Allergen-Specific Immunotherapy in the Treatment of Pediatric Asthma: A Systematic Review

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abstract

CONTEXT: Treatment options for allergic asthma include allergen avoidance, pharmacotherapy, and allergen immunotherapy.

OBJECTIVES: Summarize and update current evidence for the efficacy and safety of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) in pediatric allergic asthma.

DATA SOURCES: PubMed, Embase, Cochrane Central Register of Controlled Trials (January 1, 2005, through May 8, 2017), ClinicalTrials.gov, and the US Food and Drug Administration Adverse Event Reporting System. We reevaluated trials from our 2013 systematic review.

STUDY SELECTION: We included studies with children ≤18 years of age in which researchers reported on prespecified outcomes and had an intervention arm receiving aeroallergen SCIT or SLIT. Only randomized controlled trials (RCTs) were included for efficacy. RCTs and non-RCTs were included for safety outcomes.

DATA EXTRACTION: Two reviewers extracted data. We included 40 studies (17 SCIT trials, 11 SLIT trials, 8 non-RCTs for SCIT safety, and 4 non-RCTs for SLIT safety).

RESULTS: We found moderate-strength evidence that SCIT reduces long-term asthma medication use. We found low-strength evidence that SCIT improves asthma-related quality of life and forced expiratory volume in 1 second. There was also low-strength evidence that SLIT improves medication use and forced expiratory volume in 1 second. There was insufficient evidence on asthma symptoms and health care use.

LIMITATIONS: There were no trials in which researchers evaluated asthma symptoms using a validated tool. Study characteristics and outcomes were reported heterogeneously.

CONCLUSIONS: In children with allergic asthma, SCIT may reduce long-term asthma medication use. Local and systemic allergic reactions are common, but anaphylaxis is reported rarely.

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Dr Suarez-Cuervo drafted the protocol with contributions by each author, conducted the search, screened studies, developed tables and flowcharts, assisted with drafting the review manuscript, and coordinated contributions from the coauthors; Dr Robinson drafted the protocol with contributions by each author; Dr Rice drafted the initial manuscript and reviewed and revised the manuscript; and all authors assessed studies for inclusion, extracted data, assessed the risk of bias, critically reviewed the manuscript for important intellectual content, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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Asthma is a chronic respiratory disease characterized by lower airway inflammation, bronchial hyperreactivity, and airflow obstruction.[1] As of 2015, over 6 million or 8.4% of children in the United States had asthma,[2] and approximately half of these cases were attributable to atopy.[3] The majority of children with allergic asthma are polysensitized.[3]

Treatment options for allergic asthma include allergen avoidance, pharmacotherapy, and allergen immunotherapy (AIT). The goal of AIT is to induce allergen-specific immune tolerance, and it is the only allergic disease–modifying therapy available.[4] AIT can be given via a subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT) route. At this time, there are only 4 US Food and Drug Administration (FDA)–approved SLIT tablets available in the United States (house dust mite [HDM], 5-grass, Timothy grass, and ragweed) for treatment of allergic rhinitis; treatment of asthma is off-label.[5]

In preparation for an update to the asthma management guidelines,[1] a National Heart, Lung, and Blood Institute (NHLBI) working group identified the efficacy and safety of SCIT and SLIT in asthma management as an important topic for an updated systematic review. Our objective in this review is to provide an update to our previous 2013 systematic review (efficacy outcomes included symptoms and medication use for children with asthma and allergic rhinoconjunctivitis) and summarize the current evidence for the efficacy (symptoms, quality of life [QoL], medication use, health care use, and lung function) and safety of SCIT and SLIT, specifically in pediatric allergic asthma.[6] This report is derived from a larger review in which the efficacy and safety of SCIT and SLIT in adults and children with allergic asthma was evaluated, which was commissioned by the US Agency for Healthcare Research and Quality (AHRQ).[7]

METHODS

We developed a protocol for the review with guidance from a technical expert panel and input from representatives from both the AHRQ and the NHLBI. The protocol was registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO), registration number CRD42016047749, and was posted on the AHRQ Web site (https://effectivehealthcare.ahrq.gov/ehc/products/644/2311/asthma-immunotherapy-protocol-160913.pdf). Detailed methods are available in the full evidence report.[7]

Data Sources and Searches

We conducted a search of PubMed, Embase, and the Cochrane Central Register of Controlled Trials from January 1, 2005, through May 8, 2017. We requested scientific information packages from industry representatives, searched previous reviews and guidelines,[8–11] searched ClinicalTrials.gov, and reviewed the FDA Adverse Event Reporting System. We also reevaluated all of the included studies in our previous 2013 systematic review[6] to confirm eligibility for this review.

For the main report, we included studies of patients of any age with diagnosis of allergic asthma. For this review, only studies of children ≤18 years of age in which researchers reported on prespecified outcomes were included. Trials were required to have an intervention arm receiving SCIT or SLIT (tablet or aqueous). We excluded studies on food allergies if aeroallergens were not related to asthma, if the type of allergen was not specified, or if the study population did not report data separately for patients with asthma. Study inclusion was not restricted by language of publication. We included only randomized controlled trials (RCTs) for efficacy and RCTs, observational studies, case series, and case reports in which researchers examined safety.

Trial 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 meetings.

Data Extraction and Quality Assessment

Two reviewers extracted data and assessed risk of bias (ROB). Efficacy outcomes that were graded per our protocol included the following: asthma symptoms as reported by asthma control composite scores, QoL, medication use, health care use, and pulmonary physiology (forced expiratory volume in 1 second [FEV_1]). Safety outcomes included anaphylaxis, local effects, systemic effects, and deaths. Details regarding immunotherapy including allergen, formulation, dose, and treatment duration were extracted.

For RCTs, the ROB was assessed by using the Cochrane Collaboration's tool.[12] Overall ROB was graded as low, moderate, or high. For observational trials, ROB was assessed by using the Risk Of Bias In Nonrandomized Trials of Interventions, or ROBINS-I tool,[13] and overall ROB 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 serious adverse event (AE).[14] Following this guidance, we reported causality as certain or probable, likely or possible, unlikely or conditional, unclassified or unassessable, or unclassifiable.

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Data Synthesis and Analysis

We completed a qualitative synthesis for all questions (Tables 1–4). We considered meta-analyses but determined that the trials were not sufficiently homogenous for quantitative synthesis because of marked variability in patient characteristics, allergen and dose, trial duration, and outcome definitions.

The strength of evidence (SOE) was graded for each outcome as specified in our protocol. We used the grading scheme recommended in the Evidence-based Practice Center Methods Guide.[15,16] Five domains were considered when grading the SOE for an outcome: trial limitations (called ROB in this review), directness, consistency, precision, and reporting bias.[15] SOE was classified into 1 of 4 grades: (1) high grade (indicating high confidence that the true effect is reflected in the evidence, and further research is unlikely to change our confidence in the estimate of the effect), (2) moderate grade (indicating moderate confidence that the true effect is reflected in the evidence, 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 true effect is reflected in the evidence, 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).

RESULTS

In the full report, we identified 91 trials in which researchers addressed SCIT and SLIT. Of these, 40 included children: 17 trials of SCIT, 11 trials of SLIT, 8 non-RCTs for SCIT safety, and 4 non-RCTs for SLIT safety. Trial characteristics are summarized in Supplemental Table 5 and 6.

Efficacy Outcomes of SCIT

The efficacy of SCIT was reported in 8 trials that included 644 children aged 5 to 14 years (Supplemental Table 5). Asthma severity was graded as mild to moderate persistent in most trials.[17–20] Only 2 trials included those with severe persistent asthma,[21,22] and researchers did not specify asthma severity in 1 trial.[23] Most authors did not specify the level of asthma control, but in 1 trial, children were considered not well controlled.[18] In 5 of the trials, patients were monosensitized and received a single allergen (HDM was evaluated in 4,[17,19,20,22,23] mold was evaluated in 1[18]); in 2 trials, polysensitized patients received multiple allergens[21,24]; and in 1 trial, it was unclear if patients were monosensitized or polysensitized, and these patients were treated with HDM.[17] The maintenance-dosing interval varied from biweekly to every 6 weeks, and duration of therapy ranged from 3 months to 3 years. SCIT dosing and dosing units were variable.

Asthma Control

There were no trials in which researchers reported on asthma control using a validated tool.

QoL

In 2 RCTs including 57 children, authors reported on asthma-specific QoL using a validated tool (Asthma Quality of Life Questionnaire [AQLQ]) (Supplemental Table 7).[18,19] Researchers in both trials compared single allergen SCIT (HDM and mold) to pharmacotherapy in children with mild to moderate persistent asthma and found a significant improvement in AQLQ scores in the SCIT arm but no difference between study arms. Although these trials had consistent results, there is low SOE that SCIT improves asthma-related QoL based on 2 small trials with medium and high ROB.

Medication Use

In 2 RCTs of HDM SCIT including 70 children, authors reported on quick-relief medication use (Supplemental Table 8).[19,23] One of these revealed a significant decrease in the days of salbutamol used per year over the 3-year trial period in the SCIT arm versus the control arm (results in a figure).[23] Researchers in the other trial did not find a difference within arms after 8 months and did not report a comparison between arms.[19] These 2 small trials with medium and high ROB had inconsistent and direct results, providing low SOE that SCIT improves quick-relief medication use.

In 4 trials, authors reported on long-term control medication use. Two of these trials (both low ROB) included children with mild to moderate persistent asthma, and researchers found a significant decrease in the dose of inhaled corticosteroids (ICSs) used between treatment and comparator arms.[17,20] In 1 of the trials with 88 children, blinded study investigators adjusted controller medications per a protocol based on symptom control every 1 to 3 months and found that the dosage of budesonide in the SCIT arm decreased from 196.7 μg at baseline to 71.3 μg at 3-year follow-up, and the final dosage was significantly lower than the comparator arm, which received a desensitization vaccine (101.3 μg).[20] Researchers in the other trial evaluated SCIT ± vitamin D (650 IU per day) versus pharmacotherapy (n = 50); ICS doses were only expressed in a figure, but SCIT + vitamin D had a significantly lower ICS dose than the pharmacotherapy arm. Researchers in this trial also had blinded investigators and patients record their doses of ICSs on daily diary cards that were monitored at each study visit. Authors of both trials also reported that significantly more patients in the SCIT arm

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TABLE 1 SCIT Efficacy Summary

Outcome	No. Studies, Participants	Allergen (*n* Studies)	Comparators (*n* Studies)	Summary of Findings	SOE
Asthma symptoms	0	—	—	Unable to draw conclusions.	Insufficient
QoL	2, 57	Dust mite (1), Alternaria (1)	SCIT versus pharmacotherapy (2)	The SCIT arm improved in both trials. Control arm also improved in 1 trial. In 1 trial, researchers measured difference between arms and found no difference	Low SOE that SCIT improves asthma-related QoL
Quick-relief medication use	2, 70	Dust mite (2)	SCIT versus placebo (1) versus control (1)	1 study revealed significant reduction in No. d with salbutamol treatment in the SCIT arm when compared with control. The second study did not reveal any significant difference for either arm	Low SOE that SCIT reduces short-term medication use
Long-term control medication use	4, 300	Dust mite (3), multiple (1)	SCIT versus placebo (1) versus pharmacotherapy (1) versus vitamin D + pharmacotherapy (1) versus desensitization vaccine (1)	2 studies revealed significant reductions in medication use for SCIT versus comparator arm. In 1 study, researchers didn't compare arms, and researchers in 1 study found no difference between arms. 2 studies revealed significant decrease in medicine use for SCIT arm at follow-up compared with baseline but not in the comparator arm	Moderate SOE that SCIT reduces long-term medication use
Systemic corticosteroids	2, 150	Dust mite (1), multiple (1)	SCIT versus placebo (1) versus control (1)	The study on dust mite revealed significant decrease in No. d with systemic steroid use in the SCIT group when compared with control. The study on multiple allergens revealed no difference between groups	Low SOE that SCIT reduces systemic steroid use
Health care use	2, 161	Dust mite (1), multiple (1)	SCIT versus placebo (1) versus pharmacotherapy (1)	1 study in which researchers report increase in clinic visits but do not explain the reason or if study related. The second study revealed no difference	Insufficient
Pulmonary physiology: FEV_1	5, 378	Dust mite (3), mold (1), multiple (1)	SCIT versus pharmacotherapy (3) versus vitamin D + pharmacotherapy (1) versus control (1)	1 study in which researchers found significant difference in the proportion of patients with improved FEV_1 in the SCIT arm when compared with pharmacotherapy. 3 studies revealed no significant difference between arms. Researchers in 1 study reported that 100% of patients in the SCIT arm had FEV_1 >80% at follow-up	Low SOE that SCIT improves FEV_1

—, not applicable.

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TABLE 2 SLIT Efficacy Summary

Outcome	No. Studies, Participants	Allergen (*n* Studies)	Comparators (*n* Studies)	Findings	SOE
Asthma symptoms	0	NA	NA	NA	Insufficient
QoL	0	NA	NA	NA	Insufficient
Health care use	0	NA	NA	NA	Insufficient
Quick-relief medication use	2, 218	Dust mite (2)	SLIT versus placebo (2)	Neither study revealed a significant difference between arms	Low SOE that SLIT does not affect quick-relief asthma medication use
Long-term control medication use	2, 218	Dust mite (2)	SLIT versus placebo (2)	Neither study revealed a significant difference between arms	Low SOE that SLIT does not affect long-term asthma medication use
Systemic corticosteroids	1, 110	Dust mite (1)	SLIT versus placebo (1)	1 study revealed significant reduction in medication consumption in the SLIT group when compared with placebo	Insufficient
Pulmonary physiology: FEV_1	6, 375	Dust mite (5); grass (1)	SLIT versus placebo (6)	1 study revealed a significant improvement in FEV_1 in SLIT versus placebo. 4 studies revealed no difference between study arms. 3 studies revealed a significant improvement in SLIT arm only	Low SOE that SLIT improves FEV_1

NA, not applicable.

discontinued ICS treatment versus the comparator arm (20% and 35% vs 0% for SCIT ± vitamin D versus pharmacotherapy; 29% vs 20% for SCIT versus desensitization vaccine).[17,20] Researchers in the remaining 2 trials found a significant decrease in controller medication use in only the SCIT arm at follow-up compared with baseline.[19,21] In 1 of these, researchers evaluated HDM SCIT versus pharmacotherapy ($n = 41$) for 8 months, and noted that at baseline, 7 (33%) patients in the SCIT arm and 4 (20%) in the control arm required ICSs, and at follow-up this decreased to 2 (10%) versus no change, respectively (*P* value not reported).[19] In the final trial, researchers compared multiple-allergen SCIT to placebo in 121 children with moderate to severe asthma for 30 months and found that only patients in the SCIT arm had significantly decreased use of ICSs at follow-up (mean of 21 out of 60 days at baseline and 11.3 out of 60 days at follow-up versus 20 out of 60 days at baseline and 14.7 out of 60 days at follow-up in the SCIT and placebo arms, respectively). There was no difference between arms.[21] These 4 trials had low (3 trials) to high (1 trial) ROB and presented inconsistent but direct results. There is moderate SOE that SCIT may improve long-term controller medication use.

In 2 RCTs, researchers evaluated systemic corticosteroid use. In 1 trial, researchers evaluating HDM SCIT in 29 children over 3 years found a significant decrease in the mean number of days of treatment required in the previous year in the SCIT arm versus controls (22 days at baseline decreased to 1 day at follow-up in the SCIT group versus 25 days decreased to 12 days in the control group; $P < .01$).[23] In the other trial, researchers did not find a significant change within or between arms in the number of days of children needing systemic steroids in the previous 60 days between baseline and 30-month follow-up.[21] From these 2 small trials in which researchers presented inconsistent but direct results with low and medium ROB, we conclude that there is low SOE that SCIT improves systemic corticosteroid use.

Health Care Use

In 2 trials with 161 children, researchers evaluated SCIT and health care use (Supplemental Table 9).[21,22] A significant difference in hospitalizations or emergency department (ED) visits was not found in either trial, but researchers in 1 trial of HDM SCIT did note a significant increase in the number of office visits in the SCIT arm versus the pharmacotherapy arm (12.4 vs 17.25 visits in the previous 6 months for pharmacotherapy and SCIT arms, respectively).[22] The authors did not provide an explanation for this increase. Although these results are consistent and direct, there are only 2 small trials with low and medium ROB, so we conclude that there is insufficient evidence to draw conclusions.

Pulmonary Physiology

In 5 trials, researchers evaluated FEV_1 in 378 children (Supplemental Table 10).[17–19,23,24] Researchers in 1 evaluated multiple-allergen SCIT for 12 months in 242 children and noted that significantly more patients in the SCIT arm versus the pharmacotherapy arm had improvement in their FEV_1 (60% vs 19%, $P = .0001$).[24] In another trial of HDM SCIT, authors reported that all

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TABLE 3 SCIT Safety Summary

Type of Reaction	No. Studies and Design	Allergen (*n* Studies)	No. AEs or Affected Patients/Total No.		Description
			Treatment Arm	Comparator Arm	
Local reaction	7 RCTs; Reported as patients	Dust mite (7)	0/36 patients; 15/65 patients; 26/97 patients	0/30 patients; 0/50 patients; 0/70 patients	Local reaction not specified; Urticaria; Local edema, pruritus, and pain
	5 RCTS; Reported as events	Dust mite (2); Grass (1); Dog (1); Mold (1)	793 events/124 patients	262 events/43 patients	Redness, swelling, pain
	1 non-RCT; Reported as patients	Pollen (1)	1/1	NA	Erythema, swelling ≥5 cm
Systemic reactions					
General reactions	5 RCTS; Reported as patients	Dust mite (4); Multiple allergens (1)	22/132 patients	4/128 patients	Unspecified systemic reactions
	2 RCTS; Reported as events	Dust mite (1); Mold (1)	46 events/61 patients	NR	Unspecified systemic reactions
Respiratory reactions	6 RCTS; Reported as patients	Dust mite (4); Grass (1) Multiple (1)	13/224 patients	3/217 patients	Asthma, cough, dyspnea
	1 RCT; Reported as events	Dust mite (4)	14 events/20 patients	8 events/10 patients	Asthma, cough, dyspnea
Cutaneous reactions	1 RCT; Reported as patients	Multiple allergens (1)	8/105	0/137	Skin rash
Other reactions	1 RCT; Reported as events	Grass (1)	21 events/18 patients	9 events/17 patients	Eczema, urticaria, rhinoconjunctivitis
General reactions	3 non-RCTs; Reported as patients	Multiple allergens (2); Dust mite (1)	37/161; 1/NR	0/52	Unspecified systemic reactions
	2 non-RCTs; 1 reported as patients; 1 reported as events	Dust mite (1); Multiple (1)	2/NR; 2/NR; 2 events/NR; 4 events/NR	NA	Hives, wheezing; Rhinorrhea, ocular itching; Asthma, dyspnea; Congestion, rhinorrhea, sneezing
Anaphylaxis	4 RCTS	Dust mite (3), grass (1)	2/96	0/69	Systemic reactions requiring epinephrine
	1 non-RCT	Dust mite (1)	0/67	NA	
Death	5 non-RCTs	Dust mite (3); Multiple (3); Pollens (1)	0/NR; 1/1	NA	Death; 1 case report of death

NA, not applicable; NR, not reported.

patients in the SCIT arm had an FEV_1 >80% predicted at 8 month follow-up (19 out of 21 patients had FEV_1 >80% at baseline), but comparator arm results were not reported.[19] In the remaining 3 trials (2 HDM and 1 mold), researchers found no significant differences between SCIT and comparator arms.[17,18,23] In 1 of these (mold), researchers did find a significant increase in both arms.[18] Overall, inconsistent results were reported in 5 trials with low to high ROB; therefore, there is low SOE that SCIT improves FEV_1.

Efficacy Outcomes of SLIT

In 6 RCTs including 392 children aged 5 to 18 years, authors reported on the clinical efficacy of SLIT (Supplemental Table 6).[25–30] Asthma severity was graded as mild or mild to moderate persistent in all trials. Control status was only specified in 2 trials; authors of 1 mentioned that patients had controlled symptoms,[30] and authors of the other reported that patients had ongoing respiratory symptoms despite ICSs and allergen avoidance.[26] Only monosensitized patients were included, and HDM SLIT was evaluated in 5,[25,26,28–30] and grass was evaluated in 1 trial.[27] Maintenance dosing ranged from daily to 2 days per week for 6 to 18 months, and the maintenance dose was variable between trials.

Asthma Control

No authors reported on asthma control by using a validated tool.

QoL

No authors reported on asthma-related QoL.

Medication Use

In 2 trials in which HDM SLIT (aqueous and tablet) (n = 218) was used, researchers reported on asthma medication use (Supplemental Table 11).[25,29] No significant difference between arms for quick-relief or long-term control medication use was found in either trial. In 1 trial, researchers evaluated the use of systemic corticosteroids and did

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TABLE 4 Safety Summary SLIT

Type of Reaction	No. Studies and Design	Allergen (*n* studies)	No. AEs or Affected Patients/Total No.		Description
			Treatment Arm	Comparator Arm	
Local reactions	3 RCTs	Grass (1)	35%/20 patients	20%/15 patients	Oral itching
	Reported as patients	Dust mite (2)	5%/20 patients	6.6%/15 patients	Stomach ache
			0/55	0/46	No local AEs
	2 RCTs	Dust mite (2)	561 events/108 patients	10 events/73 patients	Oral itching, ear itching, stomatitis, throat irritation
	Reported as events		19 events/54 patients	2 events/55 patients	Unspecified GI events
	1 non-RCT	Dust mite (1)	1 event/1 patient	NA	Eosinophilic esophagitis
	Reported as patients				
Systemic reactions					
Respiratory	1 RCTs	Multiple (1)	1/46 patients	1/22 patients	Worsening asthma
	Reported as patients				
	4 RCTs	Dust mite (3)	82 events/352 patients	73 events/152 patients	Rhinitis and/or asthma, dyspnea
	Reported as events	Grass (1)			
Other	10 RCTs	Dust mite (6)	50%–68%/46 patients	32%–46%/22 patients	Unspecified AEs
	Reported as patients	Multiple (1)	115/236 patients	117/236 patients	Headache
		Grass (2)	0/20 patients	6.6%/15 patients	No systemic AEs
		Tree (1)	0/200	0/156	
	2 non-RCTs	Dust mite (2)	3 events/1 patient	NA	Wheezing
	Reported as events		0 event/39 patients	NA	No systemic reactions
Anaphylaxis	3 RCTs	Dust mite (2)	0/266	0/183	Anaphylaxis
	Reported as patients	Multiple (1)			
	1 non-RCT	Tree (1)	1/1	NA	Anaphylactic shock after overdose
	Reported as patients	Dust mite (1)			
Death	1 RCT	Grass (1)	0/55	0/50	Death
	Reported as patients				

GI, gastrointestinal; NA, not applicable.

not find any significant difference between arms at follow-up.[29] Evidence is low on the basis of only 2 small trials with consistent results and low to medium ROB that SLIT does not reduce quick-relief or long-term control medication use. There is insufficient evidence about the effect of SLIT on systemic corticosteroid use to draw conclusions.

Health Care Use

No authors reported on health care use.

Pulmonary Physiology

Of the 6 trials in which authors reported on FEV_1 (5 HDM and 1 grass mix), only 1 revealed a difference between arms at follow-up (Supplemental Table 12). In this trial, researchers evaluated the efficacy of grass SLIT (ultra-rush) for 2 years in 35 children and found a significant improvement in FEV_1 percent predicted for SLIT compared with placebo (mean at follow-up = 100.4 vs 88.2 for SLIT and placebo, respectively; $P = .005$).[27] In 3 other HDM SLIT trials, researchers noted a significant improvement in FEV_1 at 6-month follow-up compared with baseline in only the SLIT arm (predicted FEV_1 of 83.4% at baseline improved to 92.6% at follow-up; $P < .001$; results for the other trials were presented in a figure).[28–30] Overall, there is low SOE that SLIT improves FEV_1 on the basis of results from 6 trials with inconsistent results and low to medium ROB.

Safety of SCIT and SLIT

In our review, we found that local and systemic reactions to both SCIT and SLIT occurred more frequently in the treatment than the comparator arms (Supplemental Tables 13–21).

For SCIT, local reactions, including urticaria, swelling, and redness or pain at the injection site, occurred in 0% to 27% of trial patients in the treatment arm or 6.4 events per patient. In the comparator arms, such events occurred in 0% of patients or 0 to 6 events per patient. In the SLIT trials, local reactions, including oral itching, stomatitis, throat irritation, stomach ache, and unspecified GI complaints occurred in 0% to 35% or 0.35 to 5.2 events per patient in the treatment arms versus 0% to 20% or 0.04 to 0.14 events per patient in the comparator arms. There was 1 episode of eosinophilic esophagitis reported in a patient treated with SLIT that resolved after discontinuation of SLIT (non-RCT).

In the SCIT trials, systemic reactions (cough, dyspnea, asthma, hives, rhinoconjunctivitis, eczema, and

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unspecified reactions) occurred in 6% to 17% or 0.7 to 1.1 events per patient in the treatment arms versus 0% to 3% or 0.5 to 0.8 events per patient in the comparator arms. Anaphylaxis was reported in 2% of patients receiving SCIT in trials (2 of 96 patients) versus no events in the comparator arms (0 of 69 patients). In 1 non-RCT, researchers specifically reported no anaphylactic events in 67 children treated with HDM SCIT. Unspecified systemic reactions were also reported in 23% of patients receiving SCIT in non-RCTs. Other reactions including hives, wheezing, rhinorrhea, asthma, and congestion were also reported in the non-RCTs.

There was 1 case report of death occurring in a 17-year-old girl with moderate persistent asthma who had received SCIT in childhood for 4 years and stopped because of a skin reaction. The authors report that 12 hours after initiation of a new regimen, she complained of abdominal pain, vomiting, and diarrhea without fever. Two days later, she developed acute respiratory failure and was referred to the ICU. She had markedly elevated creatine kinase, elevated troponin, leukopenia, thrombocytopenia, and bilateral interstitial markings on chest radiograph. On day 4, she developed a hypoxic coma leading to intubation and mechanical ventilation, followed by shock and acute renal impairment. By day 5, she developed multiorgan failure and died. The authors considered immunologic mechanisms secondary to manipulation or the way the dose was escalated and considered causality probable. Following WHO criteria for assessing case reports, we also determined that the likelihood of SCIT causing this death (causality) was possible, as the event was related to intervention but was not dose related.[31]

In the SLIT trials, systemic reactions (asthma, dyspnea) were rare, occurring in 2% or 0.23 events per patient in the treatment arms versus 4.5% or 0.48 events per patient in the comparator arms. Unspecified adverse reactions occurred in 0% to 68% of patients receiving SLIT versus 0% to 46% in the comparator arms. A researcher in 1 non-RCT described wheezing that occurred 3 times in 1 patient. There was 1 episode of anaphylaxis in 267 patients receiving SLIT. In this case report, a 16-year-old girl with well-controlled intermittent asthma receiving HDM SLIT had 2 episodes of self-resolving wheezing during maintenance therapy, and then in her third year of SLIT, after a 3-week break in maintenance dose, the patient (for unknown reasons) administered herself 60 drops of 100 IR/mL instead of 10 drops and had an episode of anaphylactic shock.[32] No deaths were reported for SLIT.

DISCUSSION

In this systematic review of the evidence for the clinical efficacy and safety of SCIT and SLIT for pediatric allergic asthma, we found moderate-strength evidence that SCIT reduces long-term asthma controller medication use. We otherwise found either low or insufficient evidence for the other outcomes, including asthma-related QoL, quick-relief medication and systemic corticosteroid use (SCIT), asthma-related medication use (SLIT), lung function (FEV_1), and health care use. We did not identify any trials in which researchers used validated symptom scales, and therefore we were unable to evaluate this outcome.

In our 2013 systematic review of AIT for pediatric asthma and rhinoconjunctivitis that included 34 trials, we found moderate-strength evidence that SCIT improves asthma symptoms and low-strength evidence that SCIT improves asthma medication scores.[33] Unlike this previous review, our search for outcomes relating to asthma symptoms was limited to RCTs in which researchers used validated measurement tools, which we did not find, so we do not have an update for this outcome. Although we did not include medication scores as an outcome, we similarly found that SCIT may decrease medication use.

Our review found that adverse local and systemic reactions to both SCIT and SLIT occurred more frequently in the treatment arms than the comparator arms. Similar to previous reviews, local reactions were commonly reported in both SCIT and SLIT trials. For SCIT, local reactions included urticaria, swelling, redness, or pain at the injection site, and in SLIT trials, local reactions included oral itching and gastrointestinal complaints. Similar to previous reviews, we found rare reports of anaphylaxis associated with SCIT, and although rarely reported, we are including a case report of death associated with SCIT as well as a case report of anaphylactic shock associated with an overdose of HDM SLIT. Per the practice guidelines, AIT should be administered in a setting that can monitor for and manage adverse reactions, and patients should be monitored for 30 minutes after therapy (this includes the first dose of SLIT). After the first dose, SLIT can be administered at home. Patients administering SLIT at home should, however, be instructed on how to manage adverse reactions and situations when SLIT should be held.[34] For patients with asthma, AIT should not be given to patients with severe, unstable, or poorly controlled symptoms.[11,34]

Challenges and Trial Limitations

The trials included in our review were heterogeneous in patient and intervention characteristics and in how outcomes were measured. Because of this heterogeneity, we were only able to synthesize the data qualitatively.

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The studies in this review included only children ≤18 years of age. Other studies in the full report included children and adults but did not report the results for children separately; therefore, they could not be used in this review (n = 9). Additional studies that we were not able to include had mixed populations of children with asthma and allergic rhinitis but did not report outcomes separately for those with asthma. Although researchers in several trials reported asthma symptoms as an outcome, we did not find any that reported this outcome by using a validated tool.

Applicability

Our results are applicable to children and adolescents with allergic asthma due to inhalant allergens. The majority of SCIT trials and all of the SLIT trials used a single allergen (HDM) AIT in monosensitized patients, and it's possible that results may not be generalizable to patients with allergic asthma who are polysensitized, patients treated with multiple allergens, or other inhalant allergen AIT. Finally, most of the trials included children and adolescents with mild to moderate persistent asthma. Patients with severe, uncontrolled asthma are at increased risk for systemic reactions, therefore AIT should not be initiated unless asthma symptoms are stable.[11]

Future Research Needs

Future researchers should consider evaluating multiple-allergen AIT as well as other inhalant allergens in polysensitized patients. In our review, we did not find studies in which researchers evaluated the effect of single versus multiple-allergen AIT in patients who are polysensitized, which is an important clinical question to address in future trials. We also did not find any trials in which researchers reported asthma symptoms using a validated scale, and we would encourage this in future trials so that this important outcome can be more easily compared across trials. None of the researchers in the efficacy trials directly compared different lengths of treatment or followed patients for an extended period of time after completion of therapy, so the question of how long AIT must be given to see a lasting effect on asthma symptoms remains an important unanswered clinical question. Because there are only 4 FDA-approved SLIT tablets at this time, the use of other sublingual drops or tablets would be considered off-label. There is a need for rigorous trials to evaluate these SLIT products in United States populations.[34]

CONCLUSIONS

In children with allergic asthma, SCIT may reduce the need for asthma medication, improve FEV_1, and improve asthma-related QoL. SLIT may improve FEV_1, but does not seem to improve asthma medication use. Local and systemic allergic reactions to SCIT and SLIT are common. Life-threatening events such as anaphylaxis and death were reported rarely.

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ABBREVIATIONS

AE: adverse event
AHRQ: Agency for Healthcare Research and Quality
AIT: allergen immunotherapy
AQLQ: asthma quality of life questionnaire
ED: emergency department
FDA: US Food and Drug Administration
FEV_1: forced expiratory volume in 1 second
HDM: house dust mite
ICS: inhaled corticosteroid
NHLBI: National Heart, Lung, and Blood Institute
QoL: quality of life
RCT: randomized controlled trial
ROB: risk of bias
SCIT: subcutaneous immunotherapy
SLIT: sublingual immunotherapy
SOE: strength of evidence
WHO: World Health Organization

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Supplemental Information

SUPPLEMENTAL TABLE 5 Studies Characteristics SCIT

Study	Study Design Comparators	Patient Characteristics	Allergy Diagnosis: Sensitization Status and Allergen Provided in AIT	*N*	AIT Characteristics	ROB
Tsai et al[22]	RCT	Asthma diagnosis criteria GINA	SPT and IgE	40	Initial dose 0.5 AU/mL weekly and then biweekly for 3 mo	Medium
	SCIT	Severity moderate and severe	Monosensitized		Allergen content Dp and Df (10 000 AU/mL)	
Asia	Pharmacotherapy	Control status: NR	Single allergen: dust mite			
		Age range (5–14 y)				
Lozano et al[19]	RCT	Asthma diagnosis not reported	SPT and IgE	43	10 000 AU Eq, monthly for 8 mo	High
Europe	SCIT	Severity mild and moderate	Monosensitized			
	Pharmacotherapy	Control status: NR	Single allergen: dust mite			
		Age range (6–14 y)				
Pifferi et al[23]	RCT	Asthma diagnosis per doctor criteria	SPT	29	800 UI every 4–6 wk for 3 y	Medium
Europe	SCIT	Severity NR	Monosensitized			
	No treatment	Control status: NR	Single allergen: dust mite			
		Age range (6–14 y)				
Hui et al[20]	RCT	Asthma diagnosis per Breathing Group of Pediatric Academy; Chinese Medical Association	SPT and IgE	90	100 000 U/mL every 4–6 wk for 51 wk	Low
	SCIT	Severity mild to moderate	Monosensitized			
Asia	Other (desensitization vaccine)[a]	Control status: NR	Single allergen: dust mite			
		Age range (5–14 y)				
Baris et al[17]	RCT	Asthma diagnosis GINA criteria (FEV_1 changes)	SPT and IgE	55	Buildup NS, maintenance monthly for 12 mo (44.1 μg of Der p 1 and 62.1 μg of Der f 1)	Low
Asia	SCIT	Severity mild and moderate	Mono versus Polysensitized unclear			
	SCIT + vitamin D	Control status: NR	Single allergen: dust mite			
	Pharmacotherapy	Age range (5–15 y)				
Kilic et al[18]	RCT	Asthma diagnosis GINA criteria	SPT	24	Buildup NS, maintenance monthly for 12 mo	Medium
Asia	SCIT	Severity mild and moderate	Monosensitized			
	Pharmacotherapy	Control status: NR	Single allergen: Alternaria			
		Age range (7–14 y)				
Adkinson et al[21]	RCT	Asthma diagnosis physician diagnosed	SPT and IgE	121	(4.3 μg Der p1- 5 μg Der f1- 26 μg Amb a1-38 μg group 1 in 0.7 mL of concentrate) biweekly for 24 mo, then every 3 wk after 24 mo for 27 mo	Low
United States	SCIT	Severity moderate to severe	Polysensitized			
	Placebo	Control status: NR	Multiple allergens			
		Age range (5–12 y)				
Alzakar and Alsamarai[24]	RCT	Asthma diagnosis criteria GINA and NHLBI	SPT and IgE	242	0.5 of stock standardized extracts biweekly and then every 4–6 wk for 12 mo	Medium
Asia	SCIT	Severity excluded severe asthma	Polysensitized			
	Pharmacotherapy	Control status: NR	Multiple allergens			
		Age range (7–12 y)				
Schubert et al[35]	RCT	Asthma diagnosis GINA criteria	SPT and IgE	34	5000 TU after 6 wk	Low
	SCIT cluster	Severity mild to moderate	Poly and monosensitized		5000 TU after 14 wk	
	SCIT classic	Control status: NR	Single allergen: dust mite		16 wk total	
		Age range (6–18 y)				

TABLE 5 Continued

Study	Study Design Comparators	Patient Characteristics	Allergy Diagnosis: Sensitization Status and Allergen Provided in AIT	*N*	AIT Characteristics	ROB
Arroabarren et al[36]	RCT	Asthma diagnosis NHLBI	SPT and IgE	63	Mix of conventional and cluster	Medium
Europe	SCIT 3 y	Severity mild and moderate	Poly and monosensitized		3.6 μg Der P1 per dose, monthly for 3 or 5 y	
	SCIT 5 y	Control status: NR	Single allergen: dust mite			
		Age range (5–15 y)				
Ibero and Castillo[37]	RCT	Asthma diagnosis per GINA	SPT and IgE	30	42.5 μg, monthly for 4 mo	Medium
Europe	SCIT	Severity mild and moderate	Monosensitized			
	Pharmacotherapy	Control status: NR	Single allergen: dust mite			
		Age range (8–16 y)				
Zielen et al[38]	RCT	Asthma diagnosis criteria GINA	SPT and IgE	66	0.6 mL of 10 000 TU/mL every 6 wk for 2 y	Medium
Europe	SCIT	Severity mild to moderate	Polysensitized			
	Pharmacotherapy	Control status: well controlled	Single allergen: dust mite			
		Age range (6–17 y)				
Altintaş et al[39]	RCT	Asthma diagnosis criteria NR	SPT and IgE	35	6–10 IR 10 IR = 1000 wt/vol Every 4 wk for 2 y	High
Asia	SCIT versus	Severity mild to moderate	Mono versus polysensitized unclear			
	SCIT versus	Control status: poorly controlled	Single allergen: dust mite			
	SCIT versus Placebo	Age range (5–18 y)				
Valovirta et al[40]	RCT	Asthma diagnosis criteria-NR	SPT and IgE	27	100 000 SQ-U Every 6 wk for 1 y	Low
United States	SCIT	Severity NR	Polysensitized			
	Placebo	Control status: NR	Single allergen: dog			
		Age range (5–18 y)				
Dreborg et al[41]	RCT	Asthma diagnosis GINA criteria	SPT and IgE	30	100 000 BU every 4 wk for 10 mo	Low
Europe	SCIT	Severity mild to moderate	Monosensitized			
	Placebo	Control status: controlled (stable dose of ICS)	Single allergen: Cladosporium			
		Age range (5–17 y)				
Roberts et al[42]	RCT	Asthma diagnosis criteria NR	SPT and IgE	39	100 000 SQ-U every 6 wk for 2 y	Low
	SCIT	Severity all severities	Poly and monosensitized			
	Placebo	Control status NR	Single allergen: grass			
		Age range (3–16 y)				
Hill et al[43]	RCT	Asthma diagnosis criteria NR	SPT and IgE	20	75–1000 PNU seasonal; every 2 wk until the start of the season; then every 4 wk until the end of season	High
Australia	SCIT (rush)	Severity NR	Both mono and polysensitized			
	Placebo	Control status: NR	Single allergen: grass			
		Age range (9–14 y)				
Gozde Kanmaz et al[44]	Non-RCT	Asthma diagnosis GINA criteria	SPT	102	100 000 SQ-U weekly for 33 mo	Serious
United States	SCIT versus SCIT	Severity mild persistent and moderate persistent	Monosensitized			
		Control status: NR	Single allergen: dust mite			
		Age range (6–18 y)				

TABLE 5 Continued

Study	Study Design Comparators	Patient Characteristics	Allergy Diagnosis: Sensitization Status and Allergen Provided in AIT	*N*	AIT Characteristics	ROB
Chen et al[45]	Non-RCT	Asthma diagnosis NR	SPT and IgE	67	100 000 SQ-U/mL every 6 wk	Moderate
Asia	Children undergoing SCIT	Severity NR	Both mono and polysensitized			
		Control status: NR	Single allergen: dust mite			
		Children age mean (9.6 ± 3)				
Sana et al[31]	Non-RCT	Asthma diagnosis criteria NR	NR	1	Dose, interval and duration not reported	Possible
Europe	SCIT	Severity moderate persistent	Sensitization status NR			
	Wo comparator	Control status: NR	Pollens (Alustal, respiratory allergens)			
		Age 17 y				
Kartal et al[46]	Case report	Asthma diagnosis not described	SPT	NR	HDM: 0.5 mL of 2000 AU/mL	Unassessable
Europe	SCIT	Severity NR	Mono and polysensitized		Pollen/mold: 0.5 mL of 1/200 wt/vol	
	Wo comparator	Asthma control NR	Multiple allergens		Years 2003–2013: standardized depot	
		Age NR for asthma only			0.8 mL/5000 TU/mL and 0.8 mL/10 IR/mL	
					Every 4–6 wk for 4 y	
Copenhaver et al[47]	Case report	Asthma diagnosis physician	NR	NR	Last dose = 0.5 mL of 1:1	Probably/likely
United States	SCIT cluster	Severity NR	Multiple allergens			
	Wo comparator	Control status: NR				
		Age NR for asthma only				
Cardona et al[48]	Case report	Asthma diagnosis NR	Mono and polysensitized	NR	0.5 mL (50 DPP) monthly	Probably/likely
South America	SCIT ultrarush	Severity NR	Dust mite			
	Wo comparator	Control status: controlled and not controlled				
		Age NR for asthma only				
Santos et al[49]	Non-RCT	Asthma diagnosis not described	Not reported	NR	Conventional, ultra rush, and rush	Moderate
Europe	SCIT	Severity NR	Multiple allergen			
	Wo comparator	Asthma control NR				
		Age NR for asthma only				
Dong et al[50]	Case report	Asthma diagnosis per GINA guidelines	SPT and IgE	44	100 000 SQ-U every 6 wk	Probably/likely
Asia	SCIT wo comparator	Severity NR	Mono and polysensitized			
		Control status: NR	Dust mite			
		Children <18 y				

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 is followed by multiple allergen and then by allergen provided (dust mite, trees, and multiple allergen). DPP, Depigmenting and Polymerizing; GINA, Global Initiative for Asthma; IgE, immunoglobulin E; NR, not reported; SPT, skin prick test.

[a] The control group received standardized glucocorticoid management and a desensitization vaccine (details not provided).

SUPPLEMENTAL TABLE 6 Studies Characteristics SLIT

Study	Study Design Comparators	Patient Characteristics	Allergy Diagnosis Sensitization Status and Allergen Provided in AIT	*N*	AIT Characteristics	ROB/ Causality
Pham-Thi et al[25]	RCT	Asthma diagnosis pulmonary tests	SPT and IgE	111	300 IR daily for 18 mo	Low
Europe	SLIT (T)	Severity mild and moderate	Monosensitized		6.9 mg Der p 1 and 14.7 mg Der f 1	
	Placebo	Control status: NR; age range (5–16 y)	Single allergen: dust mite			
Bahçeciler et al[26]	RCT	Asthma diagnosis GINA criteria	SPT and IgE	15	20 drops of 100 IR/mL daily × 4 wk then weekly × 4 mo (6 mo total)	Medium
Asia	SLIT (A)	Severity mild	Monosensitized		1 mL of 100 IR = 9 μg D pter and 14 μg D.far	
	Placebo	Control status: ongoing respiratory symptoms despite HDM avoidance and ICS	Single allergen: dust mite			
		Age range (7–18 y)				
Lue et al[28]	RCT	Asthma diagnosis NR	SPT and IgE	20	20 drops of 300 IR/mL daily × 24 wk	Medium
Asia	SLIT (A)	Severity mild and moderate	Monosensitized		3 mg Der F and 1.7 mg Der P (cumulative)	
	Placebo	Control status: NR	Single allergen: dust mite			
		Age range (6–12 y)				
Niu et al[29]	RCT	Asthma diagnosis GINA criteria	SPT and IgE	110	20 drops of 300 IR/mL daily × 24 wk	Medium
Asia	SLIT (A)	Severity mild and moderate	Monosensitized		3 mg Der F and 1.7 mg Der P (cumulative)	
	Placebo	Control status: NR	Single allergen: dust mite			
		Age range (5–12 y)				
Ippoliti et al[30]	RCT	Asthma diagnosis NR	SPT and IgE	86	5 drops of 10 BU/mL 3 times per wk × 6 mo	Medium
Europe	SLIT (A)	Severity mild and moderate	Monosensitized		2.4 μg/ml Der p1 and 1.2 μg/ml Der p2 (per wk)	
	Placebo	Control status: controlled	Single allergen: dust mite			
		Age range (5–12 y)				
Stelmach et al[27]	RCT	Asthma diagnosis pulmonary tests	SPT and IgE	50	120 IR daily × 6 mo	Low
	SLIT (A) ultrarush	Severity excluded severe asthma	Monosensitized		3.65 mg of major allergens (5 grasses)	
Europe	Placebo	Control status: NR	Single allergen: grass mix			
		Age range (6–17 y)				
Mösges et al[51]	RCT	Asthma diagnosis criteria NR	SPT and IgE	54	Targeted: 300 IR within 90 min	High
Europe	SLIT (A)	Severity mild and moderate	Polysensitized			
	Placebo	Control status: NR	Single allergen: Birch			
		Age range (6–14 y)				
Shao et al[52]	RCT	Asthma diagnosis GINA	SPT and IgE	218	0.15 mL daily for 12 mo allergen content 333 μg/mL	Medium
Asia	SLIT (A)	Severity excluded severe	Polysensitized			
	Pharmacotherapy	Control status: controlled	Single allergen: dust mite			
		Age range (3–13 y)				
Corzo et al[53]	RCT	Diagnosis: NR	SPT and IgE	72	0.5–12 DU	Low
Europe	SLIT (T)	Severity mild and moderate	Monosensitized			
	Placebo	Control status: NR	Single allergen: dust mite			
		Age range (5–14y)				
Bufe et al[54]	RCT	Asthma diagnosis GINA criteria	SPT and IgE	105	75 000 SQ-T/2800 bioequivalent allergen units, ∼15 μg Phl p5 major allergen	Medium
Europe	SLIT (T)	Severity mild, moderate, severe	Poly and monosensitized			
	Placebo	Control status: NR	Single allergen: grass			
		Age mean (5–16 y)				

TABLE 6 Continued

Study	Study Design Comparators	Patient Characteristics	Allergy Diagnosis Sensitization Status and Allergen Provided in AIT	*N*	AIT Characteristics	ROB/ Causality
Maloney et al[55]	RCT	Asthma diagnosis GINA criteria	SPT and IgE	68	6 SQ-HDM	Low
United States	SLIT (T) 6 SQ-HDM	Severity not specified (excluded severe)	Mono and polysensitized		12 SQ-HDM	
	SLIT (T) 12 SQ-HDM	Control status: controlled	Dust mite		Daily × 28 d	
	Placebo	12–17 y				
Blazowski[32]	Non-RCT	Asthma diagnosis criteria NR	Allergy diagnosis not reported	1	10 drops of 100 IR/mL daily for 3 y	Certain
	SLIT	Severity intermittent	Sensitization status not reported			
	Wo comparator	Control status: well controlled	Dust mite			
		Age 16 y				
Nuhoglu et al[56]	Non-RCT	Asthma diagnosis criteria ATS	SPT	39	20 drops of 100 IR 3 times/wk for 3 y	Moderate
	SLIT	Severity mild to moderate	Monosensitized			
	Wo comparator	Control status: controlled	Single allergen: dust mite			
		Age range (6–14)				
Galip and Bahceciler[57]	Non-RCT	Asthma diagnosis: pulmonary tests persistent asthma	SPT	1	300 IR/mL, total duration 3 y	Certain
Europe	SLIT (A)	Control status: controlled on daily ICS	Monosensitized			
	Wo comparator	Age 6 y	Single allergen: dust mite			
Béné et al[58]	Non-RCT	Asthma diagnosis criteria NR	Allergy diagnosis not reported	1	300 IR. Duration of treatment NR	Probable/ likely
Europe	SLIT (A)	Severity NR	Monosensitized			
	Wo comparator	Control status: NR	Single allergen: dust mite			
		Age 10 y				

The table is organized first by study design and outcomes assessed (RCT and then non-RCT, with all studies assessing only safety at the bottom). The table is organized within each category by sensitization status (monosensitized, both monosensitized and polysensitized, polysensitized, and unclear). The table is organized within each subcategory by single allergen followed by multiple allergen and then by allergen provided (dust mite, trees, and multiple allergen). A, aqueous; ATS, American Thoracic Society; GINA, Global Initiative for Asthma; IgE, immunoglobulinE; IR, index of reactivity; NR, not reported; NS, not significant; SPT, skin prick test; SQ-HDM, standardized quality house dust mite; T, tablet.

SUPPLEMENTAL TABLE 7 SCIT Efficacy Outcome: Asthma-Specific AQLQ

Study	Allergen and Asthma Severity	Arms	*N*	Time of Measure	Outcome Description	Value Pre	Value Post	Comparative Values
Kiliç et al[18]	Alternaria	SCIT	9	12 mo	AQLQ	Median (IQR) (minimum to maximum)	Median (IQR) (minimum to maximum)	SCIT pre versus post $P = .002$
	Mild and moderate	Pharmacotherapy	7			3.8 (1.3) (2.73–5.21)	6.52 (0.57) (5.78–7)	Control pre versus post $P = .01$
						4.91 (1.13) (3.91–5.82)	5.86 (2) (4.21–7)	SCIT versus control post $P = .09$
Lozano et al[19]	Dust mite	SCIT	21	8 mo	AQLQ	Mean	Mean	SCIT versus pharm pre $P = .488$
	Mild and moderate	Pharmacotherapy	20			4.9	6.4	SCIT pre versus post $P = .012$
						5.14	5.42	Pharm pre versus post $P = .658$

No study contained reporting on asthma QoL by using Pediatric AQLQ (PAQLQ). NR, not reported; NS, not significant; Pre, baseline; Post, after intervention.

SUPPLEMENTAL TABLE 8 SCIT Efficacy Outcome: Medication Use

Study	Arms	*N*	Time of Measure	Outcome Description	Value Pre	Value Post	Comparative Values
Quick relief medications							
Lozano et al[19]	SCIT	21	8 mo	No. d rescue treatment required	NR	SCIT: median (range) Baseline versus 4 mo = 6.5 (0–36) 4 vs 8 mo = 2 (0–18) pharm: baseline versus 4 mo 7 (0–90) 4 vs 8 mo 1 (0–120)	SCIT $P = .374$ Pharmacotherapy $P = .755$
	Pharmacotherapy	20					
Pifferi et al[23]	SCIT	15	3 y	No. d with salbutamol treatment/y	SCIT: 40.7 ± 17.4	NR (in a figure)	Significant reduction in SCIT versus control, $P < .01$
	Control	14			Control: 50.9 ± 19.9		Baseline SCIT versus control = NS
Long-term control medications							
Baris et al[17]	SCIT + vitamin D	17	12 mo	ICSs	NA	6/17 (35%)	SCIT with and without vitamin D versus pharmacotherapy alone $P = .02$
	SCIT alone	15		Rate of discontinuation		3/15 (20%) 0/18 (0)	
	Pharmacotherapy	18		Dose of ICSs	NR	NR	SCIT + vitamin D versus SCIT = NS SCIT + vitamin D significantly lower dose versus pharmacotherapy $P = .01$
Lozano et al[19]	SCIT	21	8 mo	No treatment	*n* (%)	*n* (%)	
	Pharmacotherapy	20		Changes in the need for medication	4 (19) 9 (45)	13 (62) 7 (35)	SCIT pre versus post $P = .046$ pharmacotherapy pre versus post $P = .158$
				ICSs	*n* (%)	*n* (%)	
				Changes in the need for medication	7 (33) 4 (20)	2 (10) 4 (20)	
				LTRAs	*n* (%)	*n* (%)	
				Changes in the need for medication	7 (33) 5 (25)	4 (18) 5 (25)	
				IC + LTRA	*n* (%)	*n* (%)	
				Changes in the need for medication	2 (10) 1 (5)	1 (5) 1 (5)	
				IC + LABA	*n* (%)	*n* (%)	
				Changes in the need for medication	1 (5) 1 (5)	1 (5) 3 (15)	
Hui et al[20]	SCIT	43	3 y	Steroids dose	196.7 ± 65.6	71.3 ± 53.8	SCIT versus vaccine pre $P = .494$
	Desensitization vaccine[a]	45		Budesonide Eq (μg)	206.7 ± 45	101.3 ± 48.5	SCIT versus vaccine post $P = .027$
Adkinson et al[21]	SCIT	61	30 mo	Use of inhaled steroids (No. d	21.4 ± 26	Change	SCIT pre versus post $P < .001$
	Placebo	60		in previous 60 d baseline versus follow-up)	20.1 ± 24.9	−10.1 ± 24	Placebo pre versus post $P = .16$
						−5.4 ± 27.8	Mean difference in change (placebo versus SCIT) = 4.7 (95% CI −4.7 to 14) $P = .26$
Systemic corticosteroids							
Pifferi et al[23]	SCIT	15	3 y	Systemic steroids	22.4 ± 4.8	1	Significant decrease in SCIT versus control $P < .01$
	Control	14		No. d with treatment/y	24.9 ± 3.7	12	

TABLE 8 Continued

Study	Arms	*N*	Time of Measure	Outcome Description	Value Pre	Value Post	Comparative Values
Adkinson et al[21]	SCIT	61	30 mo	Use of oral steroids (No. d in previous 60 d baseline versus follow-up)	5.3 ± 13.3	−1.9 ± 12.4	SCIT pre versus post *P* = .19
	Placebo	60			4.4 ± 10.8	−1.7 ± 12.1	Placebo pre versus post *P* = .75 Mean difference in change (placebo versus SCIT) = 0.1 (95% CI −4.2 to 4.5) *P* = .49

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 is followed by multiple allergen and then by allergen provided (dust mite, trees, and multiple allergen). CI, confidence interval; GINA, Global Initiative for Asthma; IgE, immunoglobulin E; LABA, long- acting β agonist; LTRA, leukotriene receptor antagonist; NR, not reported; NS, not significant; pre, baseline; post, after intervention; SPT, skin prick test.

[a] The control group received standardized glucocorticoid management and a desensitization vaccine (details not provided).

SUPPLEMENTAL TABLE 9 SCIT Efficacy Outcome: Health Care Use

Study	Arms	*N*	Time of Measure	Outcome Description	Value Pre	Value Post	Comparative Values
Adkinson et al[21]	SCIT versus Placebo	61 60	30 mo	No. office visits (No. in previous 60 d baseline versus follow-up)	0.05 ± 0.28 0.03 ± 0.18	Change −0.03 ± 0.38 0 ± 0.26	SCIT pre versus post: *P* = .75 Placebo pre versus post *P* > .99 Mean difference change Placebo versus SCIT = 0.03 (95% CI −0.07 to 0.14) *P* = .71
				No. ED visits (No. in previous 60 d baseline versus follow-up)	0.08 ± 0.33 0.03 ± 0.18	Change −0.05 ± 0.38 −0.02 ± 0.37	SCIT pre versus post *P* > .53 Placebo pre versus post *P* > .99 Mean difference change Placebo versus SCIT = 0.03 (95% CI −0.08 to 0.15) *P* = .73
				No. hospitalizations (No. in previous 60 d baseline versus follow-up)	0.11 ± 0.64 0.2 ± 0.90	Change −0.11 ± 0.64 −0.10 ± 0.77	SCIT pre versus post *P* = .5 Placebo pre versus post *P* = .63 Mean difference change Placebo versus SCIT *P* = .01 (95% CI −0.24 to 0.27) *P* = .43
Tsai et al[22]	SCIT Pharmacotherapy	20 20	6 mo	No. clinic visits in 6 mo	NR	17.25 ± 4.6 12.4 ± 5.87	Mean difference SCIT versus pharm 4.8, *P* = .006
				No. ED visits or hospitalizations in 6 mo	NR	0.76 ± 0.17 0.95 ± 0.21	Mean difference SCIT versus pharm −0.19 *P* = .267

CI, confidence interval; NR, not reported; pre, baseline; post, after intervention.

SUPPLEMENTAL TABLE 10 SCIT Eficacy Outcome: Pulmonary Physiology- FEV_1

Study	Arms	*N*	Time of Measure	Outcome Description	Value Pre	Value Post	Comparative Values
Baris et al[17]	SCIT + vitamin D	17	12 mo	FEV_1 (%)	92 ± 14	98 ± 15	NS differences between groups at baseline and follow-up
	SCIT alone	15			89 ± 14	90 ± 9	
	Pharmacotherapy	18			87 ± 18	93 ± 11	
Lozano et al[19]	SCIT	21	8 mo	FEV_1 (% of patients with FEV_1 >80%)	SCIT: mean = 99.01% (19/21 with FEV_1 >80% at baseline)	SCIT: at 8-mo, 100% of patients had an FEV_1 >80%	NR
	Pharmacotherapy	20			Pharmacotherapy: mean = 99.1% (18/20 with FEV_1 >80% at baseline)		
Kiliç et al[18]	SCIT	9	12 mo	FEV_1 %	73 (9.5) [60–80]	96 (19.5) [83–119]	SCIT pre versus post $P = .008$
	Pharmacotherapy	7		Median (IQR) [minimum to maximum]	75 (8) [65–97]	85 (15) [80–117]	Pharm pre versus post $P = .02$ SCIT versus pharm $P = .09$
Pifferi et al[23]	SCIT	15	3 y	FEV_1 % predicted	93.5 ± 15	NR (in a figure)	SCIT versus control = NS
	Control	14			89.5 ± 13.6		
Alzakar and Alsamarai[24]	SCIT	105	12 mo	FEV_1: patients with improvement in pulmonary function test	NR	51/85 (60%)	SCIT versus pharmacotherapy $P = .0001$
	Pharmacotherapy	137				21/112 (19%)	

NR, not reported; NS, not significant; pre, baseline; post, after intervention.

SUPPLEMENTAL TABLE 11 SLIT Efficacy Outcome: Medication Use

Study	Allergen and Asthma Severity	Arms	*N*	Time of Measure	Outcome Description	Value Pre	Value Post	Comparative Values
Quick relief medication								
Niu et al[29]	Dust mite	SLIT (A)	56	24 wk	Inhaled β agonist (puffs/d)	Mean (SD)	Mean (SD)	SLIT pre versus post *P* = .371
	Mild and moderate	Placebo	54			SLIT: 0.06 (0.09)	SLIT: 0.02 (0.31)	Placebo pre versus post *P* = .185
						Placebo: 0.03 (0.01)	Placebo:0.05 (0.27)	SLIT versus placebo change from baseline *P* = .951
Pham-Thi et al[25]	Dust mite	SLIT (T)	54	18 mo	Inhaled β2-agonist (terbutaline puffs/d)	Mean ± SD	Mean ± SD	SLIT versus placebo = NS
	Mild and moderate	Placebo	54			0.87 ± 0.5	0.55 ± 0.6	
						0.9 ± 0.8	0.47 ± 0.5	
Long-term control medication								
Pham-Thi et al[25]	Dust mite	SLIT (T)	54	18 mo	Use of inhaled steroids (ICS) (Budesonide) μg/d	Mean ± SD	Mean ± SD	SLIT versus placebo = NS
	Mild and moderate	Placebo	55			548 ± 220	257 ± 232	
						534 ± 237	223 ± 270	
Niu et al[29]	Dust mite	SLIT (A)	56	24 wk	ICS (puffs/d)	Mean (SD)	Mean (SD)	Change from baseline
	Mild and moderate	Placebo	54			SLIT: 0.6 (1.14)	SLIT: 0.43 (1.09)	SLIT pre versus post *P* = .782
						Placebo: 0.47 (0.84)	Placebo: 0.37 (0.86)	Placebo pre versus post *P* = .522
								SLIT versus placebo *P* = .215
Systemic corticosteroids								
Niu et al[29]	Dust mite	SLIT (A)	56	24 wk	Oral steroids (tablets/d)	Mean (SD)	Mean (SD)	Change from baseline
	Mild and moderate	Placebo	54			SLIT: 0.11(0.35)	SLIT: 0.03 (0.22)	SLIT pre versus post *P* = .183
						Placebo: 0.04 (0.15)	Placebo: 0.04 (0.22)	Placebo pre versus post *P* = 1.000
								SLIT versus placebo *P* = .195

Comparative values: SLIT versus comparator post intervention data unless otherwise noted. A, aqueous; NS, not significant; pre, baseline; post, after intervention; T, tablet.

SUPPLEMENTAL TABLE 12 SLIT Efficacy Outcome: Pulmonary Physiology - FEV_1

Study	Allergen and Asthma Severity	Arms	*N*	Time of Measure	Outcome Description	Value Pre	Value Post	Comparative Values
Niu et al[29]	Dust mite	SLIT (A)	56	24 wk	FEV_1 (mL)	In a figure	In a figure	SLIT pre versus post *P* = .048
	Mild and moderate	Placebo	54					Placebo pre versus post NS
								SLIT versus placebo NS
Ippoliti et al[30]	Dust mite	SLIT (A)	47	6 mo	FEV_1 % predicted	83.4	92.6	SLIT pre versus post *P* < .001
	Mild and moderate	Placebo	39			80.7	81.2	Placebo pre versus post *P* NS
								SLIT versus placebo NR
Lue et al[28]	Dust mite	SLIT (A)	10	6 mo	FEV_1 (mL)	NR	NR	SLIT pre versus post improved *P* = .01
	Mild and moderate	Placebo	10					Placebo pre versus post = NS
								SLIT versus placebo = NS
Pham-Thi et al[25]	Dust mite	SLIT (T)	54	18 mo	FEV_1 (% predicted)	Mean ± SD	Mean ± SD	SLIT versus placebo post NS
	Mild and moderate	Placebo	55			91.9 ± 13.4	88.5 ± 13.4	
						95.1 ± 15.1	94.5 ± 14.6	
Bahçeciler et al[26]	Dust mite	SLIT (A)	8	6 mo	FEV_1 (%)	95 (75–113)	100 (78–119)	NS between or within groups
	Mild	Placebo	7			101 (75–115)	93 (61–104)	
Stelmach et al[27]	Grass mix	SLIT (A) ultrarush	20	2 y	FEV_1	Mean (95% CI)	Mean (95% CI)	SLIT versus placebo pre *P* = .649
	Excluded severe asthma	Placebo	15		Mean % predicted	92.9 (87.7 to 98.1)	100.4 (95 to 105)	SLIT versus placebo post *P* = .005
						87.9 (82.8 to 92.9)	88.2 (81 to 94)	

A, aqueous; NR, not reported; NS, not significant; pre, baseline; post, after intervention; T, tablet.

SUPPLEMENTAL TABLE 13 SCIT Safety Outcomes: Local Reactions

Study	Allergen and Asthma Severity	Arms	*N*	Event Description	Reported as Patients *N* (%)	Reported as Events *N* (%)
Reported in RCTs						
Pifferi et al[23]	Dust mite	SCIT	15	Local reactions	0	0
	Severity NR	Control	10		0	0
Altintaş et al[39]	Dust mite	SCIT versus	10	I and II: local swelling >3 cm during up dosing	I: 1	NR
	Mild and moderate	SCIT versus	10		II: 3	
		SCIT	9		III: 0	
		Placebo	5		IV: 0	
Lozano et al[19]	Dust mite	SCIT	21	Local AEs requiring dose modification	0	NR
	Mild and moderate	Pharmacotherapy	20		0	NR
Baris et al[17]	Dust mite	SCIT + vitamin D	17	Local urticarial plaques at their injection sites	6	NR
	Mild and moderate	SCIT alone	15		7	NR
		Pharmacotherapy	18		0	NR
Ibero and Castillo[37]	Dust mite	SCIT	15	Pain and heat over a 24-h period after the first 2 injections	1	1
					0	0
	Mild and moderate	Placebo	13	Pain immediately after the second maintenance dose	1	1
					0	0
				Induration (1 cm in diameter) and pruritus after the third maintenance dose	1	1
					0	0
Zielen et al[38]	Dust mite	SCIT	33	Injection site pain, pruritus, swelling	11 (33.3%)	NR
	Severity NR	Pharmacotherapy	32		0	NR
				Urticaria	1 (6.1%)	NR
					0	NR
Schubert et al[35]	Dust mite	Cluster schedule	20 (341 injections)	Local events classified as mild	NR	185 (54%)
	Mild and moderate	Classic schedule	10 (151 injections)	Redness: 97 (28%), swelling <5 cm: 57 (16%), swelling >5 cm: 22 (6%), painful swelling >3 h: 8 (2%)		80 (53%)
				Local events classified as moderate		
				Redness: 40 (26%), swelling <5 cm: 20 (13%), swelling >5 cm: 17 (11%), painful swelling >3 h: 3 (2%)		
Dreborg et al[41]	Cladosporium	SCIT versus	16	Urticaria	25%	4
	Severity NR	Placebo	14		0	0
Roberts et al[42]	Grass	SCIT	18	Episodes of pruritus, pain, or swelling. Treated with antihistamines and ice	NR	13
	Mild, moderate, and severe asthma	Placebo	17		NR	11
Hui et al[20]	Dust mite	SCIT	45	Local induration, induced cough and urticaria	NR	202/1735 (11.7%) injections
	Mild and moderate	Desensitization vaccine[a]	45			
Tsai et al[22]	Dust mite	SCIT	20	Local red swelling at injection site	8	NR
	Moderate and severe	Pharmacotherapy	20		0	NR
Valovirta et al[40]	Dog	SCIT	15	309: 227 <1 cm, 71 1–3 cm, 11 >3 cm	NR	309
	Severity NR	Placebo	12	251: 163 <1 cm, 82 1–3 cm, 6 >3 cm		251
Reported in non-RCTs						

TABLE 13 Continued

Study	Allergen and Asthma Severity	Arms	*N*	Event Description	Reported as Patients *N* (%)	Reported as Events *N* (%)
Kartal et al[46]	Multiple Severity NR	SCIT	No. children NR	Large local reaction (erythema and/or swelling at injection site ≥5 cm) in a 7-y-old girl receiving SCIT aqueous pollen. SCIT was discontinued	1	1

NR, not reported.

[a] The control group received standardized glucocorticoid management and a desensitization vaccine (details not provided).

SUPPLEMENTAL TABLE 14 SCIT Safety Outcomes: Systemic Reactions

Study	Allergen and Asthma Severity	Arms	*N*	Event Description	Reported as Patients *N* (%)	Reported as Events *N* (%)
Reported in RCTs						
Dreborg et al[41]	Cladosporium	SCIT versus	16	General reactions	81%	45
	Severity NR	Placebo	14			NR
Pifferi et al[23]	Dust mite	SCIT	15	Systemic side effects	0	0
	Severity NR	Control	10		0	0
Lozano et al[19]	Dust mite	SCIT	21	Systemic AEs requiring dose modification	0	NR
	Mild and moderate	Pharmacotherapy	20		0	
Baris et al[17]	Dust mite	SCIT + vitamin D	17	2 in SCIT + vitamin D = mild asthma attack treated with β agonist	2	NR
	Mild and moderate	SCIT alone	15	1 in SCIT group "systemic reaction" within 20 min after injection of vial 4,	1	NR
		Pharmacotherapy	18	requiring epinephrine	0	NR
Ibero and Castillo[37]	Dust mite	SLIT aqueous	15	1 mild rhinitis and asthma	2	2
	Mild and moderate	Placebo	13	1 mild dyspnea	0	0
				No medications were needed to treat any of the reactions		
Zielen et al[38]	Dust mite	SCIT + ICS	33	Cough, rhinitis	2 (6.1%)	NR
	Severity NR	ICS alone	32		0	
Schubert et al[35]	Dust mite	Cluster schedule	20 (341 injections)	Reactions classified as mild	0.7 events per patient	12 reactions
	Mild and moderate	Classic schedule	10 (151 injections)	12 reactions: 10 cough and 2 dyspnea	0.8 events per patient	(3.5% of injections)
				7 reactions: 6 cough and 1 dyspnea		7 reactions (4.6% of injections)
				Bronchial asthma: classified as moderate	0.3 events per patient	2 reactions (0.6% of injections)
					0.2 events per patient	1 reaction (0.7% of injections)
Roberts et al[42]	Grass	SCIT	18	Pulmonary reactions that responded to bronchodilators	4	4
					3	3
	Mild, moderate, and severe asthma	Placebo	17	Others: eczema, urticaria, rhinoconjunctivitis	NR	21
						9
Hui et al[20]	Dust mite	SCIT desensitization vaccine[a]	45	Not specified and not divided by group	NR	1/1735 injections (0.05%)
	Mild and moderate		45			
Alzakar and Alsamarai[24]	Dust mite, grass, mold, pets, and trees	SCIT	105	1 "mild respiratory involvement"	9 (11%)	NR
	Excluded severe asthma	Pharmacotherapy Beclomethasone + Aminophylline	137	8 "skin rash"	0	
Arroabarren et al[36]	Dust mite	5-y IT	36	2 subjects had an asthma episode treated with bronchodilators	2	NR
	Mild and moderate	3-y IT	27		NR	
Tsai et al[22]	Dust mite	SCIT	20	There were no apparent systemic reactions to the injections	0	NR
	Moderate and severe	Pharmacotherapy	20		0	
Adkinson et al[21]	Multiple	SCIT	61	114 total systemic reactions (52 treated with adrenergic drugs and all	21 (34%)	2.6/100 injections
	Moderate to severe asthma	Placebo	60	responded to treatment)	4 (7%)	
Reported in non-RCTs						

TABLE 14 Continued

Study	Allergen and Asthma Severity	Arms	*N*	Event Description	Reported as Patients *N* (%)	Reported as Events *N* (%)
Gozde Kanmaz et al[44]	Grass and dust mite	SCIT	50	Worsening of condition attributed to mild systemic reaction	1 0	NR
	Mild and moderate	Pharmacotherapy	52	Undercurrent illnesses, or worsening of condition	5 0	NR
Kartal et al[46]	Multiple Severity NR	SCIT	Total No. children not reported	Systemic reactions per WHO: 1 systemic reaction (grade 2) reported in a 7-y-old girl receiving SCIT aqueous; pollen- SCIT was discontinued	1	1
Chen et al[45]	Dust mite Severity NR	SCIT children	67	Total nonfatal systemic reactions No grade IV (anaphylactic shock) systemic reactions occurred in children	16 (23.88%)	27/2045 injections (1.32%)
Santos et al[49]	Pollen and dust mites	SCIT	Total No. children not reported	1 = age 13 receiving HDM SCIT (conventional). Injection 2 induction had late onset facial pruritus, nasal and conjunctival congestion; Induction 3 had immediate nasal congestion and rhinorrhea; Induction 8 had late onset nasal pruritus and rhinorrhea, Induction 10 had late onset asthma exacerbation	3	6
	Severity NR	Wo comparator		2 = age 11 receiving pollen SCIT (ultrarush). Injection 4 (maintenance) had late onset sneezing 3 = age 11 receiving pollen (rush). Injection 3 had late onset dyspnea. No treatment		
Dong et al[50]	Multiple and single allergens	SCIT	44	Systemic reactions	15	NR
	Severity NR	Wo comparator				

IT, immunotherapy; NR, not reported.

[a] The control group received standardized glucocorticoid management and a desensitization vaccine (details not provided).

SUPPLEMENTAL TABLE 15 SCIT Safety Outcomes: Anaphylaxis

Study	Allergen and Asthma Severity	Arms	*N*	Description	Reported as Patients *N* (%)	Reported as Events *N* (%)
Reported in RCTs						
Hill et al[43]	Grass Severity NR	SCIT versus placebo	11 9	Anaphylaxis after maximal dose- subsequent injections given with a lower dose	1	1
Zielen et al[38]	Dust mite Severity NR	SCIT + ICS ICS alone	33 32	No anaphylaxis occurred during the study	0	0
Baris et al[17]	Dust mite Mild and moderate	SCIT + vitamin D SCIT alone Pharmacotherapy	17 15 18	Systemic reaction not specified, treated with epinephrine[a]	0 1 0	NR
Schubert et al[35]	Dust mite	Cluster schedule	20 (341 injections)	Anaphylaxis	0	0
	Mild and moderate	Classic schedule	10 (151 injections)		0	0
Reported in non-RCTs						
Chen et al[45]	Dust mite Severity NR	SCIT children	67	No grade IV (anaphylactic shock) systemic reactions occurred in children	0	0

[a] Not defined as anaphylaxis but symptoms and treatment are consistent with anaphylaxis.

SUPPLEMENTAL TABLE 16 SCIT Safety Outcomes: Deaths

Study	Allergen and Asthma Severity	Arms	*N*	Event Description	Reported as Patients *N* (%)	Reported as Events *N* (%)
Reported in non-RCTs						
Dong et al[50]	Multiple and single allergens. Severity NR	SCIT wo comparator	No. children not reported	There were no fatal reactions	0	0
Kartal et al[46]	Multiple	SCIT wo comparator	No. children not reported	No fatality reported in 30 y	0	0
Copenhaver et al[47]	Multiple allergens severity NR	SCIT cluster wo comparator	No. children not reported	No fatalities occurred during cluster SCIT	0	0
Cardona et al[48]	Dust mite severity NR	Ultrarush SCIT wo comparator	No. children not reported	There were no fatalities	0	0
Sana et al[31]	Alustal: pollen, moderate asthma	SCIT wo comparator	1	12 h after initiation of treatment, patient complained of abdominal pain, vomiting, and diarrhea without fever. Two d later she had acute respiratory failure requiring ICU treatment. On d 4 she developed hypoxic coma leading to intubation and mechanical ventilation. Rapidly, she experienced intractable shock and acute renal impairment. By d 5 she developed multiorgan failure and died	1	1

Data abstracted only if studies specifically contained reporting on deaths. No deaths reported in RCTs.

SUPPLEMENTAL TABLE 17 SLIT Safety Outcomes: Local Reactions in RCTs

Study	Allergen and Asthma Severity	Arms	*N*	Event Description	Reported as Patients *N* (%)	Reported as Events *N* (%)
Reported in RCTs						
Pham-Thi et al[25]	Dust mite	SLIT tablet	54	Mouth itching and/or lip swelling	NR	10
	Mild and moderate	Placebo	55		NR	5
Stelmach et al[27]	Grass mix	SLIT (A) ultrarush	20	Sublingual itching	35	NR
	Excluded severe asthma	Placebo	15		20	
Corzo et al[53]	Dust mite	SLIT (T)	54	Oral pruritus	NR	263
	Mild and moderate	Placebo	18		NR	5
				Mouth edema	NR	96
					NR	0
				Stomatitis	NR	8
					NR	0
				Throat irritation	NR	151
					NR	0
				Oral paresthesia	NR	0
					NR	0
				Ear pruritus	NR	330
Pham-Thi et al[25]	Dust mite	SLIT (T)	54	Gastrointestinal complaint	NR	19
	Mild and moderate	Placebo	55		NR	2
Stelmach et al[27]	Grass mix	SLIT (A) ultrarush	20	Stomach ache	5	NR
	Excluded severe asthma	Placebo	15		6.6	
Mösges et al[51]	Tree pollen	SLIT	27	Most frequent symptoms were application site itching and application site paresthesia	NR	NR
	Mild and moderate	Placebo	27			
Reported in non-RCTs						
Béné et al[58]	Dust mite	SLIT	1	Eosinophilic esophagitis: patient presented reflux and vomiting 6 wk after starting SLIT. Did not respond to treatment. Histopathology confirmed diagnosis of eosinophilic esophagitis. Resolved after SLIT discontinuation	1	1
	Severity NR	Wo comparator				

A, aqueous; NR, not reported; T, tablet.

SUPPLEMENTAL TABLE 18 SLIT Safety Outcomes: Systemic Reactions

Study	Allergen and Asthma Severity	Arms	*N*	Event Description	Reported as Patients *N* (%)	Reported as Events *N* (%)
Reported in RCTs						
Pham-Thi et al[25]	Dust mite	SLIT (T)	54	Respiratory (rhinitis and/or asthma)	NR	64
	Mild and moderate	Placebo	55	1 patient in placebo group withdrew after a severe acute exacerbation of asthma	1	67
Corzo et al[53]	Dust mite	SLIT (T)	54	Asthma worsening or asthma exacerbations	12 total	7
	Mild and moderate	Placebo	18			6
Maloney et al[55]	Grass, cat, dog, mold, birch, mugwort	6 SQ-HDM	22	Worsening asthma (moderate)	1	1
	Severity NR	12 SQ HDM	24	SLIT: treated with low dose ICS and resolved 1 wk later	0	0
		Placebo	22	Placebo: no treatment needed, resolved next d	1	1
Bufe et al[54]	Grass	SLIT	105	11-y-old boy with allergic rhinoconjunctivitis and mild asthma presented itchy tongue and swelling, tightness, lip blister, and shortness of breath	1	3
	Mild, moderate, and severe	Placebo		Patient was withdrawn on d 17 because of 3 severe AEs (oral pruritus, dyspnea, and tongue disorder). Treated with desloratadine, salbutamol, and cetirizine. He recovered fully		
Shao et al[52]	Dust mite	SLIT (A)	139	Aggravating asthma (there were no acute attacks of asthma reported)	NR	8 (14.82%)
	Mild asthma	Pharmacotherapy	79		NR	0 (0)
Reported in non-RCTs						
Galip and Bahceciler[57]	Dust mite Persistent asthma	SLIT (A) wo comparator	1	When patient reached 8 pumps of allergen extract as the maintenance dose he developed wheezing within 2 min, which lasted 20–25 min. Wheezing requiring β agonists and dose reduction of SLIT. He completed 3 y of SLIT at reduced dose	1	3
Nuhoglu et al[56]	Dust mite Mild and moderate	SLIT (T) wo comparator	39	No significant side effects were reported	0	0
Blazowski[32]	Dust mite Intermittent asthma	SLIT (A) wo comparator	1	Self-resolving wheezing during first 3 mo of maintenance	1	2

A, aqueous; NR, not reported; T, tablet.

SUPPLEMENTAL TABLE 19 SLIT Safety Outcomes: Anaphylaxis

Study	Allergen and Asthma Severity	Arms	*N*	Event Description	Reported as Patients *N* (%)	Reported as Events *N* (%)
Reported in RCTs						
Pham-Thi et al[25]	Dust mite	SLIT (T)	54	There were no anaphylactic reactions	0	0
	Intermittent, mild and moderate asthma	Placebo	55		0	0
Mösges et al[51]	Tree pollen	SLIT (A) (ultrarush)	27	There were no anaphylactic reactions	0	0
	Mild and moderate asthma	Placebo	27		0	0
Maloney et al[55]	Grass, cat, dog, mold, birch, mugwort	SLIT: 6 SQ-HDM (T)	22	There were no anaphylactic reactions	0	0
	Severity NS	SLIT: 12 SQ-HDM (T)	24		0	0
		Placebo	22		0	0
					0	0
Shao et al[52]	Dust mite	SLIT (A)	139	There were no anaphylactic reactions	0	0
	Intermittent and mild asthma	Pharmacotherapy	79		0	0
Reported in non-RCTs						
Blazowski[32]	Dust mite Intermittent asthma	SLIT aqueous	1	Anaphylactic shock after overdose In the third y, after a 3 wk break in maintenance dosing (10 drops of 100 IR/mL) the patient gave herself 60 drops of 100 IR/mL = 9.7 μg of D.pter and 17.2 μg of D. far	1	NR

A, aqueous; NR, not reported; SQ-HDM, standardized quality house dust mite.

SUPPLEMENTAL TABLE 20 SLIT Safety Outcomes: Deaths

Reported in RCTs						
Study	Allergen and Asthma Severity	Arms	*N*	Event Description	Reported as Patients *N* (%)	Reported as Events *N* (%)
Bufe et al[54]	Timothy grass Mild, moderate, and severe	SLIT (T) Placebo	55 50	There were no deaths reported	0	0

Data abstracted only if studies specifically contained reporting on deaths. No deaths reported in non-RCTs. T, tablet.

SUPPLEMENTAL TABLE 21 SLIT Safety Outcomes: Other Reactions

Study	Allergen and Asthma Severity	Arms	*N*	Event Description	Reported as Patients *N* (%)	Reported as Events *N* (%)
Mösges et al[51]	Tree pollen	SLIT (A) ultrarush	27	No serious systemic effects were observed	0	NR
	Mild and moderate	Placebo	27		0	
Corzo et al[53]	Dust mite	SLIT tablet	54	There were no serious AEs	0	0
	Mild and moderate	Placebo	18		0	0
Pham-Thi et al[25]	Dust mite	SLIT tablet	54	There were no multiple-organ life-threatening	0	0
	Mild and moderate	Placebo	55	events	0	0
Lue et al[28]	Dust mite	SLIT	10	No severe drug related AE was reported	0	0
	Mild to moderate asthma	Placebo	10			
Bahçeciler et al[26]	Dust mite	SLIT (A)	8	No local or systemic side effects reported	0	0
	Mild asthma	Placebo	7		0	0
Ippoliti et al[30]	Dust mite	SLIT	47	No local or systemic side effects reported	0	NR
	Mild and moderate	Placebo	39		0	
Maloney et al[55]	Grass, cat, dog, mold, birch, mugwort	SLIT: 6 SQ-HDM T	22	AEs not specified (TEAEs)	68	NR
	Severity NR	SLIT: 12 SQ-HDM T	24		50	
		Placebo	22		46	
				AEs not specified (TRAEs)	55	
					50	
					32	
Pham-Thi et al[25]	Dust mite	SLIT T	54	Total No. AEs, local and systemic	0	NR
	Mild and moderate	Placebo	55		4 (10)	
Bufe et al[54]	Timothy grass	SLIT (T)	126	The pattern of AEs was similar for subjects with	109 (87)	426
	Mild, moderate, and severe asthma	Placebo	127	and without asthma symptoms	106 (83)	278
Stelmach et al[27]	Grass mix	SLIT (A) ultrarush	20	AEs leading to discontinuation	0	NR
					0	
	Excluded severe asthma	Placebo	15	Headache	0	NR
					6.6	
Niu et al[29]	Dust mite	SLIT	56	No incidence of serious drug related AEs reported. All AEs (6 in SLIT versus 7 in placebo)	NR	NR
	Mild and moderate	Placebo	54	Drug related AEs (5 in SLIT versus 3 in placebo) Serious events (1 in SLIT versus 4 in placebo) Tongue disorder, vomiting, abdominal pain, circumoral paresthesia in 5 patients (10 incidences) in the SLIT group No significant difference in AEs between SLIT and placebo No further detail of AEs provided		

A, aqueous; NR, not reported; SQ-HDM, standardized quality house dust mite; T, tablet; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

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