Comparative Effectiveness Review
Number 196

Effective Health Care Program

The Role of Immunotherapy in the Treatment of Asthma

Evidence Summary

Background

Asthma is a chronic inflammatory disorder of the airways, characterized by varying degrees of airflow obstruction. Approximately 56 percent of individuals with asthma also have environmental allergies.[1] Allergic asthma and non-allergic asthma generally have the same symptoms; however, allergic asthma is triggered by inhaling airborne allergens (aeroallergens).

There are currently three treatment options for patients with allergic asthma: allergen avoidance, pharmacotherapy including biologics, and allergen immunotherapy (AIT). AIT consists of the repeated administration of one or multiple allergens to which the patient is sensitized. In subcutaneous immunotherapy (SCIT) a solution containing an allergen(s) is injected under the skin. Sublingual immunotherapy (SLIT), which may be dosed at home, consists of exposure to the allergen via an aqueous solution or tablet formulation placed under the tongue.

In 2007, the Expert Panel Report (EPR-3) from The National Heart, Lung, and Blood Institute (NHBLI)[2] included SCIT as a therapy to be considered in cases of mild to moderate persistent asthma. A working group was convened in 2015 to select the most relevant topics for systematic review to update the EPR-3. This systematic review focuses on one of those high

Purpose of Review

To assess the efficacy and safety of immunotherapy for treating allergic asthma.

Key Messages

- Subcutaneous immunotherapy reduces use of long-term control medications. It may also improve quality of life and FEV1, (a measure of the ability to exhale) and reduce the use of quick-relief medications (short-acting bronchodilators) and systemic corticosteroids.
- Sublingual immunotherapy improves asthma symptoms, quality of life and FEV1, and reduces the use of long-term control medications. It may also reduce the use of quick-relief medications.
- Local and systemic reactions to subcutaneous immunotherapy and sublingual immunotherapy are common but infrequently required changes in treatment. Life-threatening events (such as anaphylaxis) are reported rarely.

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priority topics: expanding the scope of a prior evidence report to assess the efficacy and safety of SCIT and SLIT, in aqueous and tablet forms, in people with allergic asthma.

Key Questions

Key Question 1. What is the evidence for the efficacy of subcutaneous immunotherapy (SCIT) in the treatment of asthma?

Key Question 2. What is the evidence for the safety of subcutaneous immunotherapy (SCIT) in the treatment of asthma?

Key Question 3. What is the evidence for the efficacy of sublingual immunotherapy (SLIT), in tablet and aqueous form, for the treatment of asthma?

Key Question 4. What is the evidence for the safety of sublingual immunotherapy (SLIT), in tablet and aqueous form, for the treatment of asthma?

Methods

The protocol was registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO), registration number CRD42016047749, and posted on the AHRQ Web site (http://www.effectivehealthcare.ahrq.gov/).

We rescreened all of the included studies from our prior 2013 evidence report.[3] We searched PubMed, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 1, 2005 through May 8, 2017.

As for all evidence reports, our draft report was peer reviewed and posted for public comment.

Results

We identified 31 randomized controlled trials (RCTs) (35 articles) that addressed the efficacy of SCIT (Key Question [KQ] 1), 26 RCTs (31 articles) and 18 non-RCTs that addressed the safety of SCIT (KQ2), 18 RCTs (20 articles) that addressed the efficacy of SLIT (KQ3), and 20 RCTs (23 articles) and 10 non-RCTs that addressed the safety of SLIT (KQ4). We provide details of studies identified per age group in Table A.

Table A. Number of studies included per Key Question, study design, age group, and setting

		KQ1 SCIT Efficacy	KQ2 SCIT Safety (RCT/Non-RCT)	KQ3 SLIT Efficacy	KQ4 SLIT Safety (RCT/Non RCT)	SCIT vs. SLIT	TOTAL
Study Design	RCTs	31	26	18	20	5	61
	Non-RCTs	0	18	0	10	1	29
Age Group	Adult	13	19 (12/7)	11	14 (9/5)	3	43
	Mixed Age	15	23(10/13)	4	9 (7/2)	1	34
	Children	3	6 (3/3)	3	7 (4/3)	2	12
Setting	Clinic	28	36 (24/12)	2	6 (4/2)	5	48
	Home	0	0	4	6 (4/2)	0	8
	Not Specified	3	8 (2/6)	12	13 (10/4)	0	23
	Both	0	0	0	5 (2/3)	1	5
	TOTAL	**31**	**44**	**18**	**30**	**6**	**90**

KQ = Key Question; RCT = randomized controlled trial; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy

Key Question 1. What is the evidence for the efficacy of subcutaneous immunotherapy (SCIT) in the treatment of asthma?

Key Points

- SCIT reduces the need for long-term control medication (moderate strength of evidence [SOE]).
- SCIT may improve asthma-specific quality of life, decrease use of quick-relief medications, decrease use of systemic corticosteroids, and improve FEV1 (forced expiratory volume) (low SOE).
- There was insufficient evidence regarding the effect of SCIT on asthma symptom control and health care utilization.
- There was insufficient evidence about any differential effect of SCIT in pediatric patients.

Table B. Summary of the strength of evidence for the efficacy of subcutaneous immunotherapy

Outcome	N of studies (n of patients)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Conclusion	SOE
Asthma Symptoms: ACT	No RCTs	NA	NA	NA	NA	Undetected	Unable to draw conclusions	Insufficient
Quality of Life: AQLQ	4 RCTs.[4-7] N=194	Medium	Consistent	Direct	Imprecise	Undetected	SCIT may improve asthma-quality of life	Low
Medication Use: Quick-relief medication	1 RCT[8] N=31	Low	Unknown	Direct	Imprecise	Undetected	SCIT may reduce the use of quick-relief medications	Low
Medication Use: Long-term medication	6 RCTs [5, 6, 8-11] N=404	Medium	Consistent	Direct	Precise	Undetected	SCIT reduces the use of long-term control medications	Moderate
Medication Use: Systemic corticosteroids use	2 RCTs[11, 12] N=150	Low	Unknown	Direct	Imprecise	Undetected	SCIT may reduce the use of systemic corticosteroids	Low
Health care Utilization	2 RCTs1[1, 13] N=161	Medium	Consistent	Direct	Imprecise	Undetected	Unable to draw conclusions	Insufficient
Pulmonary Physiology: FEV1	6 RCTs[4, 5, 14-16] N=548	High	Consistent	Direct	Precise	Undetected	SCIT may improve pulmonary function when measured with FEV1	Low

ACT = asthma control test; AQLQ = asthma quality of life questionnaire; FEV1= forced expiratory volume; NA = not applicable; RCT = randomized controlled trial; SCIT = subcutaneous immunotherapy

Key Question 2. What is the evidence for the safety of subcutaneous immunotherapy (SCIT) in the treatment of asthma?

Key Points

- Local reactions to SCIT were frequent; however, reactions also commonly occurred with placebo injections (risk differences ranged from -0.317 to 0.4), and local reactions infrequently required a change in the SCIT dosing.
- Systemic allergic reactions to SCIT were reported frequently (risk differences ranged from 0 to 0.319). The majority of systemic allergic reactions were mild, and only a small number was consistent with anaphylaxis and required treatment with injectable epinephrine.
- There was insufficient evidence to draw conclusions regarding the effect of SCIT on anaphylaxis or death.
- Serious adverse events such as anaphylaxis and death were not reported in the included studies in the pediatric population (total of 462 patients in 4 RCTs).
- None of the studies reported providing patients SCIT in the home setting.

Table C. Summary of the strength of evidence for the safety of subcutaneous immunotherapy

Outcome	N of studies (n of patients)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Conclusion	SOE
Anaphylaxis	5 RCTs[9, 15, 17-19] N=245 6 cases	Medium	Inconsistent	Indirect	Imprecise	Undetected	Unable to draw conclusions	Insufficient
	1 non-RCT[20] 1 case series[21] 1 case report[22] N=792 55 cases	Likely (Likelihood of causality)						
Death	No RCTs or non-RCTs						Unable to draw conclusions	Insufficient
	1 case report[23] 1 case series[24] N=145 1 case	Possible (Likelihood of causality)						

RCT = randomized controlled trial; SOE = strength of evidence

Key Question 3. What is the evidence for the efficacy of sublingual immunotherapy (SLIT), in tablet and aqueous form, for the treatment of asthma?

Key Points

- SLIT improves asthma symptoms, as measured by validated instruments (high SOE).
- SLIT improves disease-specific quality of life and decreases use of long-term control medications (specifically, ICS), and improves FEV1 (moderate SOE).
- SLIT may decrease quick-relief medication use (short-acting bronchodilators) and may improve disease-specific quality of life (low SOE).
- There is insufficient evidence on the effect of SLIT on systemic corticosteroid use or health care utilization.
- There is insufficient evidence about the efficacy of SLIT in children.

Table D. Summary of the strength of evidence for the efficacy of sublingual immunotherapy

Outcome	N of studies (n of patients)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Conclusion	SOE
Asthma Symptoms: ACT	4 RCTs[25-28] N=1193	Low	Consistent	Direct	Precise	Undetected	SLIT improves asthma symptoms	High
QOL: AQLQ	3 RCTs[25-27] N=1120	Low	Consistent	Direct	Precise	Undetected	SLIT may improve asthma QOL	Low
Medication Use: Quick-relief medication	5 RCTs[28-32] N=298	Medium	Consistent	Direct	Imprecise	Undetected	SLIT may reduce the need of quick-relief medication	Low
Medication Use: Long-term control medication	4 RCTs[26, 27, 31, 33] N=1409	Medium	Consistent	Direct	Precise	Undetected	SLIT reduces the need for long-term control medication	Moderate
Medication Use: Systemic Corticosteroids use	1 RCT[31] N=110	Medium	NA	Direct	Imprecise	Undetected	Unable to draw conclusions	Insufficient
Health care Utilization	No RCTs	NA	NA	NA	NA	Undetected	Unable to draw conclusions	Insufficient
Pulmonary Physiology: FEV1	10 RCTs[26-28, 30-37] N=1694	Medium	Consistent	Direct	Precise	Undetected	SLIT improves pulmonary function (FEV1)	Moderate

FEV1 = forced expiratory volume; QOL = quality of life; RCT = randomized controlled trial; SLIT = sublingual immunotherapy; SOE = strength of evidence

Key Question 4. What is the evidence for the safety of sublingual immunotherapy (SLIT) in the treatment of asthma?

Key Points

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

Table E. Summary of the strength of evidence for the safety of sublingual immunotherapy

Outcome	N of studies (n of patients)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Conclusions	SOE
Anaphylaxis	6 RCTs[25, 26, 33, 38-40] N=1772 No cases No Non-RCTs	Medium	Inconsistent	Direct	Imprecise	Undetected	Unable to draw conclusions	Insufficient
	3 case reports[41-43] 2 Certain 1 Likely (Likelihood of causality)					Unable to draw conclusions		
Death	3 RCTs specifically reported no deaths[25, 27, 44] N=4231 Events 0	Medium (1 low, 1 medium, 1 high)	Consistent	Direct	Precise	Undetected	SLIT does not increase the risk of death	Moderate

RCT = randomized controlled trial; SLIT = sublingual immunotherapy; SOE = strength of evidence

Discussion

Our findings are consistent with our prior JHU EPC evidence report and other prior systematic reviews and support the efficacy of SCIT and SCIT for asthma in the allergic patient. The Cochrane review of SCIT concluded that it resulted in significant reduction in asthma symptoms and the need for asthma medications, as well as improvement in allergen-specific bronchial hyper-reactivity.[45] Our prior evidence report similarly concluded that there was high strength of evidence that SCIT reduces asthma symptoms and medication use.[3] Both of these reviews noted the significant heterogeneity between the studies, as we found. In contrast, we could not draw conclusions about the effect of SCIT on asthma symptoms, as we limited our review to studies that used validated tools to measure asthma symptoms and identified none. A 2015 Cochrane review found there was low-quality evidence supporting the use of SLIT in changing ICS use and very low quality evidence regarding bronchial provocation.[46] This Cochrane review further noted that the largely non-validated asthma symptom scores, medications scores, and available data for quality of life precluded meaningful synthesis of these outcomes. Our prior evidence report examined SLIT in aqueous form only, and concluded that SLIT reduced asthma symptoms.[3] This review expanded our scope to consider SLIT in tablet form and came to similar conclusions.

Future Research Needs

We were limited in our ability to synthesize results owing to lack of studies for specific populations, interventions, and outcomes; substantial heterogeneity; and limited reporting. We detail below specific areas for future research.

Population

- The overwhelming majority of studies that met inclusion criteria for this review included patients with mild to moderate asthma; there is a need to investigate the safety and efficacy of immunotherapy in patients with severe asthma.
- Not all studies provided information about asthma severity or control of study patients. Because severity and control are potentially important modifiers of treatment effect, studies are needed that clearly report the severity and control of enrolled patients.
- There were few studies conducted in children only, and few studies of all ages that reported outcomes for children separately. To inform asthma treatment guidelines, investigators should consider including only

children 5 to 11 years of age in studies, or, if a broader age is studied, reporting separately findings on children 5 to 11 years of age and older.

Intervention and Comparison

- There is a specific need for studies investigating the efficacy and safety of multiple-allergen regimens for SCIT or SLIT. Multiple-allergen treatment is frequently used in the United States, but most of the studies include single-allergen regimens. There is increasing discussion in the scientific community about the clinical use and efficacy of single-allergen versus multiple-allergen therapy, and there is a lack of studies which compare these head-to-head.
- For both SCIT and SLIT, additional studies are needed to assess compliance/adherence, and the effect compliance may have on management.
- Immunotherapy dosing quantity, frequency, and formulation varied substantially and details were often lacking. Standardized methods and reporting of therapy would be helpful.
- Most studies we identified were of house dust mite allergen; additional studies of the efficacy of SCIT or SLIT treatment with other allergens would be useful.

Outcomes

- For both SCIT and SLIT, studies are needed that address health care utilization.
- Many studies used nonvalidated scoring of outcomes. For instance, we found no trials of SCIT that assessed asthma symptoms using a validated tool. Future studies would benefit from standardized methods and validated instruments to report outcomes such as asthma symptoms and adverse events.

Conclusion

SCIT reduces the need for long-term control medication and may improve asthma-specific quality of life, use of quick-relief medications, systemic corticosteroids use, and FEV1. SLIT improves asthma symptoms, reduces long-term control medication use, improves disease-specific quality of life, and may reduce the need for quick-relief medication and improve FEV1. Local and systemic allergic reactions to SCIT and SLIT are common but infrequently required changes in treatment. Life-threatening events (such as anaphylaxis) are reported rarely. There is insufficient evidence on the comparative effectiveness of SCIT versus SLIT or for differential effects by patient age, type of allergen, or setting.

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Full Report

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