Allergen immunotherapy: an updated review of safety

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Purpose of review
Allergen immunotherapy is the only modality that can modify the immune response upon exposure to aeroallergens and venom allergens. This review will update the allergist on recent studies evaluating safety of sublingual and subcutaneous allergen immunotherapy.

Recent findings
Multiple clinical trials and retrospective studies have been published evaluating overall safety of these therapies. The risk of systemic reactions with subcutaneous immunotherapy remains quite low, but near-fatal and fatal anaphylaxis does occur, requiring physicians to be aware of potential risks for such events. Sublingual immunotherapy has a high incidence of local site application reactions, but severe anaphylactic events are very uncommon.

Summary
Subcutaneous immunotherapy and sublingual immunotherapy are beneficial in treating allergic rhinitis and venom hypersensitivity but should be administered only by physicians familiar with potential risk factors and able to manage treatment-related local and systemic allergic reactions.

Keywords
allergen immunotherapy, safety, subcutaneous immunotherapy, sublingual immunotherapy

INTRODUCTION

Allergic rhinitis is one of the most prevalent chronic illnesses, ranking fifth in the United States, and accounting for significant estimated costs (6.1–11.2 billion dollars) [1,2]. Allergic rhinitis is also a major predictor and risk factor for asthma, further expanding its potential economic impact.

Allergen immunotherapy (AIT) is the only modality that can modify TH2-directed immune responses and reduce allergic nasal and ocular symptoms upon exposure to aeroallergens. The two major AIT modalities used in clinical practice are subcutaneous allergen immunotherapy (SCIT) and sublingual allergen immunotherapy (SLIT). Although both approaches have been found to be efficacious in reducing both symptoms and the need for rescue medications, risk of rare systemic reactions following administration is a significant patient safety concern.

SUBCUTANEOUS ALLERGEN IMMUNOTHERAPY

SCIT was first introduced by Noon and Freeman [3] over 100 years ago, when grass pollen-allergic patients were inoculated with grass pollen extracts. The use of SCIT in the present day involves administering increasing amounts of allergen extract, eventually attaining an optimal 'maintenance dose' in the range of concentrations previously demonstrated to be clinically effective for a specific treatment allergen. This approach has effectively been used in clinical practice for decades for treatment of patients with allergic rhinitis, allergic asthma, and stinging insect anaphylaxis. For seasonal allergic rhinitis, 3 years of SCIT or SLIT with grass pollen has been shown to offer continued sustained clinical benefit for up to 2 years after discontinuation [4].

The benefits of SCIT must be weighed against the real risks of rare life-threatening systemic allergic reactions and fatal anaphylaxis. Between 1990 and

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KEY POINTS

- Both SCIT and SLIT are efficacious in treatment of allergic rhinitis.
- Although the safety profile of SCIT has improved with development of practice guidelines, physician administering the therapy should be cognizant of risk factors for severe adverse reactions.
- SLIT has a favorable safety profile with a higher rate of local reactions but low incidence of systemic reactions and should strongly be considered in treatment of allergic rhinitis, when applicable.

2001, a national survey of allergists in North America estimated that one fatal reaction occurred after every 2.5 million injection visits, averaging 3.4 fatal reactions per year [5]. Recognized risk factors for fatal reactions include uncontrolled asthma at the time of administration of injections, dosing errors, delay or inadequate administration of epinephrine during anaphylaxis, a prior history of injection-related systemic reactions, and administration of injections during peak allergy seasons [5,6].

Adverse allergic reactions to SCIT are classified as either local or systemic reactions. Large local reactions (LLRs) are defined as pruritus and/or erythema (>2.5 cm) at the site of injection and are common among recipients. As many as 26–86% of patients receiving SCIT experience local reactions [7–10]. However, in a retrospective study by Roy *et al.* [11] patients with a history of systemic reactions had a rate of systemic reactions that was four-fold greater than those without a history of systemic reactions, and one-third of these systemic reactions had been preceded by LLRs. Although conflicting data exist on risks of prior LLRs, practice guidelines recommend that there is generally no need for dose adjustment of SCIT, as such adjustments have not demonstrated significant reduction in the risk of subsequent systemic reactions [9,12,13]. Nevertheless, it is reasonable to repeat or adjust the dose for individual patients considered to be at greater risk for a systemic reaction.

The rate of SCIT-associated systemic reactions of varying severity is relatively low at 0.1–0.2% with conventional build-up protocols [14]. The rate of systemic reactions is increased with accelerated cluster build-up regimens [3,15,16]. Due to the persistent concern regarding serious or fatal systemic reactions, a North American surveillance project was initiated to annually survey fatal SCIT reactions among certified allergists and data for the years 2008–2013 have been reported [17▪]. During this period, two direct reports of fatal reactions were confirmed in patients treated by allergists, and two indirectly reported events occurred under the care of nonallergists. Although this survey could be criticized for variable and low respondent rates, these data suggest an apparent decrease in the number of injection-related fatal events among practicing allergists when compared with the aforementioned 12-year retrospective survey of 1990–2001. Although unproven, this trend could be explained by guideline recommendations emphasizing careful preinjection screening and the withholding of injections from patients with uncontrolled asthma, which is widely considered the most important risk factor for fatal reactions [5,13].

One important finding from these surveys was that 14% of reported systemic reactions began 30 min after injection administration. Most of these late-onset systemic reactions were rated as mild or moderate in severity, none was fatal, and patients rarely self-administered epinephrine during these events [18]. This observation and other reports have encouraged debate on whether all patients receiving SCIT should be prescribed epinephrine autoinjectors [19]. Current guidelines do not recommend routine prescription of self-injectable epinephrine and state that the decision to prescribe epinephrine to patients receiving SCIT should be at the discretion of the physician [13].

A recent report from the national surveillance study [17▪] has identified characteristics of systemic reactions associated with SCIT. During years 4 and 5, the annual survey project has utilized the five-level grading system developed by the World Allergy Organization (WAO) to assess the severity of reported systemic reactions with Grade 1 representing mild reactions and Grade 5 designated as a fatal event [20]. Data from years 4 and 5 revealed that one life-threatening Grade 4 systemic reaction was reported in every 100 000 injection visits [17▪]. It was noteworthy that clinical practices that never administered injections to uncontrolled asthmatics reported significantly fewer severe systemic reactions (Grades 3 and 4 in severity) compared with other practices. Practices that reduced allergen SCIT doses in highly sensitized patients during peak pollen seasons also experienced fewer systemic reactions [17▪].

Rodriguez *et al.* [21] conducted a prospective European survey in over 1500 patients evaluating the safety data of AIT in the pediatric population (aged 18 or younger). Both SCIT and SLIT were used for single-allergen allergic rhinitis in 90% of patients, and while 1.53% of the patients experienced 29 systemic reactions (respiratory and skin symptoms were the most common), only three were

identified with anaphylaxis, two of which were treated with epinephrine. The risk of systemic reactions was found to be lower in dust mite-sensitized patients compared with pollen-allergic patients.

SUBLINGUAL IMMUNOTHERAPY

SLIT is another form of immunotherapy used in 45% of patients receiving allergen immunotherapy in Europe. SLIT-tablet formulations have only recently been approved by the FDA, but their current use in the United States is not as widespread as SCIT. In well designed, double-blind, placebo-controlled trials, treatment with SLIT tablets reduce both symptoms scores and medication requirements in patients with seasonal allergic rhinitis caused by grass and ragweed pollen and nasal/ocular symptoms in patients with perennial allergic rhinitis due to house dust mite (HDM). In the United States, efficacy and safety have been demonstrated in children for grass SLIT tablets, and studies examining efficacy and safety of ragweed tablets are currently underway in this population.

SLIT has a more favorable safety profile than SCIT. When considering severe systemic reactions, patients receiving SLIT appear to be at considerably lower risk than patients receiving SCIT. One recent review documented 11 reported cases of nonfatal anaphylaxis, per the WAO criteria, out of 1 billion SLIT doses given since 2000 [22]. A comprehensive review estimated that 2.7 reactions occur per 1000 SLIT doses, and of these reactions, only 0.056% were classified as severe (i.e. abdominal pain, vomiting, urticaria, and uvular edema) [23]. The most commonly reported reactions to SLIT are local adverse reactions involving the oromucosal or gastrointestinal regions. These tend to be mild in nature and occur most frequently in the build-up phase of treatment [24,25]. Lower gastrointestinal symptoms such as diarrhea, nausea, and abdominal pain may be reported, and while these symptoms may be suggestive of a mild systemic reaction, the WAO recommends that these be defined as local reactions unless accompanied by other systemic manifestations [26]. Despite the lessened risk of systemic reaction, 3% of patients discontinue therapy due to local reactions, though one placebo-controlled trial reported a 6% discontinuation rate [27,28].

More recently, multiple large placebo-controlled studies have demonstrated both the safety of SLIT in patients with seasonal and perennial allergic rhinitis. In a large trial of 1500 children and adults treated with SLIT grass tablets for seasonal allergic rhinitis, Maloney *et al.* [29] reported local reactions in 79% of treated patients, defined by throat irritation, oral pruritus or paresthesia, mouth edema, and ear pruritus. These were generally transient and self-resolved. There were no instances of severe treatment-related anaphylaxis present in this trial, but 6% of individuals discontinued treatment due to treatment-related local adverse reactions.

SLIT also appears to present no greater risk for adverse reactions in well controlled asthmatics participating in published clinical trials. A post-hoc analysis of eight trials using SLIT-tablet treatment for Timothy grass allergic rhinitis with or without conjunctivitis evaluated the frequency of adverse reactions in adult and pediatric patients with and without reported asthma [28]. Of the individuals evaluated, 24% of adult patients and 31% of pediatric patients had well controlled, mild asthma, and these patients did not have an increased rate of treatment-related adverse reactions when compared to individuals without asthma. In a large double-blind placebo-controlled (DBPC) trial, patients with uncontrolled HDM allergy-related asthma were randomized to either placebo or HDM SLIT-tablet therapy at two doses (six SQ-HDM and 12 SQ-HDM) in addition to inhaled corticosteroid (ICS) with salbutamol [30▪▪]. During the last 6 months of the trial, ICS was reduced and then weaned completely. Patients receiving active HDM SLIT-tablet treatment versus placebo had increased time to first moderate or severe asthma exacerbation during ICS reduction. The most frequent adverse event was mild to moderate oral pruritus (13% in six SQ-HDM group, 20% in 12 SQ-HDM group), mouth edema, and throat irritation. No anaphylactic episodes, severe systemic allergic reactions, reactions requiring epinephrine, or local reactions compromising the airway were reported. Out of the 28 participants who reported serious adverse events during the trial, two in the six SQ-HDM group and one in the 12 SQ-HDM group were thought to be treatment-related – arthralgia and moderate laryngeal edema in the former, moderate asthma in the latter.

Like the previously mentioned study, a DBPC multicenter trial of HDM SLIT of patients with allergic rhinitis showed that this treatment was generally well tolerated in the entire study population, including patients with reported history of asthma [31]. The incidence of local treatment-related adverse events was 84%: these were characterized as mild or moderate. Seven of 1400 individuals were administered epinephrine; three systemic reactions were attributed to the active treatment product.

Although the previous studies focused on monotherapy SLIT, another trial examined simultaneous treatment with both Timothy grass and ragweed tablets [32]. The rate of local reactions was as high as 71%; however, severe swelling, systemic allergic reactions, asthma attacks, or reactions requiring

epinephrine were not reported. The authors concluded that sequential treatment with grass SLIT tablets followed by concomitant treatment with ragweed tablets was well tolerated.

VENOM IMMUNOTHERAPY

Although not an aeroallergen, subcutaneous immunotherapy with hymenoptera venoms is generally well tolerated by most patients with a history of stinging insect anaphylaxis. A major concern has arisen among venom allergic patients with systemic mastocytosis who have been reported to be at high risk for severe systemic reactions to field stings as well as after subcutaneous venom immunotherapy (VIT) injections. Verburg *et al.* [33▪▪] reported that a rush VIT build-up protocol with wasp venom was safely accomplished in nine patients with cutaneous mastocytosis and/or systemic mastocytosis. One patient with cutaneous and indolent systemic mastocytosis experienced a systemic reaction upon injection during the updosing phase that responded rapidly to treatment. This patient successfully continued treatment following dose adjustment. As such, the authors felt that this form of AIT could be successfully administered in patients with cutaneous mastocytosis; however, caution should be exercised in patients with systemic mastocytosis.

Compared with wasp VIT, honeybee VIT injections present a relatively higher risk of systemic reactions, although the reasons for this are not well understood. One study [34▪▪] evaluated the build-up phase of ultrarush honeybee VIT through comparison of systemic reactions to immunological, patient-specific, and sting-specific factors in 93 patients. Out of the 13 patients who experienced severe systemic reactions, five discontinued the therapy. The basophil activation (CD63) assay was the predictor of severe systemic reactions with VIT; short interval between the sting and onset of symptoms (<5 min) and low specific IgE to rApi m1 were also associated with severe systemic reactions. The authors recommended routine measurement of basophil CD63 activation sensitivity prior to administration of honeybee VIT to identify patients at high risk for severe systemic reactions during treatment.

CONCLUSION

Ongoing development of older and newer modalities of allergen immunotherapy for treating allergic disorders requires rigorous evaluation of safety both during clinical trials and through post-marketing surveillance. This review highlighted recent evidence examining local and systemic reactions associated with SCIT and SLIT. SLIT-tablet formulations have good safety profiles and are approved for self-administration in Europe and North America. Identifying predictors of risk for severe AIT reactions is essential and can enable implementation of quality improvement measures in clinical practice aimed at reducing future risk.

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Conflicts of interest

D.I.B. is a medical adviser for Merck, Circassia; investigator for Clinical trials Merck, Circassia, Allergy Therapeutics, and Director for AAAAI/ACAAI Allergy Immunotherapy Surveillance Study. C.J. has no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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