidence that SLIT reduces asthma symptoms. There was moderate-grade evidence for the benefit of SLIT in reducing the use of long-term control medications (ICS) and improving FEV₁. SLIT may also reduce the need for quick-relief medication and improve disease-specific quality of life. There was insufficient evidence to draw conclusions on the effect of SLIT on systemic corticosteroid use and health-care utilization. The evidence

appeared to be strongest in studies in which pollen SLIT was used. Overall, we found SLIT to be beneficial for the majority of asthma-related outcomes included in this systematic review.

We found that local adverse events were common with use of SLIT but that systemic and life-threatening events were reported in only 3 studies.^{39,40,42} Two of 3 cases of reported anaphylaxis events occurred in patients receiving multiple-allergen therapy, perhaps signaling that multiple-allergen SLIT poses higher risk for systemic adverse effects, as suggested in a recent publication.⁴⁹ Of note, the package insert for SLIT tablets approved by the FDA does recommend that an epinephrine autoinjector device be prescribed for patients taking SLIT tablets.⁵⁰

The current findings are consistent with our earlier 2013 JHU EPC evidence report and other previous systematic reviews. A 2015 Cochrane Review found there was low-quality evidence that SLIT decreases ICS use and very low-quality evidence regarding improvement in bronchial provocation.⁵¹ The Cochrane Review further noted that the largely nonvalidated asthma symptom scores, medications scores, and available data for quality of life precluded meaningful synthesis of these outcomes. Our evidence report from 2013 examined SLIT in aqueous form only, and concluded that SLIT reduced asthma symptoms.³

There are several limitations to our current study. We found considerable heterogeneity in the outcomes reported and in the measurement of outcomes, which precluded quantitative pooling of the data. Many studies did not report relevant statistical information on continuous variables (such as confidence interval, standard deviation, and standard error), and some studies did not report results between arms. In addition, it was not possible to make comparisons between different allergen targets due to insufficient data and lack of studies for specific allergens. We found variability in the dosing and treatment schedules from study to study. However, as the general mechanism of immunotherapy is the same across targeted allergens, we judged it appropriate to pool results qualitatively. There was also variability from study to study regarding the standardization of allergen used for the included studies. In addition, almost all studies were performed using a single allergen; therefore, we were unable to perform an analysis of multiple-allergen immunotherapy. Many of the studies allowed concomitant treatment with standard controller interventions, which may have blunted the beneficial effects of SLIT.

There was much variability across studies in methods and criteria used for asthma diagnosis, as well as grading of asthma severity and control status. Also, some studies did not provide information about baseline asthma severity or control. These issues may affect the ability to generalize the findings to certain patients with asthma and limited our ability to determine whether asthma health status at the beginning of treatment affects the observed outcomes.

TABLE 2. Safety outcomes summary for included studies, RCTs and non-RCTs

	Allergen (number of studies)	Comparator: asthma severity (number of studies)	Number of patients in studies reporting adverse events (n/total)	Calculated risk difference AEs	Description or classification
Local reactions, 12 RCTs	Dust mite (8)	Placebo (7); pharmacotherapy (1); mild and moderate (5), moderate and severe (1), mild (1), NS (1)	SLIT arms: NR ⁷ /1310, comparator arms: NR/672	Range for dust mite −0.336 to 0.15	From oral, tongue, and throat irritation to laryngeal edema, nasopharyngitis, and paresthesia.
	Grass (3)	Placebo (3); mild and moderate (2), excluded severe (1)	SLIT arms: NR/113, comparator arms: NR/58	Range for grass −0.003 to 0.01	
	Multiple allergen (1)	Placebo (1); mild and moderate (1)	SLIT arms: 1/27, comparator arms: 0/27	NA	Erosive esophagitis.
	All RCTs (12)			Range for all allergens −0.03 to 0.765	
Local reactions, 2 non-RCTs	Dust mite (2)	WO comparator (2), NS (1)	SLIT arms: 2/2	NA	One case of abdominal pain and 1 case of eosinophilic esophagitis.
Systemic reactions, 12 RCTs	Dust mite (7)	Placebo (6); pharmacotherapy (1); mild and moderate (5), mild (1), NS (1)	SCIT arms: 29/405, comparator arms: 8/219 (reported as patients); SCIT arms: 25/405, comparator arms: 14/219 (reported as events)	Range for dust mite 0.057–0.25	Dyspnea or asthma exacerbations, headache, infections, reactions leading to discontinuation, and unspecified systemic reactions.
	Grass (3)	Placebo (2), SCIT (1); mild and moderate (1), moderate and severe (1), NS (1)	SCIT arms: 4/58, comparator arms: 3/23 (reported as patients); SCIT arms: 35/39, comparator arms: 9/23 (reported as events)	NA (all AEs reported differently)	Dyspnea or asthma exacerbations, headache, infections, reactions leading to discontinuation, and unspecified systemic reactions.
	Birch (1)	Pharmacotherapy (1); mild (1)	SCIT arms: 2/58, comparator arms: 0/18	0.001	Generalized itching. ¹⁶
	Multiple allergens (1)	Placebo (1); NS (1)	SLIT arms: 50%–68%, comparator arms: 32%–46%	NA	AEs not specified (both TEAEs and TRAEs). ²⁹
	All RCTs (12)			Range for all allergens −0.03 to 0.06	

(Continued)

TABLE 2. Continued

	Allergen (number of studies)	Allergen; comparator and asthma severity (n)	Number of patients in studies reporting adverse events (n/total)	Calculated risk difference AEs	Description or classification
Systemic reactions, 4 non-RCTs	Dust mite (3)	WO comparator (3); NS (1)	41 cases in 2 case series ^{44,45}	NA	Wheezing, asthma attacks, or worsening of asthma. One study did not specify number and type of AEs in the 77 patients included. ⁴²
	Multiple allergen (grass and dust mite) (1)	Control (1); NS (1)	SLIT arms: 1/50, comparator: 0/48	NA	Flushing, congestion, and chest tightness.
Anaphylaxis, 5 RCTs	Dust mite (3)	Placebo (2), pharmacotherapy (1); mild and moderate (1), mild (1), NS (1)	SLIT arms: 0/752, comparator: 0/409	NA	There were no anaphylactic reactions.
	Tree (1)	Placebo (1); mild and moderate (1)	SLIT arms: 0/27, comparator: 0/27	NA	
	Multiple (1)	Placebo (1); NS (1)	SLIT arms: 0/46, comparator arms: 0/33	NA	
Anaphylaxis, 3 non-RCTs	Dust mite (1)	WO comparator (1), NS (1)	1 case	NA	Anaphylactic shock. ⁴²
	Multiple (2)	WO comparator (2), NS (2)	2 cases	NA	One case described as anaphylaxis. ⁴⁰ One case described as dyspnea, dizziness, and mild hypotension. ³⁹

AE = adverse event; NA = not applicable; NR = not reported; NS = not specified; RCT = randomized, controlled trial; SLIT = sublingual immunotherapy; TRAES = Total Reported Adverse Events; TEAES = Treatment Emergent Adverse Events; WO = without.

There is a need for studies investigating the efficacy and safety of multiple-allergen regimens for SLIT. Multiple-allergen treatment is frequently used in the US, but most of the studies included single-allergen regimens. The majority of studies we identified were of HDM allergen; additional studies of the efficacy of SLIT treatment with other allergens would be useful. Future studies would be more informative if standardized methods to grade asthma, and validated instruments to report outcomes, such as asthma symptoms and adverse events, were used. Future studies would benefit from reporting objective data with pathophysiologic measures and biomarkers of asthma.

Conclusion

There is moderate- to high-strength evidence that SLIT improves allergic asthma symptoms, reduces long-term control medication use, and improves FEV₁ based on studies of HDM, birch, and grass. SLIT is rarely associated with life-threatening adverse events. 

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Appendix Table 1.

Detailed Electronic Database Search Strategies

PubMed,

(immunotherapy[mesh] OR immunotherap*[tiab]) AND (asthma[mh] OR asthma[tiab]) NOT ("occupational diseases" [mh]) NOT (animals[mh] NOT humans[mh])

1. immunotherapy [mh]
2. immunotherap*[tiab]
3. 1 OR 2
4. asthma [mh]
5. asthma [tiab]
6. 4 OR 5
7. "occupational diseases" [mh]
8. 6 NOT 7
9. 3 AND 8
10. (animals[mh] NOT humans[mh])
11. 9 NOT 10
12. 11 AND (2005 to present [date-publication])

Embase

('immunotherapy'/exp OR immunotherapy) AND ('asthma'/de OR asthma)

1. 'immunotherapy'/exp OR immunotherapy
2. 'asthma'/de OR asthma
3. 1 AND 2
4. 3 AND (2005 to present)

Cochrane Central Register of Controlled Trials (CENTRAL).

"immunotherapy" AND "asthma" in Title, Abstract, Keywords, Publication Year from 2005 to 2017 in Trials'

Appendix Table 2.

STUDY CHARACTERISTICS

(Organization in tables first by study design and outcomes assessed (RCT and then Non-RCT, with all studies assessing ONLY safety at the bottom). Within each category by sensitization status (monosensitized, both monosensitized and polysensitized, polysensitized and unclear). Within each subcategory single allergen followed by multiple allergen and then by allergen provided (Dust mite- trees- and multiple allergen)

Study	Study design Comparators	Patients characteristics	Allergy Diagnosis Sensitization status and allergen provided in AIT	N	AIT characteristics	Outcomes assessed	Risk of Bias/ Causality
Pham-Thi, 2007(22) Europe	RCT SLIT (T) Placebo	Asthma diagnosis pulmonary tests Severity; mild and moderate Control status NR Age range (5-16)	SPT and IgE Monosensitized Single allergen- Dust mite	111	300 IR 6.9mg Der p 1 and 14.7mg Der f 1	Quick Relief Medications Long term Control Medications FEV1 Safety	Low
Bahceciler, 2001(33) Asia	RCT SLIT (A) Placebo	Asthma diagnosis GINA criteria Severity Mild Control status – ongoing respiratory symptoms despite HDM avoidance and ICS Age range (7-18)	SPT and IgE Monosensitized Single allergen- Dust mite	15	20 drops of 100 IR/mL 1ml of 100 IR= 9 ug D pter and 14 ug D.far	FEV1 Safety	Medium
Lue, 2006(23) Asia	RCT SLIT (A) Placebo	Asthma diagnosis NS Severity; mild and moderate Control status NR Age range (6-12)	SPT and IgE Monosensitized Single allergen- Dust mite	20	20 drops of 300 IR/mL 3 mg Der F -1.7 mg Der P (Cumulative)	Healthcare Utilization FEV1 Safety	Medium

Study	Study design Comparators	Patients characteristics	Allergy Diagnosis Sensitization status and allergen provided in AIT	N	AIT characteristics	Outcomes assessed	Risk of Bias/ Causality
Niu, 2006(20) Asia	RCT SLIT (A) Placebo	Asthma diagnosis GINA criteria Severity; mild and moderate Control status NR Age range (5-12)	SPT and IgE Monosensitized Single allergen- Dust mite	110	20 drops of 300 IR/ml 3 mg Der F -1.7 mg Der P (Cumulative)	Quick Relief Medications Long term Control Medications Systemic Corticosteroids FEV1 Safety	Medium
Ippoliti, 2003(24) Europe	RCT SLIT (A) Placebo	Asthma diagnosis NS Severity; mild and moderate Control status controlled Age range (5-12)	SPT and IgE Monosensitized Single allergen- Dust mite	86	5 drops of 10 BU/mL 2.4 Der p1 -1.2 Der p2 (per week)	FEV1 Safety	Medium
Virchow, 2016(13) Europe	RCT SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ-HDM Placebo	Asthma diagnosis GINA criteria Severity; moderate to severe asthma Control status Poorly Controlled Age range (17-75)	SPT and IgE Both mono and polysensitized Single allergen- Dust mite	834	6 or 12 SQ-HDM. Cumulative dose 360 SQ or 720 SQ /month for 12 months	Asthma control QOL Safety	Low
de Blay, 2014(14) Mosbech, 2014(27) Mosbech, 2015(28) Europe	RCT SLIT(T) 6 SQ-HDM SLIT(T) 3 SQ-HDM SLIT(T) 1 SQ-HDM Placebo	Asthma diagnosis GINA criteria Severity; mild and moderate Control status Controlled (ACQ scores and ICS dose of 100 to 800 mg/d) Age; Older than 14yo	SPT and IgE Both mono and polysensitized Single allergen - Dust mite	604	1, 3 or 6 SQ-HDM. Cumulative dose not reported for 12 months	Asthma control QOL Long term Control Medications FEV1 Safety	Low

Study	Study design Comparators	Patients characteristics	Allergy Diagnosis Sensitization status and allergen provided in AIT	N	AIT characteristics	Outcomes assessed	Risk of Bias/ Causality
Gomez, 2004(21) Mexico	RCT SLIT (A) Placebo	Asthma diagnosis GINA criteria Pulmonary tests (FEV change >14% after salbutamol) Severity; mild and moderate Control status NR Age <18	SPT and IgE Mono vs Polysensitized unclear* Single allergen - Dust mite	60	300IR of 28ug Der p 1 and 50 ug Der f 1 for 52 weeks	Quick Relief Medications FEV1 Safety	Medium
Devillier, 2016(15) Wang, 2014(30) Multisite	RCT SLIT (A) Placebo	Pulmonary tests (bronchial reversibility test and methacoline challenge) Severity; mild and moderate Control status NR Age range (14-50)	SPT and IgE Polysensitized Single allergen - Dust mite	484	300 IR daily (28ug Der p1 and 50 ug Der f 1) for 52 weeks	Asthma control QOL Long term Control Medications FEV1 Safety	Medium
Stelmach, 2009(26) Europe	RCT SLIT (A) ultra rush Placebo	Asthma diagnosis pulmonary tests (reversible bronchial obstruction – salbutamol inhalation ≥12%) Severity Excluded severe asthma Control status NR Age range (6-17)	SPT and IgE Monosensitized Single allergen- Grass mix	50	120IR 3.65 mg of major allergens (5 grasses)	Long term Control Medications FEV1 Safety	Low
Calderon, 2006(25) Europe	RCT SLIT (A) Placebo	Asthma diagnosis criteria NS Severity; mild and moderate Control status Controlled asthma Age range (18-65)	SPT and IgE Monosensitized Single allergen – Grass (Phleum)	43	75000, 150000, 300000 or 500000 SQT daily for 28 days	FEV1 Safety	Low

Study	Study design Comparators	Patients characteristics	Allergy Diagnosis Sensitization status and allergen provided in AIT	N	AIT characteristics	Outcomes assessed	Risk of Bias/ Causality
Marogna, 2010(19) Europe	RCT SLIT (A) Pharmacotherapy	Asthma diagnosis GINA criteria Severity Mild Control status controlled Age range (18-65)	SPT and IgE Monosensitized Single allergen – Grass mix	33	5 drops of 10,000 RU/ml 3 times/week for 5 years. (100 µg Bet v 1 per year)	Quick Relief Medications FEV1	High
Marogna, 2013(16) Europe	RCT SLIT (T) Pharmacotherapy	Asthma diagnosis GINA criteria Severity Mild Control status Poorly controlled Age range (18-65)	SPT and IgE Monosensitized Single allergen- Birch	84	1000 AU day/ 5 days a week for 12 weeks/ season for 3 years (214,200µg of modified major allergen)	Asthma control Quick Relief Medications FEV1 Safety	Low
Marogna, 2009(18) Europe	RCT SLIT (A) Pharmacotherapy	Asthma diagnosis GINA criteria Severity Moderate Control status controlled Age range (18-65)	SPT Monosensitized Single allergen- Birch	51	5 drops of 10,000 RU/ml 3 times/week for 5 years. (70 Phl p1 per year)	Quick Relief Medications	Medium
Corzo, 2014(34) Europe	RCT SLIT (T) Placebo	Diagnosis: NR Severity; mild and moderate Control status NR Age range (5-14)	SPT and IgE Monosensitized Single allergen- Dust mite	72	0.5-12 DU	Safety	Low

Study	Study design Comparators	Patients characteristics	Allergy Diagnosis Sensitization status and allergen provided in AIT	N	AIT characteristics	Outcomes assessed	Risk of Bias/ Causality
Maloney, 2016(29) US	RCT SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ- HDM Placebo	Asthma diagnosis GINA criteria Severity not specified Control status Controlled (FEV, use of SABAs and exacerbations) Age range (12-17)	SPT and IgE Both mono and polysensitized Single allergen - Dust mite	195	6 or 12 SQ-HDM. Cumulative dose 168 SQ or 336 SQ /month for 28 days	Safety	Low
La Grutta, 2007(35)	RCT SLIT (T) Pharmacotherapy	Asthma diagnosis criteria NS Severity NS Control status NR Age range (7-68)	SPT Both mono and polysensitized Single allergen - Dust mite	56	1000 AU biweekly for 1 year	Safety	High
Shao, 2014(32) Asia	RCT SLIT (A) Pharmacotherapy	Asthma diagnosis Pulmonary tests Severity and control NR Age range (3-13)	SPT and IgE Polysensitized Single allergen- Dust mite	264	5 drops daily for 12 months allergen content NR	Safety	Medium
Voltolini 2010(38) Europe	RCT SLIT (A) Placebo	Asthma diagnosis GINA criteria Severity Moderate to severe Control status NR	SPT and IgE Monosensitized Single allergen- Birch	24	300IR daily for 4 months (6.9 µgBet v1 per season)	Safety	Medium
Mosges, 2010(37) Europe	RCT SLIT(A) placebo	Asthma diagnosis criteria NS Severity; mild and moderate Control status NR Age range (6-14)	SPT and IgE Polysensitized Single allergen- Birch	54	Targeted: 300 IR within 90 days	Safety	High

Study	Study design Comparators	Patients characteristics	Allergy Diagnosis Sensitization status and allergen provided in AIT	N	AIT characteristics	Outcomes assessed	Risk of Bias/ Causality
Dahl, 2006(31) Europe	RCT SLIT (T) Placebo	Asthma diagnosis GINA criteria Severity Moderate persistent Control status NR	SPT and IgE Monosensitized Single allergen - Grass mix	114	7500 SQT daily for 137 days (15 phl p5)	Safety	Medium
Bufe, 2009(36) Europe	RCT SLIT (T) placebo	Asthma diagnosis GINA criteria Severity mild, moderate, severe Control status NR Age range (5-16)	SPT and IgE Poly and Monosensitized Single allergen- Grass	105	NR	Safety	Medium
Dunsky, 2006(39) US	Non-RCT SLIT wo comparator	Asthma diagnosis criteria NR Severity NS Control status NR Age- 31yo	SPT Polysensitized Multiple allergens	1	Dosing and duration NR	Safety	Certain
Vovolis, 2013(40)	Non-RCT SLIT (A) wo comparator	Asthma diagnosis criteria NR Severity NS Control status NR Age- 25yo	SPT and IgE Polysensitized Multiple allergens	1	3 drops daily (content NR) Duration NR	Safety	Probable/Likely
Ventura, 2008(41) Europe	Non-RCT SLIT wo comparator	Asthma diagnosis criteria NR Severity Mild and moderate Control status NR Age- 39yo	SPT and IgE Polysensitized Single allergen- Dust mite	1	Dosing and allergen content NR Duration 1 month	Safety	Probable/Likely

Study	Study design Comparators	Patients characteristics	Allergy Diagnosis Sensitization status and allergen provided in AIT	N	AIT characteristics	Outcomes assessed	Risk of Bias/ Causality
Blazowski, 2008(42)	Non-RCT SLIT wo comparator	Asthma diagnosis criteria NR Severity NS Control status NR Age- 16yo	Allergy diagnosis Not reported Sensitization status not reported Single allergen – Dust mite	1	60 drops of 100IR/ml daily for 3 years	Safety	Certain
Moral, 2016(48)	Non-RCT SLIT (A) wo comparator	Asthma diagnosis criteria NR Mild to moderate persistent Control status NR Age NR	SPT and/or IgE Both mono and polysensitized Single allergen - Dust mite	93	300 SRU daily for 3 months	Safety	Probable/Likely
Roger, 2011(43) Europe	Non-RCT SLIT wo comparator	Asthma diagnosis criteria NR Severity Mild persistent and moderate persistent Control status NR Age Mean 20.4 (SD NR)	SPT and IgE Mono vs Polysensitized unclear* Single allergen-Dust mite	NR	240 IR 3 times/week for 2 weeks	Safety	Low
De Castro, 2013(44)	Non-RCT SLIT (T) Control	Asthma diagnosis criteria NR Mild and moderate Controlled Age NR	SPT and IgE Both mono and polysensitized Single allergen - Grass	98	Tablets of 1000UA, 2- 5/week for 3 years	Safety	Low
Nuhoglu, 2007(45)	Non-RCT SLIT wo comparator	Asthma diagnosis criteria NR Severity Intermittent Control status Controlled Age range (6-14)	SPT Monosensitized Single allergen- Dust mite	39	100IR 3 times/week for 3 years	Safety	High

Study	Study design Comparators	Patients characteristics	Allergy Diagnosis Sensitization status and allergen provided in AIT	N	AIT characteristics	Outcomes assessed	Risk of Bias/ Causality
Galip, 2015(46) Europe	Non-RCT SLIT (A) wo comparator	Pulmonary tests (PFT with bronchodilator reversibility of 18%) persistent asthma Control status controlled on daily ICS Age 6yo	SPT Monosensitized Single allergen- Dust mite	1	Allergen content NR, daily for 3 years	Safety	Certain
Bene, 2016(47) Europe	Non-RCT SLIT (A) wo comparator	Asthma diagnosis criteria NR Severity NS Control status NR Age 10yo	Allergy diagnosis Not reported Monosensitized Single allergen- Dust mite	1	300IR. Duration of treatment NR	Safety	Probable/Likely

Appendix 3: Sublingual Immunotherapy (SLIT) and Asthma Outcomes Evidence Tables

Asthma Symptoms

Study	Allergen and Asthma Severity	Arms	N	Outcome Description	Time of Measure	Value Pre	Value post	Comparative Values
Virchow, 2016 (13)	Dust mite Moderate to severe	SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ-HDM Placebo	275 282 277	ACQ	1 year	Mean (SD) [IQR] 1.24 (0.17) [0.86-1.71] 1.23 (0.17) [0.71-1.57] 1.22 (0.18) [0.86-2.00]	Improvement 218 (78.88%) 221 (80.63%) 232 (83.02%)	OR (95% CI): 6SQ-HDM vs placebo 1.12 (0.73 to 1.70) 12SQ-HDM vs placebo 1.31 (0.85 to 2.01) <i>P</i> = 0.22
de Blay, 2014 (14)	Dust mite Mild and moderate	SLIT (T) 6 SQ-HDM SLIT (T) 3 SQ-HDM SLIT (T) 1 SQ-HDM Placebo	29 27 25 27	ACQ	1 year	Mean score 1.15 1.16 1.21 1.20	Change within group -0.41 -0.22 -0.16 0	SLIT 6SQ-HDM pre vs post <i>P</i> =0.0002 SLIT vs Placebo <i>P</i> >0.05
Devillier, 2016 (15)	Dust mite Mild and moderate	SLIT (A) Placebo	113 62	ACQ	1 year	1.81 +/- 0.88 1.78 +/- 0.90	Percentage improvement 56.6% 40%	SLIT vs Placebo <i>P</i> <0.039 in moderate asthmatic subgroup
Marogna, 2013 (16)	Birch Mild asthma	SLIT(T)+Budesonide Budesonide 800 µg Budesonide 1600 µg Budesonide + LTRA	19 19 20 18	ACT	3 years	Mean 14.1 16.1 15.3 13.4	Mean 24 17.2 19.1 18.4	SLIT vs all other arms <i>P</i> <0.05

ACT: Asthma control test ACQ: Asthma control questionnaire T: Tablet SQ-HDM: standard quality house dust mite tablet A: Aqueous
LTRA: Leukotriene receptor antagonist SLIT vs comparator post data unless otherwise noted

Asthma Specific Quality of Life (QOL) – Asthma Quality of Life Questionnaire (AQLQ)

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post
Virchow, 2016 (13)	Dust mite Moderate to severe	SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ-HDM Placebo	275 285 277	1 year	Mean +/- SD 5.46 +/- 0.88 5.49 +/- 0.78 5.54 +/-0.78	Improvement 231 (84.98%) 236 (84.39%) 233 (84.80%)	6SQ-HDM vs placebo post OR (95% CI); 1.01 (0.63- 1.62) 12SQ-HDM vs placebo post OR (95% CI): 0.97 (0.61- 1.53) <i>P</i> = 0.89 P>0.05
de Blay, 2014 (14)	Dust mite Mild and moderate	SLIT (T) 6 SQ-HDM SLIT (T) 3 SQ-HDM SLIT (T) 1 SQ-HDM Placebo	29 27 25 27	1 year	5.62 5.58 5.75 5.52	Change within group + 0.52 + 0.32 + 0.30 0	SLIT 6SQ-HDM pre vs post <i>P</i> =0.01 Between arms comparisons P>0.05
Devillier, 2016 (15)	Dust mite Mild and moderate	SLIT (A) Placebo	13 62	1 year	Mean +/- SD 4.6 +/-1.0 4.5 +/- 1.1	Mean +/- SD 6.0 +/-0.9 5.9 +/- 0.9	P>0.05

Medication Use

A. Quick Relief Medication

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post	Comparative Values
Marogna, 2009 (16)	Birch Moderate asthma	SLIT (A) Pharmacotherapy (montelukast)	5 6	5 years	SABA, (Doses used over 3 month period)	20.1 +/- 0.7 19.4 +/- 0.9	4.0 +/- 0.9 15.8 +/- 1.0	SLIT pre vs post $P < 0.01$, Montelukast pre vs post $P = 0.019$ SLIT vs montelukast $P < 0.001$
Marogna, 2013 (18)	Birch Mild asthma	SLIT (T) + Budesonide Budesonide 800 µg Budesonide 1600 µg Budesonide + LTRA	21 21 21 21	3 years	SABAS (doses used over 3 month period)	Mean +/- SE 11.1 +/- 0.6 11.1 +/- 0.6 11.2 +/- 0.6 11.9 +/- 0.9	Mean +/- SE 1 +/- 0.2 10.4 +/- 1.2 8.3 +/- 1.3 7.4 +/- 1.1	SLIT vs all budesonide control groups $P < 0.001$
Marogna, 2010 (19)	Grass mix Mild asthma	SLIT (A) Pharmacotherapy (budesonide)	17 16	5 years	SABA (doses over 3 month period)	23.0 +/- 1.5 22.4 +/- 0.9	5.1 +/- 1.4 13.0 +/- 1.2	SLIT vs budesonide $P < 0.001$
Gomez, 1993 (21)	Dust mite Mild-moderate asthma	SLIT (A) Placebo	30 30	6 months	SABA; Inhaled B agonist use reduction (Salbutamol)	NA	50% 21%	SLIT vs. placebo $z = 1.44$ $P < 0.03$
Niu, 2006 (20)	Dust mite Mild-moderate asthma	SLIT (A) Placebo	56 54	6 months	Inhaled B agonist (puff/ day)	Mean (SD) SLIT: 0.06 (0.09) Placebo: 0.03 (0.01)	Mean (SD) SLIT: 0.02 (0.31) Placebo: 0.05 (0.27)	SLIT pre vs. post $P = 0.371$ Placebo pre vs. post $P = 0.185$ SLIT vs. placebo change from baseline $P = 0.951$

T: Tablet

A: Aqueous

SQ-HDM: standard quality house dust mite tablet

SABA; Short acting Beta Agonist

LTRA: Leukotriene receptor antagonist

SLIT vs comparator post data unless otherwise noted

B. Long Term Control Medication

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post	Comparative Values
Devillier, 2016 (15)	Dust mite Mild and moderate	SLIT (A) Placebo	322 164	1 year	Inhaled corticosteroid (ICS) Absolute decrease in budesonide dose	NR NR	218.5 126.5	SLIT vs placebo post $P = 0.004$
de Blay, 2014 (14)	Dust mite Mild and moderate	SLIT (T) 6 SQ-HDM SLIT (T) 3 SQ-HDM SLIT (T) 1 SQ-HDM Placebo	156 159 146 143	6 months	Inhaled corticosteroid (ICS) Average daily use (μg)	541 648 636 641	-327 -75 -103 -50	SLIT 6HQ-HDM pre vs post $P < 0.05$
Pham-Thi, 2007 (22)	Dust mite Mild and moderate	SLIT (T) Placebo	54 54	18 months	Use of inhaled steroids (ICS) (Budesonide) $\mu\text{g}/\text{day}$	Mean +/- SD 548 +/- 220 534 +/-237	Mean +/- SD 257 +/- 232 223 +/-270	$P > 0.05$
Niu, 2006 (20)	Dust mite Mild asthma	SLIT (A) Placebo	56 54	6 months	ICS (puff/ day)	Mean (SD) SLIT: 0.6 (1.14) Placebo: 0.47 (0.84)	Mean (SD) SLIT: 0.43 (1.09) Placebo: 0.37 (0.86)	change from baseline SLIT pre vs. post $P = 0.782$ Placebo pre vs. post $P = 0.522$ SLIT vs. placebo $P = 0.215$

T: Tablet

A: Aqueous

SQ-HDM: standard quality house dust mite tablet

LTRA: Leukotriene receptor antagonist

PULMONARY PHYSIOLOGY: FEV₁

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post	Comparative Values
Devillier, 2016 (15)	Dust mite Mild and moderate	SLIT (A) Placebo	322 164	52 weeks	FEV1	NR	NR	The mean FEV1% predicted remained above 80% during the treatment period in both SLIT and placebo groups. SLIT vs Placebo $P>0.05$
Niu, 2006 (20)	Dust mite Mild asthma	SLIT (A) Placebo	56 54	24 weeks	FEV1	85 90	95 90	SLIT pre vs post $P=0.048$ Placebo pre vs post NS SLIT vs Placebo $P>0.05$
Ippoliti, 2003 (24)	Dust mite Mild-moderate asthma	SLIT (A) Placebo	47 39	6 months	FEV1	83.4 80.7	92.6 81.2	SLIT pre vs post $P<0.001$ Placebo pre vs post P NS SLIT vs Placebo $P>0.05$
Lue, 2006 (23)	Dust mite Mild-moderate asthma	SLIT (A) Placebo	10 10	6 months	FEV1	NR	NR	SLIT pre vs post improved $P=0.01$ Placebo $P=0.48$ SLIT vs Placebo = 0.929
Marogna, 2010 (19)	Grass mix Mild asthma	SLIT (A) Pharmacotherapy (Montelukast)	17 16	5 years	FEV1	78.5(1.0) 76.4 (1.3)	96.2(1.2) 81.2(1.4)	SLIT vs Pharm $P<0.0001$
Marogna, 2013 (16)	Birch Mild asthma	SLIT (T) + Budesonide Budesonide 800 µg Budesonide 1600 µg Budesonide + LTRA	21 21 21 21	3 years	FEV1	Mean +/-SE 85.2 +/- 0.6 88.3 +/- 0.8 87 +/- 0.8 86.2 +/- 0.6	Mean +/- SE 103.3 +/- 1.5 90.3 +/- 2.1 92.4 +/- 2.0 96.5 +/- 2.9	SLIT vs all other arms $P<0.05$

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post	Comparative Values
Calderon, 2006 (25)	Phleum pratense Mild and moderate	SLIT 75000 SQ-T SLIT 150000 SQ-T SLIT 300000 SQ-T SLIT 500000 SQ-T Placebo	32 11	1 month	FEV1	NR	NR	SLIT vs placebo P>0.05
Pham-Thi, 2007 (22)	Dust mite Mild and moderate	SLIT (T) Placebo	54 54	18 months	FEV1	Mean +/- SD 91.9 +/- 3.4 95.1 +/-15.1	Mean +/- SD 88.5 +/- 13.4 94.5 +/- 14.6	SLIT vs placebo P>0.05
de Blay, 2014 (14)	Dust mite Mild and moderate	SLIT(T) 6 SQ-HDM SLIT(T) 3 SQ-HDM SLIT(T) 1 SQ-HDM Placebo	156 159 146 143	1 year	FEV1	NR	NR	SLIT versus placebo P>0.05
Gomez, 1993 (21)	Dust mite Mild-moderate asthma	SLIT (A) Placebo	30 30	6 months	FEV1 Median	Median 2.16 2.58	Median 2.86 2.81	SLIT versus placebo Z=0.66 P<0.03
Stelmach, 2009 (26)	Grass mix Excluded severe asthma	SLIT (A) Ultrarush Placebo	20 15	2 years	FEV1 Mean % predicted	92.9 87.9	Mean (95% CI) 100.4 (95-105) 88.2 (81 – 94)	SLIT vs Placebo P=0.005

T: Tablet

A: Aqueous

SQ-T: standard quality tablet

FEV: Flow expiratory volume

NR: Not reported