Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: Subcutaneous Immunotherapy for the Treatment of Allergies: A Review of the Clinical Efficacy, Safety, and Guidelines

DATE: 24 July 2012

CONTEXT AND POLICY ISSUES

Subcutaneous immunotherapy (SCIT) was introduced a century ago.[1-3] It represents the third most important mainstay treatment offered to patients with allergies and is currently the only means of altering the abnormal immune response that underlies allergic disease. SCIT involves the gradual administration of increasing amounts of allergen to induce protective immunologic responses during a period of three to five years. The beneficial effects are usually seen within the first year of treatment.[4] The mechanisms of action of SCIT are multiple and complex. The allergens that are known to be effective for use in SCIT include several tree, grass, and weed pollens, cat and dog dander, dust mites, certain molds, and cockroaches.[1,4] The allergen used could be single or a mixture of multiple allergens. There is no standard approach for the specific allergen or dose schedule to guide clinical practice. Although some guidelines have recommended against the use of multiple allergen mixes in treatment, this approach is not uncommon in the US.[1] SCIT has shown to be effective in the management of allergic rhinitis and asthma,[1,5-7] and has been used in the treatment of atopic dermatitis,[8] fungal allergic sinusitis,[9] anaphylaxis to bee or wasp stings,[10] food allergy,[4] and hymenoptera venom allergy;[11] but it has not been recommended for peanut allergy[12] or for drug allergies.[4] The magnitude of the effect of SCIT for allergic rhinitis is believed to be approximately equivalent to that of glucocorticoid.[4] Contraindications for SCIT include severe or unstable asthma, and patients receiving beta blockers.[4] Subcutaneous injections with aqueous food extracts may be effective for persistent and severe allergies to fish and peaches, but has proven to be accompanied by anaphylactic side effects.[13] Classic SCIT protocols begin with an initial dose-increase period (subcutaneous injections of gradually ascending dosages of the allergen extract in weekly intervals), followed by the dose-maintenance period. However, dosage schedules are not yet commonly standardized.[14] Cluster-SCIT is an accelerated procedure to achieve the maintenance dose after a shorter time interval by the application of two or three injections per treatment day.[15] SCIT is indicated for symptoms of allergic rhinitis, allergic conjunctivitis, allergic asthma, or any combination of these disorders after natural exposure to aeroallergens with demonstrable evidence of clinically relevant specific IgE and at least one of the following

conditions: poor response to pharmacotherapy; allergen avoidance; unacceptable adverse effects of medications; wish to reduce or avoid long-term pharmacotherapy and the cost of medication; coexisting allergic rhinitis and asthma; and possible prevention of asthma in patients with allergic rhinitis.[4,16]

Although SCIT is used worldwide, sublingual immunotherapy (SLIT) has been conducted with single allergen extracts more recently.[17] SLIT is considered a viable alternative to SCIT[11] and is used in many areas of Europe, Latin America, and Asia. SLIT has not been approved by the U.S. Food and Drug Administration for use there.[18] The purpose of this report is to review the evidence of comparative clinical effectiveness and the safety profile of SCIT compared with antihistamines, SLIT, or placebo in patients with allergy diseases, and identify the existing guidelines on SCIT in the treatment of allergy diseases.

RESEARCH QUESTIONS

1. What is the clinical efficacy of subcutaneous immunotherapy for the treatment of allergies?
2. What is the clinical evidence on the safety of subcutaneous immunotherapy for the treatment of allergies?
3. What are the evidence-based guidelines for the use of subcutaneous immunotherapy for the treatment of allergies?

KEY MESSAGE

Some marginal beneficial effect of SCIT was found in the treatment of patients with asthma or rhinitis compared with placebo; however, no evidence on SCIT in comparison with placebo, antihistamines, or SLIT was from Canada. Existing guidelines recommended that SCIT can only be used as a “third-line treatment” after avoidance of allergens and conventional pharmacotherapy, and the adverse events including anaphylaxis must be fully discussed with patients; however, no Canadian guidelines on SCIT were identified (one was in the US and one was in the United Kingdom).

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including Ovid MEDLINE, PubMed, The Cochrane Library (2012, Issue 6), University of York Centre for Reviews and Dissemination (CRD), ECRI (Health Devices Gold) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2007 and June 25, 2012.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

Table 1: Selection Criteria	
Population	Patients (any age) with allergies
Intervention	SCIT
Comparator	Placebo Antihistamines SLIT
Outcomes	Clinical benefit (for example, reduction in allergic reaction frequency or severity, reduction in need for additional treatment) Safety Guidelines
Study Designs	HTAs, systematic reviews (SRs) and meta-analyses, randomized controlled trials (RCTs), evidence-based guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria. Guidelines were excluded if they were superseded by more recent guidance from the same organization.

Critical Appraisal of Individual Studies

The AMSTAR checklist,[19] SIGN 50 checklist [20] and AGREE instrument[21] were used to assess the methodological quality for the included SRs, RCTs, and guidelines respectively.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 156 citations. Eighteen[7,10,11,16,18,22-34] additional citations were identified in the grey literature and by hand searching. Upon screening titles and abstracts, 130 citations were excluded, and 44 potentially relevant articles were retrieved for full-text review. Of these, 27[1,2,5,6,9,11,15,16,18,23-25,27,28,30-42] did not meet the inclusion criteria. Seventeen studies[7,10,14,22,26,29,43-53] were included in this review.

The study selection process is outlined in Appendix 1. Among the 17 included studies, four[26,47,51,53] were HTAs, SRs, or meta-analyses assessing the comparative efficacy and safety of SCIT with placebo, antihistamines, or SLIT in patients with allergic disease, 10 studies[14,22,43-46,48-50,52] were RCTs, and three[7,10,29] were evidence-based guidelines.

Summary of Study Characteristics

<u>1. What is the clinical efficacy of subcutaneous immunotherapy for the treatment of allergies?</u>

The main characteristics of the included studies evaluating the clinical efficacy and clinical evidence on the safety are summarized in Appendix 2.

Among the 14 included studies comparing clinical efficacy and clinical evidence on safety, 1 [26] was an HTA, 3[26,51,53] were SRs, and 10 were RCTs.[14,22,43-46,48-50,52]

Study Characteristics

The HTA[26] was from the UK. The three SRs were from Australia,[47] the UK,[53] and Netherlands[51] respectively.

Among the 10 RCTs, one was conducted in the UK,[52] the remainder were conducted in France,[45] German,[22] Italy,[14] Spain,[50] Turkey,[44,49] Egypt,[43] Taiwan,[54] and Iraq[46] respectively. Study sample sizes ranged from 23[55] to 410.[52] The majority of studies included had less than 70 participants.[14,22,43-45,48,50] The duration of most trials was one year, with the exception of: one RCT[22] for two to four months, one[48] for six months, one[50] for two years, and one[49] for three years plus three years follow-up

Population

Of the 10 RCTs, two[46,48] were conducted in patients with asthma. The remaining eight studies were conducted in patients with varies allergic diseases, including rhinoconjunctivitis[52] rhinoconjunctivitis with or without asthma,[22] rhinitis,[14,45,49] rhinitis with asthma,[44,50] and vernal keratoconjunctivitis.[43] Three studies[46,48,50] were conducted in children.

Interventions and Comparators

The HTA report[26] assessed the clinical effectiveness and cost-effectiveness of Pharmalgen in providing immunotherapy to individuals with a history of type 1 (immunoglobulin E-mediated [IgE]) systemic allergic reaction to bee and wasp venom. Of the three systematic reviews, one[47] assessed the effects of allergen specific immunotherapy for asthma; one[56] evaluated the efficacy and safety of subcutaneous specific allergen immunotherapy, compared with placebo, for reducing symptoms and medication requirements in patients with seasonal allergic rhinitis; and one[51] studied the effect of immunotherapy with inhalant allergens on symptoms and medication use in children and adolescents with allergic rhinoconjunctivitis. Various specific allergens used in SCIT included birch-apple extracts,[45] pollen,[14,22] house dust mites,[44,48,49] and other allergens.[43,46,50,52] In terms of comparators, four RCTs[22,44,48,52] compared SCIT with placebo, two[43,46] with pharmacotherapy, and four[14,45,49,50] with SLIT.

Outcomes

The main outcomes reported were symptom scores (for example, using a visual analog scale), medication scores (for example, a five-point ordinal scale of daily medication usage score, modified according to the management of the Global Initiative for Asthma (GINA 2004)[57] and adverse events (AEs). The symptom score measurement was not consistently defined in the included studies. One of the RCTs[48] described that the medication score was measured using a five-point ordinal scale of the daily medication usage score, modified according to the management of GINA 2004.[57] Detailed descriptions of medication score calculations were not provided in the remaining studies.

2. What is the clinical evidence on the safety of subcutaneous immunotherapy for the treatment of allergies?

Among the included studies described in question 1, nine studies[22,44-50,53] reported adverse events. Therefore, the study characteristics for research question 2 are the same as that summarized above for research question 1. No additional studies on safety were identified.

3. What are the evidence-based guidelines for the use of subcutaneous immunotherapy for the treatment of allergies?

One guideline[29] was developed in the US (2010) and two[7,10] were developed in the UK. (2012). The NHS guideline[10] provided recommendations on the use of Pharmalgen for the treatment of bee and wasp venom allergies. The SIGN guideline[7] provided recommendations on the use of SCIT for the management of asthma.[7] The US guideline[29] provided recommendations on SCIT use in the treatment of allergic rhinitis. The evidence level and grade of recommendations were reported in the SIGN and US guidelines.[7,29] The evidence level, but not the grade of recommendation was reported in NHS guidelines.[10]

Summary of Critical Appraisal

The risks of bias and applicability concerns of all included studies in the report are summarized in Appendix 3.

Overall, the included HTAs, SRs, and meta-analyses were well-conducted, and had explicit research questions and selection criteria. Multiple databases were searched. Study selection, data extraction, and quality assessment were all performed by at least two reviewers in a duplicate process. Conflicts of interest and funding sources were recorded. The common limitation was that publication bias was not reported in any HTAs or SRs. Excluded studies were not listed in one SR.[51] Overall the quality of RCTs was poor mainly because the randomization method was not clearly described.[43,46,48-50,52] One study[44] reported allocation concealment. Blinding treatment was not reported,[22,43,45,48-50] and the intention-to-treat analysis was not reported.[44-46,49,50]

All three included guidelines were based on well-conducted HTA reports or systematic review processes. Overall objectives and clinical questions, and the population for whom guidance was intended for, were well defined. Guideline development groups were generally representative of their relevant professional groups and recommendations were often peer reviewed. Conflict of interest was declared in all guidelines. Patients' involvement in the guideline development was not considered in two guidelines.[7,29] None of the three guidelines discussed the barriers to guideline implementation.

Summary of Findings

1. What is the clinical efficacy of subcutaneous immunotherapy for the treatment of allergies?

The main results and author conclusions of the included studies on the clinical efficacy and safety are summarized in Appendix 4.

Findings from HTAs/SRs

Abramson et al.[47] evaluated the effects of SCIT for the patients with asthma. Eighty-eight RCTs using various forms of allergens were included. Forty-two trials were for house mite allergy, 27 for pollen allergy, 10 for animal dander allergy, two for Cladosporium mould allergy, two for latex allergy, and six for an allergy to multiple allergens. It was found that a significant improvement in asthma symptom scores [standardized mean difference (SMD) –0.59, 95% confidence interval (CI) –0.83 to –0.35]. No consistent effect on lung function was found. More adverse events including systematic adverse event (i.e. anaphylaxis) were reported in SCIT groups. Sixteen studies reported local adverse reactions. The pooled relative risk (SCIT versus placebo) was 1.4 (95% CI, 0.97 to 2.02). Thirty-two trials reported systemic adverse reactions including any of anaphylaxis, asthma, rhinitis, or urticaria, or any combination. The pooled relative risk (95% CI) (SCIT versus placebo) was 2.45 (95% CI, 1.91 to 3.13). The authors concluded that SCIT improve the asthma symptoms and reduce the need for medications. However, the possibility of local or systemic adverse effects (such as anaphylaxis) must be considered.

Calderon et al.[53] conducted an SR to examine the efficacy and safety of SCIT compared with placebo for reducing symptoms and medication requirements in patients with seasonal allergic rhinitis. Fifty-one RCTs comprising 2,871 participants were included. The duration of SCIT varied from three days to three years. On average, each patient received 18 injections. Pooled treatment group differences of symptom scores from 15 trials showed an overall reduction in the SCIT group (SMD –0.73, 95% CI, –0.97 to –0.50, $P < 0.00001$). Pooled treatment group differences of medication scores from 13 trials showed an overall reduction in the SCIT group (SMD –0.57, 95% CI, –0.82 to –0.33, $P < 0.00001$). Clinical interpretation of the effect size is difficult. Adverse events requiring adrenaline treatment occurred in 0.13% (19 of 14,085 injections) of those on SCIT and in 0.01% (1 of 8,278 injections) of those in the placebo group for treatment of adverse events. No deaths were reported. The authors concluded that SCIT in selected patients with seasonal allergic rhinitis achieved a significant reduction in symptom scores and medication use compared with placebo. The severe adverse events were relatively low and no long-term adverse events consequences were found.

To assess the effect of SCIT compared with placebo, pharmacotherapy, or a different administration form of immunotherapy in children (age 0 to 18 years old) with allergic rhinoconjunctivitis, Roder et al.[51] reviewed six RCTs to evaluate the symptom and/or medication scores. The level of evidence for efficacy was conflicting for SCIT. It was also found that local side effects were more frequently reported in the SCIT groups. Systemic adverse events (e.g., asthma) were rare and mild. No systemic anaphylactic reactions were reported. The authors concluded that there was insufficient evidence that SCIT has a positive effect on symptoms and/or medication use in children and adolescents with allergic rhinoconjunctivitis.

The HTA report by Hockenhull et al.[26] assessed the clinical effectiveness and cost-effectiveness of Pharmalgen in immunotherapy for patients with a history of type 1 (immunoglobulin E-mediated) systemic allergic reaction to bee and wasp venom. No studies were identified that compared SCIT using Pharmalgen products with any comparator such as adrenaline auto-injector prescription, high-dose antihistamines, or advice on the avoidance of bee and wasp stings. No studies were included comparing SCIT with SLIT. Therefore, no data of interest for our review were reported.

Findings from RCTs

SCIT versus placebo (four RCTs)

In 2012, Klimek et al.[22] investigated the safety profile of SCIT with recombinant grass pollen allergens. It was found that 14 systematic reactions occurred among 661 injections in eight patients. The eight patients were distributed as follows: two patients in SCIT group 1 (20 mcg), one in SCIT group 2 (40 mcg), two in SCIT group 3 (80 mcg), and three in SCIT group 4 (120 mcg). No systematic reaction was reported in the placebo group. The author concluded that no major side effects were found for SCIT with a mixture of recombinant Phleum allergens (up to 120 mcg) in patients with rhinoconjunctivitis, with or without asthma. In a one-year RCT, Yukselen et al. [44] studied the clinical effect of SCIT versus placebo in 30 children with rhinitis and asthma. The main outcomes were symptom and medication scores, and severity of complaints using a visual analog scale. It was reported that, compared with placebo, SCIT significantly reduced the symptom score (P = 0.03 for rhinitis; P = 0.01 for asthma) and medication scores (and P = 0.05 for rhinitis; P = 0.05 for asthma) and visual analog scale. The author concluded that the clinical efficacy of SCIT on rhinitis and asthma symptoms was more evident when compared with the placebo after one year of treatment. In Taiwan, Tsai et al.[48] evaluated the clinical efficacy of SCIT with extracts of European house dust mites and American house dust mites in children with asthma. Forty children with moderate to severe asthma and positive allergen tests for European house dust mites and American house dust mites who required daily medication were randomly assigned to SCIT or no immunotherapy. Patients were followed up for more than six months. It was found that both the medication score (measured as modified medication score [GINA 2004][57]) and the symptom score (no measurement details provided) were statistically significantly reduced compared with placebo (mean treatment group difference 0.95 [P < 0.01] for medication score and 0.3 [P < 0.01] for symptom score) in favor of SCIT. While the frequencies of office visits in the SCIT group were greater than that of the controls, the number of emergency room visits and hospitalizations decreased. The author concluded that SCIT with European house dust mites and American house dust mite was beneficial for children with asthma. To assess the effect of SCIT with two doses of Alutard SQ Phleum pratense on quality of life (QoL) in patients with moderate to severe seasonal allergic rhinoconjunctivitis inadequately controlled by standard drug therapy, Powell et al.[52] conducted a double-blind, randomized, placebo-controlled study including 410 patients with seasonal allergic rhinoconjunctivitis. It was reported that while all domain scores were significantly improved when comparing 100,000 SQ-U with placebo, two domain scores were significantly improved when comparing 10,000 SQ-U with placebo. The author concluded that treatment with Alutard SQ significantly improved the seasonal QoL of patients suffering from allergic rhinoconjunctivitis. The improvement was more pronounced and widespread with the higher 100,000 SQ-U maintenance dose.

SCIT versus medication (two RCTs)

In a prospective RCT, Mahdy et al.[43] evaluated the effectiveness of SCIT versus topical treatment in the treatment of 64 Egyptian patients with vernal keratoconjunctivitis. The study revealed that 72% of patients in SCIT reported symptom reduction, while 59% in medical treatment (P < 0.05) reported symptom reduction. The author concluded that the management of vernal keratoconjunctivitis by SCIT was more effective than topical treatment in improving the clinical symptoms. In 2010, Alzakar[46] conducted a single-blind, randomized, drug-controlled trial in Iraq to clarify the comparative clinical efficacy of SCIT versus pharmacotherapy in improving the symptoms and reducing medication in primary school children with asthma. Children age

seven to 12 years (n = 242) with allergic asthma were included. Eighty-five (out of 105) children in SCIT and 112 (out of 137) children in pharmacotherapies completed the study and were included for analysis. It was found that after one year, children with SCIT showed a marked reduction in the clinical symptoms and need for medication compared with children taking conventional drugs

SCIT versus SLIT (four RCTs)

Mauro et al.[45] conducted a one-year RCT on patients with birch-apple syndrome to evaluate the outcome of SCIT compared with SLIT. Forty patients were randomized (1:1). It was reported that there was no statistically significant difference between SCIT and SLIT in the reduction of symptom scores (4.77 versus 3.63 SCIT versus SLIT) after one year. However, systemic reactions were found in SCIT (16%) compared with SLIT (0%). The author concluded that different doses of birch extract may be needed for different patients to improve the associated apple allergy and that a finer diagnostic workup in selecting patients with birch-apple syndrome is required. Ventura et al.[14] studied the efficacy of SCIT and high-dose SLIT using a purified standardized *Juniperus ashei* extract in a population of patients who are allergic and are monosensitized to cypress pollen. Forty patients with cypress-allergic rhinoconjunctivitis were administered therapeutic or placebo SLIT or SCIT for 12 months. The clinical symptoms score was measured. After SCIT and SLIT, the results showed that numerically fewer patients (n = 2) in the SCIT group had symptom scores ≥ 2.5 than in the SLIT group (n = 3). It was concluded by the author that SCIT and SLIT treatment with a major allergen of cypress is able to change the course of allergic rhinitis. In an RCT, Tahamiler et al.[49] compared the long-term efficacies of SCIT with SLIT in the treatment of patients with house dust mite allergies. Patients with house dust mite allergies were randomized into SCIT (97 patients) or SLIT (96 patients) for three years and also observed for three years after discontinuation of the treatment. The results showed that SCIT achieved a greater improvement compared to the SLIT after six years. The author suggested SCIT be used for patients with perennial allergic rhinitis. However, SLIT should be used in all patients who do not accept subcutaneous administration of immunotherapy. Antúnez et al.[50] compared children with respiratory disease monosensitized to European house dust mites receiving SLIT or SCIT during a two-year period. It was found that children with respiratory allergic diseases receiving SCIT or SLIT had a similar clinical improvement, although the immunologic response in peripheral blood during treatment was different.

2. What is the clinical evidence on the safety of subcutaneous immunotherapy for the treatment of allergies?

One HTA report,[26] two systematic reviews,[47] and seven RCTs[22,43,45,46,48-50] reported adverse results of SCIT compared with placebo. Detailed results were reported in research question 1 above and are summarized in Appendix 4.

3. What are the evidence-based guidelines for the use of subcutaneous immunotherapy for the treatment of allergies?

Three guidelines were identified. One guideline provided recommendations on the use of Pharmalgen for the treatment of bee and wasp venom allergies,[10] one provided the recommendation of SCIT for the management of asthma,[7] and the third guideline provided the recommendations for SCIT used in the management of allergic rhinitis.[29] Individual guidelines and recommendations, level of evidence, and grade of recommendations are summarized in Appendix 5.

The NHS (2012, UK) guidelines[10] indicated that (on page 3):

"Pharmalgen is recommended as an option for the treatment of IgE-mediated bee and wasp venom allergy in people who have had: a severe systemic reaction to bee or wasp venom, or a moderate systemic reaction to bee or wasp venom and who have one or more of the following: a raised baseline serum tryptase, a high risk of future stings or anxiety about future stings. Treatment with Pharmalgen should be initiated and monitored in a specialist centre experienced in venom immunotherapy." The recommendation was based on limited evidence of poor quality.

The British Guideline on the Management of Asthma (2012, SIGN)[7] recommended that SCIT can be considered in patients with asthma where a clinically significant allergen cannot be avoided. The potential for severe allergic reactions to the therapy must be fully discussed with patients.

The American Academy of Allergy, Asthma and Immunology (AAAAI), American College of Allergy, Asthma and Immunology (ACAAI), and the Joint Council of Allergy, Asthma and Immunology (JCAAI) (2010, USA)[29] recommended SCIT be used in the management of allergic rhinitis and allergic asthma as follows:

On page 74; "*We suggest subcutaneous allergen specific immunotherapy in adults with seasonal (conditional recommendation | moderate quality evidence) and perennial allergic rhinitis due to house dust mites (conditional recommendation | low quality evidence). Underlying values and preferences: This recommendation places a relatively high value on relieving the symptoms of AR, and a relatively low value on avoiding adverse effects and on resource expenditure."*

On page 75: "In children with AR, we suggest subcutaneous specific immunotherapy (conditional recommendation | low quality evidence). Underlying values and preferences: This recommendation places a relatively high value on probable reduction in symptoms of allergic rhinitis and the potential prevention of the development of asthma, and relatively low value on avoiding adverse effects in children and resource expenditure"

On page 97: "In patients with allergic rhinitis and asthma, we suggest subcutaneous specific immunotherapy for treatment of asthma (conditional recommendation | moderate quality evidence).Underlying values and preferences: This recommendation places a relatively high value on reducing the symptoms of asthma, and a relatively low value on avoiding adverse effects and limiting the cost of subcutaneous specific immunotherapy. In patients who are more averse to the side effects of subcutaneous specific immunotherapy an alternative choice may be equally reasonable. Remarks: Subcutaneous specific immunotherapy may also be used in patients with asthma and concomitant allergic rhinitis for treatment of rhinitis. Resource limitations will have stronger implications for the implementation of this recommendation."

Limitations

The methodological quality of the HTA or systematic reviews included in this report was good. Overall the quality of RCTs was limited because the randomization method was not clearly described.[43,46,48-50,52] One study[44] reported allocation concealment. Blinding to treatment was not reported,[22,43,45,48-50] and intention-to-treat analysis was not reported.[44-46,49,50] The overall quality of RCTs is also limited by several other factors, including different approaches to administration, different allergen extracts, lack of definitions of effective allergen doses, and small sample sizes.

Another quality limitation was that methods of main outcome measurements were not standardized across the studies (such as symptoms scores) or not described (such as medication score[44-46]). Furthermore, the clinical significance of the changes identified is unclear. Importantly, no study was conducted in Canada. Seasonal allergies are highly related to the local environmental allergens.

All three included guidelines were based on a well-conducted HTA report or systematic reviews. However, the methodological limitation was that the patients' involvement in the guideline development was not considered in two guidelines.[7,29] While recommendations were based on a thorough literature review, the body of evidence identified was limited. Therefore, recommendations were not based on high-quality evidence[7,29] or were based on limited and poor-quality evidence.[10] No guidelines were developed in Canada, and no recommendation was based on evidence generated in Canada, which should not be ignored in the implementation of SCIT for patients with allergies.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY-MAKING:

One HTA report, three SRs, 10 RCTs, and three guideline documents are included in this review. The majority of these studies evaluated the use of SCIT in patients with rhinitis, conjunctivitis, asthma, or any combination of these conditions.

In terms of clinical efficacy, evidence from two SRs and three RCTs reported that SCIT was more effective in reducing symptoms and the need for medications in patients with asthma or in suitably selected patients with seasonal allergic rhinitis compared with placebo. SCIT was also shown to be more effective than conventional pharmacotherapy in improving the clinical symptoms or reducing the need for medication in patients with vernal keratoconjunctivitis or in primary school children with asthma compared with pharmacotherapy. Inconsistent comparative evidence of efficacy was found that compared SCIT with SLIT. In terms of safety, based on an SR, systemic adverse events including anaphylaxis, asthma, rhinitis or urticaria, or any combination of these were rare, but did occur. Therefore, the possibility of local or systemic adverse effects (such as anaphylaxis) is an important consideration for SCIT.

In the included guidelines, SCIT was recommended for the treatment of patients with asthma only if clinical allergens cannot be avoided, and after potential severe adverse events were fully discussed with patients. The strength of the recommendations to use SCIT in patients with allergic rhinitis is weak.

In summary, even though SCIT has been used for more than a century, and SRs and RCTs conducted in the last five years have shown some marginal benefit compared with placebo in the management of rhinitis, rhinoconjunctivitis, or asthma, the information identified in this report should be interpreted with caution due the limited quality of RCTs included. Generalization of these findings to the Canadian setting is questionable since none of the included studies was conducted in a North American context.

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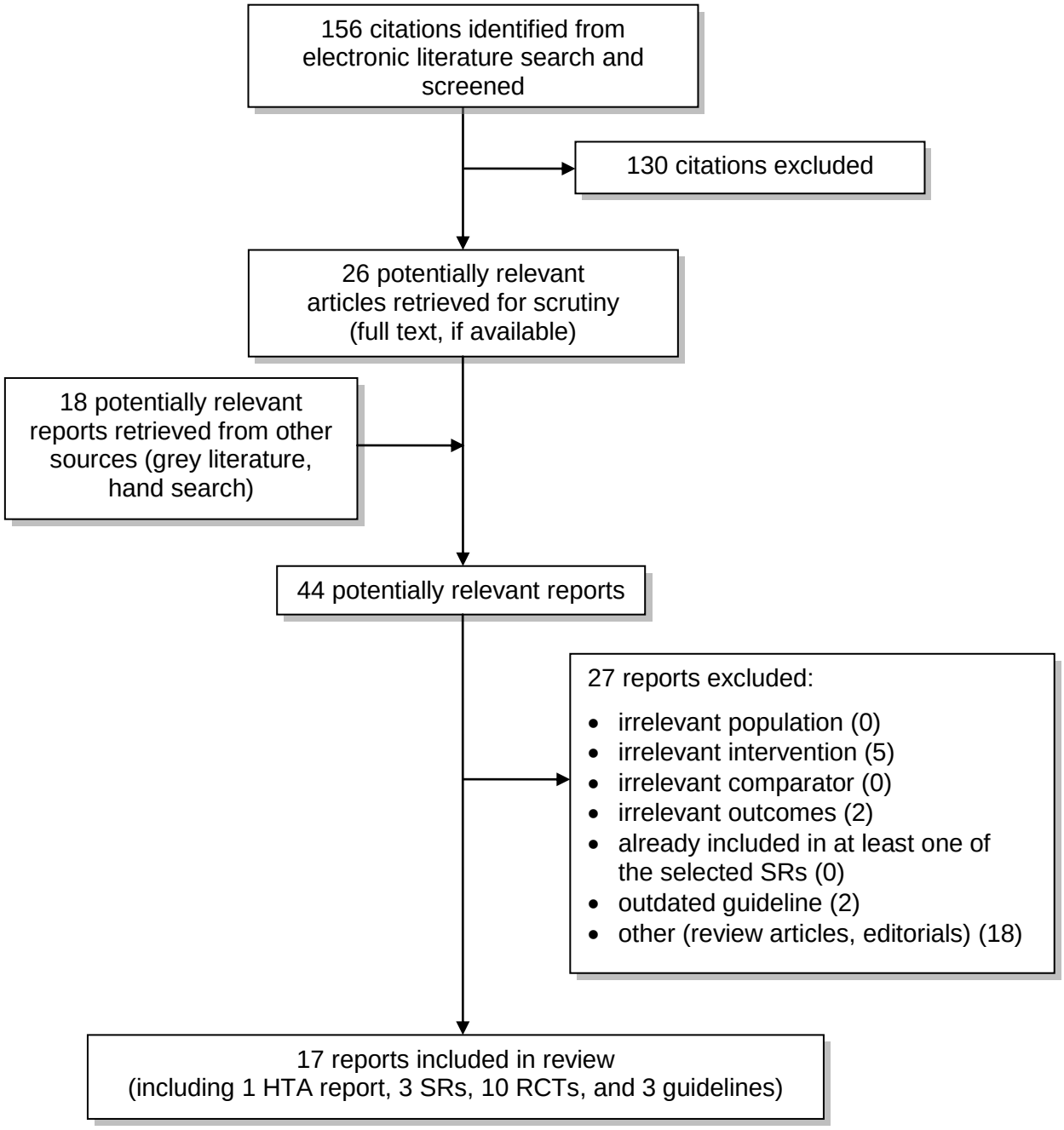
APPENDIX 1: Selection of Included Studies



APPENDIX 2: CHARACTERISTICS OF INCLUDED STUDIES ON CLINICAL EFFECTIVENESS AND SAFETY

First Author, Publication Year, Country	Study Design, Length of Study	Patient Characteristics, Sample Size	Intervention	Comparators	Main Outcomes
HTA/SR/Meta-Analysis					
Hockenhull[26] 2012 UK.	HTA	individuals with a history of type 1 (immunoglobulin E-mediated) systemic allergic reaction to bee and wasp venom # of included RCTs: nine studies (11 papers) # of included patients: NR	SCIT (Allergen: Pharmalgen)	any alternative treatment options available in the NHS without VIT, that is, advice on avoidance of bee and wasp venom or HDA or AAI prescriptions and training,	Clinical effectiveness: reaction to subsequent stings (assessed through accidental FS or SC), anxiety related to the possibility of future allergic reactions, reported ARs to treatment and QoL
Abramson[47] 2010 Australia	SR	Patients with Asthma # of included RCTs: 88 # of included patients: 3,792	SCIT (extracts of house dust mites, pollens, animal dander or moulds, chemically modified allergoids or antigen-antibody complexes)	Placebo	• asthmatic symptoms (including symptom scores); • asthma medication requirements; • lung function (including peak expiratory flow, forced • expiratory volume in one second (FEV1) and thoracic gas volume); • adverse events:
Calderon[53] 2009 UK	SR	Patients with seasonal allergic rhinitis# of included RCTs: 51 # of included patients: 2,871	SCIT (Multiple injections of high-dose immunotherapy with standardized single allergen	Placebo	• Symptom scores: typically collected using symptom diaries (any • permitted);

First Author, Publication Year, Country	Study Design, Length of Study	Patient Characteristics, Sample Size	Intervention	Comparators	Main Outcomes
			extracts)		• Patient-completed visual analogue rhinitis symptoms scores. • Medication use; • quality of life questionnaire; • Adverse reactions
Röder[51] 2008 Netherlands	SR	Children and adolescents with allergic Rhinoconjunctivitis; # of included RCTs: six	SCIT (Allergen: pollen was used or house dust mite)	Placebo or symptomatic treatment	• symptom and/or medication scores.
Randomized control trials					
Klimek[22] 2012 Germany.	RCT (phase II)	allergic Rhinoconjunctivitis with or without asthma N = 50	SCIT (recombinant grass pollen allergens at different dose)	Placebo	AE: Systematic reactions
Yuksele[44] 2012 Turkey	RCT 1 year	Children with rhinitis and asthma related to HDM allergy) N = 30	SCIT (Allergen: Novo-Helisen Depot, Allergopharma)	Placebo	Symptom scores Medication scores, VAS scores AE
Mahdy[43] 2012 Egypt.	RCT 1 year	Patients with bilateral vernal keratoconjunctivitis N = 64	SCIT (different allergens)	Topical medical treatment	Symptom
Mauro[45] 2011 France	RCT 1 year	Birch-apple syndrome N = 40	SCIT (Allergen: tree pollen, birch, alder and hazelnut from Stallergenes (Antony France)	SLIT	Symptom scores Medication scores, AE
Alzakar[46] 2010 Iraq	RCT 1 year	Allergic asthma in children. N = 242	SCIT+ Pharmacotherapy (Allergen extracts purchased from Stallergenes)	Pharmacotherapy	Symptom scores Pulmonary function Medication scores AE

First Author, Publication Year, Country	Study Design, Length of Study	Patient Characteristics, Sample Size	Intervention	Comparators	Main Outcomes
Tsai[48] 2010 Taiwan	RCT ≥ 6 months	Children with asthma N = 40	SCIT (Allergen: extracts of Dp and Df	Placebo	Symptom scores Pulmonary function Medication scores AE
Ventura[14] 2009 Italy	RCT 1 year	Patients with rhinoconjunctivitis (allergic to cypress) N = 40	SCIT (Allergen: Juniperus ashei extract)	SLIT (high dose)	Symptom score
Tahamiler[49] 2008 Turkey	RCT 3 year plus 3 yeas follow-up	Patients with perennial rhinitis, N = 193	SCIT (HDM specific immunotherapies)	SLIT	Symptom scores AE
Antúnez[50] 2008 Spain	RCT 2 years	Children with mite-allergy (respiratory disease monosensitized to Dermatophagoides pteronyssinus N = 23	SCIT (Dp 100% extract provided by ALK-Abello, Pangramin Depot-UM)	SLIT (SLIT Tratamiento sublingual)	Clinical variables (not specified) VAS AE
Powell[52] 2007 UK	RCT 1 year	Patients with moderately to severe seasonal allergic rhinoconjunctivitis inadequately controlled by standard drug therapy. N = 410	SCIT (Allergen: Alutard SQ P. pretense, ALK-Abello) 100,000 SQ-U or 10,000 SQ-U	Placebo	QoL was assessed using the rhinoconjunctivitis QoLQ

AAI = adrenaline auto-injector; AE = adverse event; AR = adverse reaction; Df = Dermatophagoides farina (American house dust mites); Dp = Dermatophagoides pteronyssinus (European house dust mites); FS= field sting; FEV1 = expiratory volume in one second; HDA = high-dose antihistamine; HDM = house dust mite; HTA = healthy technology assessment; NHS = National Health Service; NR = not reported; QoL = quality of life; QoLQ = quality of life questionnaire; RCT = randomized control trials; SC = sting challenge; SCIT = subcutaneous immunotherapy; SR = systematic review; VAS = visual analog scale; VIT = venom immunotherapy.

APPENDIX 3: CRITICAL APPRAISAL OF INCLUDED STUDIES

First Author, Publication Year, Country	Strengths	Limitations
HTAs, SRs, and Meta-Analyses Assessed with AMSTAR[19]		
Hockenhull[26] 2012 UK	• Research questions and selection criteria were defined and presented. • Comprehensive literature search based on pre-defined criteria. • Two independent investigators performed study selection and data extraction. • List of included and excluded studies provided. • Quality assessment of the included studies was described. • Appropriate methods for data synthesis. • Conflict of interests declared.	• Unclear if there was a limit on language in literature search. • Publication bias was not assessed.
Abramson[47] 2010 Australia	• Research questions and selection criteria were defined and presented. • Comprehensive literature search based on pre-defined criteria. • Two independent investigators performed study selection and data extraction. • List of included and excluded studies provided. • Quality assessment of the included studies was described. • Appropriate methods for data synthesis • Conflict of interests declared.	• Unclear if there was a limit on language in literature search. • Publication bias was not assessed.
Calderon[53] 2009 UK	• Research questions and selection criteria were defined and presented. • Comprehensive literature search based on pre-defined criteria. • Two independent investigators performed study selection, data extraction, and quality assessment. • List of included and excluded studies provided. • Quality assessment of the	• Unclear if there was a limit on language in literature search. • Publication bias was not assessed.

First Author, Publication Year, Country	Strengths	Limitations
	included studies was described. • Appropriate methods for data synthesis. • Conflict of interests declared.	
Röder[51] 2008 Netherlands	• Research questions and selection criteria were defined and presented. • Comprehensive literature search based on pre-defined criteria. • Two independent investigators performed study selection, data extraction, and quality assessment. • List of included studies provided. • Quality assessment of the included studies was described.	• Unclear if there was a limit on language in literature search. • Lack of list of excluded studies. • Publication bias was not assessed.
RCTs Assessed with SIGN 50[20]		
Klimek[22] 2012 Germany	• Research question was clearly defined. • Randomization method was adequate. • Baseline characteristics were comparable between groups. • Only difference between groups is treatment under investigation. • No dropout.	• Allocation concealment was not described. • Blinding process was not reported • Clinical outcome measurements were not standardized and not clearly described.
Yukselen[44] 2012 Turkey	• Research question was clearly defined. • Randomization method was clearly described. • Allocation concealment was clearly described. • Triple-blinding process was applied. • Baseline characteristics were comparable between groups. • Only difference between groups is treatment under investigation. • Dropout rate is acceptable (< 20%) and is comparable between the groups. • Comparable results for multi-study sites.	• Outcome measurements were not standardized and not clearly described • ITT analysis was not reported
Mahdy[43] 2012, Egypt	• Research question was clearly defined. • Only difference between groups	• Randomization method was not adequate. • Allocation concealment was not

First Author, Publication Year, Country	Strengths	Limitations
	is treatment under investigation. • No dropout.	described. • Blinding process was not applied • No detail baseline characteristics were reported. • Outcome measurements were not standardized and not clearly described.
Mauro[45] 2011 France	• Research question was clearly defined. • Randomization method was clearly reported. • Baseline characteristics were comparable between groups. • Only difference between groups is treatment under investigation.	• Allocation concealment was not described. • Blinding process was not applied. • Drop-out rate is acceptable (< 20%) in SCIT group, but not in SLIT group (25%) • ITT analysis was not reported. • Outcome measurements were not standardized and not clearly described.
Alzakar[46] 2010 Iraq	• Research question was clearly defined. • Baseline characteristics were comparable between groups. • Only difference between groups is treatment under investigation. • Dropout rate is acceptable (< 20%) and is comparable between the groups.	• Randomization method was not adequate. • Allocation concealment was not described. • Single blinding process was applied • ITT analysis was not reported. • Outcome measurements were not standardized and not clearly described.
Tsai[48] 2010 Taiwan	• Research question was clearly defined. • Baseline characteristics were comparable between groups. • Only difference between groups is treatment under investigation. • No dropout.	• Randomization method was not clearly described. • Allocation concealment was not reported. • Blinding process was not reported. • Outcome measurements were not standardized and not clearly described.
Ventura[14] 2009 Italy	• Research question was clearly defined. • Randomization method was clearly described. • Baseline characteristics were comparable between groups. • Only difference between groups is treatment under investigation. • No dropout.	• Allocation concealment was not reported. • Double blinding process was not clearly described. • Outcome measurements were not standardized and not clearly described.

First Author, Publication Year, Country	Strengths	Limitations
Tahamiler[49] 2008 Turkey	• Research question was clearly defined. • Baseline characteristics were comparable between groups. • Only difference between groups is treatment under investigation.	• Randomization method was not clearly described. • Allocation concealment was not reported. • Blinding process was not reported. • Dropout rate is acceptable,(< 20%), but not reported in each treatment group. • ITT analysis was not reported. • Outcome measurements were not standardized and not clearly described.
Antúnez[50] 2008 Spain	• Research question was clearly defined. • Baseline characteristics were comparable between groups. • Only difference between groups is treatment under investigation. • Dropout rate is acceptable (< 20%) and is comparable between the groups.	• Randomization method was not clearly described. • Allocation concealment was not reported. • Blinding process was not reported. • Outcome measurements were not standardized and not clearly described. • ITT analysis was not reported.
Powell[52] 2007 UK	• Research question was clearly defined. • Double blinding (the process was not described.). • Baseline characteristics were comparable between groups. • Only difference between groups is treatment under investigation. • ITT analysis was reported.	• Randomization method was not clearly described. • Allocation concealment was not reported. • Outcome measurements were not standardized and not clearly described. • Dropout rate was not reported.
Guidelines Assessed with AGREE[21]		
NHS[10] 2012 UK	• Clearly defined objectives, scope, and target populations. • Guideline was developed based on a well-conducted UK HTA report. • Patients' views and preferences were considered. • The recommendation was clearly presented. • Conflict of interest declared.	• Recommendations are based on limited and poor-quality evidence.
British Guideline on the Management of Asthma [7] 2012, SIGN UK	• Clearly defined objectives, scope, and target populations.	• The recommendation was based on a body of evidence including an SR of case control or cohort study or extrapolated evidence from an SR/MA or RCT.

First Author, Publication Year, Country	Strengths	Limitations
	• Guideline was updated to a previous guideline (SIGN) based on a well-conducted SR. • Guideline evidence reviewed and updated annually. • Conflict of interest declared.	• Patients' views and preferences were not considered.
AAAAI, ACAAI, JCAAAI[29] 2010 USA	• Clearly defined objectives, scope and target populations. • Guideline was updated to a previous guideline (2008) based on a well-conducted SR. • Conflict of interest declared.	• The recommendations were not based on high-quality evidence, that is, the recommendations for rhinitis were based on low-quality evidence. • The recommendations for asthma were based on moderate-quality evidence. • Patients' views and preferences were not considered.

AAAAI = American Academy of Allergy, Asthma and Immunology; ACAAI = American College of Allergy, Asthma and Immunology; HTA = health technology assessment; ITT = intention to treat; JCAAI = Joint Council of Allergy, Asthma and Immunology. Allergen immunotherapy; RCT = randomized control trials; SCIT = subcutaneous immunotherapy; SLIT= sublingual immunotherapy; SR = systematic review; UK = United Kingdom.

APPENDIX 4: MAIN STUDY FINDINGS AND AUTHORS' CONCLUSIONS

First Author, Publication Year, Country	Main Results	Author's Conclusions
SR/Meta-Analysis		
Hockenhull[26] 2012 UK	No RCTs were identified that compared SCIT using PhVIT with antihistamines, SLIT and placebo.	On page Xiii: "The current use of PhVIT in clinical practice in the NHS appears to be based on limited and poor-quality clinical effectiveness research … The assessment group did not identify any studies of PhVIT that directly addressed the original decision problem set for this appraisal …"
Abramson[47] 2010 Australia	88 trials were included. SCIT for house mite allergy: 42; pollen allergy: 27; animal dander allergy: 10; *Cladosporium* mould allergy: 2; latex allergy: 2; and multiple allergens: 6. **Efficacy** **Symptom scores:** (high score indicates worse symptom) SMD (95%CI) (SCIT – placebo) –0.59 (–0.83 to –0.35) **AE:** Large local adverse reactions were reported by 16 studies comparing SCIT with placebo. The pooled relative risk was (95%CI),1.4 (0.97 to 2.02). Systemic adverse reactions were reported by 32 studies. Systemic reactions were defined as any of anaphylaxis, asthma, rhinitis or urticaria, or any combination of these. The pooled relative risk was 2.45 (95% CI, 1.91 to 3.13)	On page 2: "Immunotherapy reduces asthma symptoms and use of asthma medications and improves bronchial hyper-reactivity. One trial found that the size of the benefit is possibly comparable to inhaled steroids. The possibility of local or systemic adverse effects (such as anaphylaxis) must be considered."
Calderon[53] 2009 UK	# of Included RCTs: 51 # of participants: 2,871 (1,645 active, 1,226 placebo), average # of injection/per patients: 18 Duration of SCIT: 3 days to 3 years.	On page 2: "This review has shown that specific allergen injection immunotherapy in suitably selected patients with seasonal allergic rhinitis results in a significant reduction in symptom scores and medication use. Injection

First Author, Publication Year, Country	Main Results	Author's Conclusions
	Efficacy **Symptom score:** pooled data from 15 RCTs (SCIT – placebo) SMD (95%CI), -0.73 (–0.97 to -0.50, P < 0.00001). Medication score data from 13 RCTs (SCIT – placebo) SMD (95%CI) -0.57 (–0.82 to –0.33, P < 0.00001)). **AE:** AE needed to be treated with adrenaline: % of injections (SCIT versus placebo) 0.13% (19 of 14,085 injections) versus 0.01% (1 of 8,278 injections). No death was reported.	immunotherapy has a known and relatively low risk of severe adverse events. We found no long-term consequences from adverse events."
Röder[51] 2008 Netherlands	• Six RCTs were identified for SCIT; the level of evidence for efficacy was conflicting. **Efficacy:** • Two RCTs (one placebo controlled, one symptomatic treatment controlled) reported there was some efficacy; • Four RCTs (three placebo controlled, and one symptomatic-treatment controlled) reported no efficacy. **AE:** • The definition of an adverse event was often unclear. • Local side-effects were more frequently reported in the SCIT groups. • Systemic side-effects (e.g. asthma) were rare and mild. • No systemic anaphylactic reactions were reported	On page 197: "In conclusion, there is at present insufficient evidence that immunotherapy in any administration form has a positive effect on symptoms and/or medication use in children and adolescents with allergic rhinoconjunctivitis."
Randomized control trials		
Klimek[22] 2012 Germany	**AE:** # of patients with systematic reactions: 8 # of systematic reaction events: 14 of 661 injections SCIT group 1 (20 mcg): 2 SCIT group 1 (40 mcg): 1 SCIT group 1 (80 mcg): 2	SCIT with a mixture of recombinant Phleum allergens in patients with rhinoconjunctivitis with or without asthma showed no major side effects in very high doses up to 120 mcg.

First Author, Publication Year, Country	Main Results	Author's Conclusions
	SCIT group 1 (120 mcg): 3 Placebo: 0	
Yukselen[44] 2012 Turkey	Symptom score reduction: Rhinitis: P < 0.005 (versus baseline) P < 0.03 (versus placebo) Asthma: P < 0.005 (versus baseline) P < 0.01 (versus placebo) Medication scores reduction: Rhinitis: P < 0.005 (versus baseline) P < 0.05 (versus placebo) Asthma: P < 0.002 (versus baseline) P < 0.05 (versus placebo) VAS Rhinitis P < 0.005 (versus baseline) P < 0.05 (versus placebo) Asthma: P < 0.007 (versus baseline) P < 0.02 (versus placebo) **AE:** # of patients Local reaction related to the injection: SCIT versus placebo: 2 versus 2 . No systematic AE occurred in SCIT, SLIT, and placebo group.	On page 288: "Based on the limited number of patients at the end of the 1-year immunotherapy, the clinical efficacy of SCIT on rhinitis and asthma symptoms was more evident when compared with the placebo."
Mahdy[43] 2012 Egypt	**Symptom** # of pts with symptom reduction 72% versus 59% (SCIT versus control, P < 0.05).	On page 525: "Treatment of vernal keratoconjunctivitis by SCIT was more effective than topical treatment in improving the clinical symptoms and reducing the total serum IgE."
Mauro[45] 2011 France	**Mean symptom-medication scores:** SCIT: 4.77 ± 1.41 SLIT: 3.63 ± 1.08. **AE:** Systematic reaction 16% versus 0% (SCIT versus SLIT, P value: NR) SAE: 0.	On page 416: "These findings suggest that different doses of birch extract may be needed in different patients to improve the associated apple allergy and that a finer diagnostic work-up in selecting patients with birch-apple syndrome who are candidates to respond to birch pollen IT also concerning apple allergy is required."
Alzakar[46] 2010 Iraq	Symptom reduction: # of patients (%) 64% versus26% (P = 0.0000, SCIT versus control). Improvement in pulmonary function: # of patients (%):	After one year, SCIT combined with pharmacotherapy showed more effective compared with standard pharmacotherapy and can prevent or decrease the onset of asthma and maintain its beneficial effect for

First Author, Publication Year, Country	Main Results	Author's Conclusions
	60% versus19% (P = 0.0001, SCIT versus control). Reduction in medication need # of patients (%) 66% versus 12% (P = 0.0001) SCIT versus control). **AE:** Nine patients (11%) with immediate systematic reactions in total. (No data for each group were reported.)	years after discontinuation
Tsai[48] 2010 Taiwan	Symptom scores: Mean difference of changes from baseline (SCIT – control) –0.3 (P < 0.01 SCIT versus control, in favor of SCIT). Pulmonary function PERP (% predicted value) Mean difference of changes from baseline (SCIT – control) 2.01 (P value: NR; SCIT versus control, in favour of SCIT). Medication scores Mean difference of changes from baseline (SCIT – control) –0.95 (P<0.01 SCIT versus control, in favor of SCIT)	SCIT with Dp and Df was beneficial for children with asthma.
Ventura[14] 2009 Italy	Symptom score (high score indicates worse symptom) # of patient with symptom score ≥ 2.5: 2 versus 3 (SCIT versus SLIT)	A clinical improvement correlated with a decline in inflammation parameters was confirmed after one year SCIT and one year SLIT.
Tahamiler[49] 2008 Turkey	Symptom scores Mean difference of changes from baseline between SCIT and SLIT at the end of 3 years: (SCIT versus SLIT) P = 0.000 in favor of SCIT) AE SCIT: ≥ 5 cm local skin reaction: 7.4% SLIT: oral pruritus 48% Rhinitis, 31% and gastrointestinal upset: 12%.	On page 144: "We suggest subcutaneous immunotherapy for patients with perennial allergic rhinitis due to the better results that were obtained during our study period. Nevertheless, sublingual immunotherapy is now accepted by WHO as a valid alternative to the subcutaneous route and should be used in all patients who require immunotherapy and do not accept the subcutaneous route of allergen administration."

First Author, Publication Year, Country	Main Results	Author's Conclusions
	No systematic reaction in SCIT or SLIT	
Antúnez[50] 2008 Spain	Clinical variables (not specified) No difference was found between SCIT and SLIT in any Clinical variables. VAS Mean ± SD: SCIT: 8.1 ± 1.4 SLIT: 8.5 ± 1.3 AE No systematic reaction. Overall well tolerated. **WDAE:** SCIT: 1 due to acute attack of atopic dermatitis after one year. SLIT: 1 for unknown reason.	Children with respiratory allergic diseases receiving SCIT or SLIT had a similar clinical improvement. Both SCIT and SLIT were well tolerated and no systematic reaction was observed.
Powell[52] 2007 UK	Rhinoconjunctivitis QoLQ In 100,000 SQ-U group: all domain scores significantly improved (P < 0.02, SCIT versus placebo). In 10,000 SQ-U groups: two of seven groups noted significant improvement (P < 0.0001 for eye symptoms and P < 0.02 for emotional function).	On page 1,335: "Treatment with Alutard SQ significantly improved the seasonal QoL of patients suffering from allergic rhinoconjunctivitis. The improvement was more pronounced and wider ranging in patients who received the higher 100,000 SQ-U maintenance dose."

AE = adverse event; CI =confidence Interval; Df = Dermatophagoides farina (American house dust mites); Dp = Dermatophagoides pteronyssinus (European house dust mites); NHS = National Health Service; NR = not reported; PERP = peak expiratory flow rate; PhVIT = venom immunotherapy using Pharmalgen products; RCT = randomized control trials; SAE = serious adverse event; SCIT = subcutaneous immunotherapy; SMD = standardized mean difference; SR = systematic review; SLIT = sublingual immunotherapy; UK = United Kingdom; VAS = visual analog scale; WDAE = withdrawal due to adverse event; WHO = World Health Organization.

APPENDIX 5: GUIDELINES AND RECOMMENDATIONS

Guidelines, First Author, Publication Year, Country	Diseases	SCIT Allergens	Recommendations	Level of Evidence	Grade of Recommendations
NHS[10] 2012 UK	Bee and wasp venom allergy	Pharmalgen	On page 3: "Pharmalgen is recommended as an option for the treatment of IgE-mediated bee and wasp venom allergy in people who have had: • a severe systemic reaction to bee or wasp venom, or • a moderate systemic reaction to bee or wasp venom and who have one or more of the following: a raised baseline serum tryptase, a high risk of future stings or anxiety about future stings. Treatment with Pharmalgen should be initiated and monitored in a specialist centre experienced in venom immunotherapy."	Indicated as "poor" and limited.	NR
British Guideline on the Management of Asthma [7] 2012 SIGN UK	Asthma (adult and children)	HDM, grass pollen, tree pollen, cat and dog allergen, and moulds	On page 33: "(SCIT) immunotherapy can be considered in patients with asthma where a clinically significant allergen cannot be avoided. The potential for severe allergic reactions to the therapy must be fully discussed with patients."	2^{++}	B
AAAAI, ACAAI, JCAAI[29] 2010 US	allergic rhinitis, allergic asthma		*Recommendation on page 74*. "We suggest subcutaneous allergen specific immunotherapy in adults with seasonal (conditional recommendation / moderate quality evidence) and perennial allergic rhinitis due to house dust mites (conditional recommendation | low quality evidence).	Low to moderate quality evidence	Conditional (or weak) recommendation

Guidelines, First Author, Publication Year, Country	Diseases	SCIT Allergens	Recommendations	Level of Evidence	Grade of Recommendations
			Underlying values and preferences: This recommendation places a relatively high value on relieving the symptoms of AR, and a relatively low value on avoiding adverse effects and on resource expenditure." *Recommendation on page 75 :* "In children with AR, we suggest subcutaneous specific immunotherapy (conditional recommendation / low quality evidence). Underlying values and preferences: This recommendation places a relatively high value on probable reduction in symptoms of allergic rhinitis and the potential prevention of the development of asthma, and relatively low value on avoiding adverse effects in children and resource expenditure." *Recommendation on page 97**:*** "In patients with allergic rhinitis and asthma, we suggest subcutaneous specific immunotherapy for treatment of asthma (conditional recommendation / moderate quality evidence). Underlying values and preferences: This recommendation places a relatively high value on reducing the symptoms of asthma, and a relatively low value on avoiding adverse effects and limiting the cost of subcutaneous specific immunotherapy. In patients who are more averse to the side effects of		

Guidelines, First Author, Publication Year, Country	Diseases	SCIT Allergens	Recommendations	Level of Evidence	Grade of Recommendations
			subcutaneous specific immunotherapy an alternative choice may be equally reasonable. Remarks: Subcutaneous specific immunotherapy may also be used in patients with asthma and concomitant allergic rhinitis for treatment of rhinitis. Resource limitations will have stronger implications for the implementation of this recommendation."		

AAAAI = American Academy of Allergy, Asthma and Immunology; ACAAI = American College of Allergy, Asthma and Immunology; JCAAI = Joint Council of Allergy, Asthma and Immunology; AR = adverse reaction; HDM = house dust mite; NR = not reported; SCIT = subcutaneous immunotherapy; UK = United Kingdom; US = United States

Note: Levels of evidence:
2++: High-quality SR of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is casual.[58]
B: indicates a body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+ (systematic reviews, meta-analyses or RCTs with low or very low risk of bias).