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.

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

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.

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

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

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

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.

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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