



Anaphylaxis: still a ghost behind allergen immunotherapy

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Purpose of review

Allergen immunotherapy has been shown to be an effective treatment for respiratory allergies and Hymenoptera venom allergy. However, concern regarding its potential to cause anaphylaxis may limit its use. This review aims to assess whether anaphylaxis is still a worry when administering subcutaneous (SCIT) and sublingual immunotherapy (SLIT).

Recent findings

Retrospective surveillance surveys and one ongoing North American prospective study have helped to characterize the incidence and risk factors for fatal and nonfatal systemic reactions to SCIT. The latest rate of very severe, World Allergy Organization grade 4, systemic reactions was similar to the previously reported rates of near-fatal reactions, that is, 1 in 1 million injections. Regarding SLIT, no fatalities have been reported. Case reports of anaphylaxis in clinical practice and in some clinical trials have been described; however, given the number of doses administered daily throughout the world, the number is very small.

Summary

Identification of possible risk factors and the introduction of safety guidelines and practice parameters have enabled the reduction in immunotherapy related systemic reactions. However, it is important that clinicians remain vigilant when administering immunotherapy and should be prepared to provide emergency treatment if required.

Keywords

allergen immunotherapy, anaphylaxis, safety, subcutaneous, sublingual

INTRODUCTION

Allergen immunotherapy (AIT) involves the administration of increasing amounts of allergen in individuals allergic to that specific allergen in order to achieve long-term immune tolerance. Hypersensitivity reactions are, therefore, a possible risk when administering such a treatment. These reactions can vary in severity from mild to life-threatening, or even lead to death. Unfortunately, some fatal anaphylactic reactions after subcutaneous immunotherapy (SCIT) injections have occurred in the last 100 years of its use. Even though such serious or life-threatening systemic reactions to SCIT are rare, concern over such events may unnecessarily limit the use of this effective treatment [1].

In this review, we will examine the incidence of anaphylaxis including fatal reactions following the administration of SCIT for respiratory allergies and Hymenoptera venom allergy. However, accurate estimates of this have been difficult because of lack of a standardized grading system and the heterogeneous reporting systems used by the different

studies worldwide. Nevertheless, some factors have been identified as increasing the risk or severity of systemic reactions. These will be discussed further and recommendations for reducing the risk of anaphylaxis will be explored.

Sublingual immunotherapy (SLIT) has been increasingly used in European countries over the last two decades. SLIT is generally considered to have a better safety profile than SCIT [2]. In SLIT, most reactions are local and transient. No fatalities have been reported following the administration of SLIT, but some case reports of anaphylaxis have been published.

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KEY POINTS

- The rate of very severe, World Allergy Organization grade 4, systemic reactions is estimated to be 1 in 1 million SCIT injections.
- Risk factors for fatal reactions following SCIT include uncontrolled asthma, dosing during peak pollen seasons, prior systemic reactions to SCIT, epinephrine administration being delayed or not given, dosing or administration errors, inadequate waiting times after injections, reactions that began after 30 min, administration in medically unsupervised settings, and concomitant beta-blocker usage.
- Systemic reactions to SLIT are rare and side-effects mostly consist of mild, local reactions, but cases of anaphylaxis have been reported.

ANAPHYLAXIS AND FATALITIES FOLLOWING SUBCUTANEOUS IMMUNOTHERAPY

The exact incidence of anaphylaxis following the administration of SCIT is not known. Over the last few decades, many surveillance studies have attempted to characterize the incidence of risk factors for anaphylaxis and death from SCIT [3[¶]]. However, as most of the data have been collected retrospectively using surveys, incidence estimates may not be accurate. Furthermore, the use of different extracts, schedules, places of administration, as well as different definitions and classifications of allergic reactions make analysis of these more difficult [4].

In 1986, the Committee on the Safety of Medicines in the United Kingdom reported 26 SCIT-related anaphylactic deaths since 1957, 11 of these occurring since 1980 [5]. In most of these cases, adequate facilities for cardiorespiratory resuscitation were not available. Asthmatic patients seemed to be particularly susceptible to severe adverse reactions.

In the United States, based on the results of retrospective surveys, at least 82 confirmed fatalities from SCIT were reported by the surveillance studies from 1945 to 2001. These studies [1,3[¶],6–8] combined estimated that a fatal anaphylactic reaction to SCIT occurred in every 2 million to 2.5 million injections or 3.4 SCIT-related deaths per year. Six fatalities were retrospectively reported that transpired between 2001 and 2007 [9].

From 2008, a web-based prospective surveillance programme was initiated in North America amongst members of the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI) to monitor annual incidences of systemic

allergic reactions of varying severity related to SCIT and allergen skin testing [9]. In the most recent AAAAI/ACAAI surveillance study from 2008 to 2012, data were gathered on 23.3 million injection visits. A shortened version of the World Allergy Organization (WAO) classification system for systemic allergic reactions was adopted in 2011 (grade 1 – mild; grade 2 – moderate; grade 3 – severe; and grade 4 – very severe). One confirmed fatality occurred in 2009. Overall systemic allergic reaction rates remained stable at 0.1%. The rate of very severe, WAO grade 4, systemic allergic reactions was similar to the previously reported rates of near-fatal reactions (1 in 1 million injections) [10^{¶¶}].

A Cochrane systematic review of SCIT for allergic rhinitis found that adrenaline was given to 0.13% (19 of 14085 injections) of those on active treatment and in 0.01% of the placebo group for the treatment of adverse events. There were no fatalities [11]. Regarding the use of SCIT for asthma, it was calculated that if nine patients were treated with SCIT, one would be expected to develop a systemic reaction of any severity [12].

In a recently published systematic review of randomized controlled trials assessing the effectiveness and safety of SCIT for allergic rhinoconjunctivitis and asthma, 13 anaphylactic reactions in 4 trials out of the 61 included studies (total 3577 individuals) were identified. No deaths were reported [13].

Regarding venom immunotherapy (VIT), a Cochrane review found that 9.3% of participants treated with VIT and 0.7% of participants treated with placebo or no treatment suffered a systemic reaction to treatment [14]. A further analysis of 11 observational studies as part of the same review found systemic adverse reactions occurred in 14.2% participants treated with bee venom VIT and 2.8% treated with wasp venom VIT [14].

A recent review of 12-year data on 818 buildup cycles (8504 VIT injections) identified that 0.6% of the buildup cycles were complicated by moderate-to-severe anaphylaxis. This occurred more rapidly than urticaria and predominantly during honeybee VIT. Patients with moderate-to-severe anaphylaxis more frequently reported severe index sting reactions and had higher baseline serum tryptase concentrations [15].

ANAPHYLAXIS FOLLOWING SUBLINGUAL IMMUNOTHERAPY

SLIT is generally considered to have a better safety profile than SCIT. However, in contrast to SCIT, SLIT is usually self-administered by the patient at home and the reporting of adverse reactions is dependent

on the patient's or a family member's recollection through questionnaires or accurate diary logs. Therefore, there is potential for inaccurate accounting of SLIT adverse events on the basis of recall bias and compliance with diary documentation [16].

Cox *et al.* [16] identified 66 published SLIT studies, in which information on safety was included (representing 4378 patients and approximately 1 181 654 doses). No serious life-threatening reactions were reported. A rate of one SLIT-related serious adverse reaction per 384 treatment years was observed; these mainly consisted of asthmatic reactions, abdominal pain or vomiting, uvula oedema, and urticaria.

A Cochrane review of SLIT for allergic rhinitis with a total of 2333 SLIT and 2256 placebo participants found no reports of severe systemic reactions or anaphylaxis. Furthermore, none of the systemic reactions reported required the use of adrenaline [17].

A recent systematic review of SLIT for allergic rhinoconjunctivitis and asthma including 63 studies with 5131 participants concluded that the local reactions were more frequent in patients receiving SLIT (range 0.2–97%) than in the comparator groups (range 3–38.5%). Systemic reactions were rarely reported, but were more common in the groups receiving SLIT than in comparator groups. There were no reported episodes of anaphylaxis, life-threatening reactions, or death in any treated patients across studies [18].

In several postmarketing surveys including a total of 1795 patients, a total of 72 systemic reactions were reported. However, epinephrine was administered only in two cases (0.1%) [19].

Twelve nonfatal cases of systemic allergic reactions described as anaphylaxis because of SLIT have been published [20,21]. Epinephrine was not used in all of these cases. Furthermore, some of these deviated from the standard clinical practice with use of nonstandardized extracts, allergen mixtures, rush protocols, overdose, and patients who had previously discontinued SCIT because of serious adverse reactions [20].

RISK FACTORS FOR ANAPHYLAXIS FOLLOWING ALLERGEN IMMUNOTHERAPY

The risk of experiencing systemic allergic reactions may vary according to the types of allergens, potency of the injected allergens, modes of allergen preparation and modification, and dosing protocols.

The North America surveillance studies have provided useful information regarding the risk factors for fatal reactions following SCIT. The key risk

factors were uncontrolled asthma (38–92%), dosing during peak pollen seasons (29–41%), prior systemic reactions to SCIT (28–42%), epinephrine administration being delayed or not given (7–18% not given; 33% delayed), dosing or administration errors (6–27%), inadequate waiting times after injections (6–13%), reactions that began after 30 min (6–18%), administration in medically unsupervised settings (4–18%), and concomitant beta-blocker usage (0–13%) [3[¶]].

However, it is difficult to extrapolate or relate such findings to risk factors for SLIT, as the factors may or may not differ from SCIT ones [20]. No patient-related risk factors for systemic reactions have been clearly defined, even if uncontrolled asthma, oral lesions or infections, and previous severe SCIT-related adverse events can be considered specific risk factors [2,19].

Uncontrolled asthma

Although AIT has been shown to reduce asthma symptoms, bronchial hyperreactivity, and the need for asthma medications in patients responding to treatment, uncontrolled asthma is a strong risk factor for fatal and near-fatal SCIT reactions [3[¶]]. Three surveys have found that fatal and near-fatal reactions from immunotherapy injections were more common in patients with severe or labile asthma. Out of 24 confirmed fatalities from SCIT reported by Lockey *et al.* [6], 50% occurred in patients with concurrent asthma. Reid *et al.* [7] reported that 77% of fatalities between 1985 and 1989 occurred in asthmatic patients. In another survey, asthma was present in 46% of near-fatal reactors and in 88% of fatal reactors [22]. Indicators of uncontrolled asthma were more common amongst patients with fatal reactions compared with near-fatal reactions, including reports of poor asthma control, labile asthma, prior emergency room visits, and prior hospitalization [22]. Thus, AIT should not be initiated in patients with poorly controlled asthma symptoms. The latest AIT Practice Parameter recommends that asthma control is assessed at each injection visit [23].

Previous reactions to allergen immunotherapy

Some studies [24,25] have found that patients who had systemic allergic reactions to SCIT were more likely to have experienced prior large local reactions (LLRs) or previous injection-related systemic allergic reactions. In another study [26], the risk of an immediate systemic allergic reaction was higher in patients who had an immediate systemic allergic

reaction with the previous dose, and late systemic allergic reactions were associated with late local reactions with the previous dose. Calabria *et al.* [27] studied individuals who had both LLRs and systemic reactions, and compared them to a control group who had a systemic reaction but no LLR. They found the rate of systemic reactions was 1.3% for those with a previous LLR and 0.4% for those without a LLR. It was concluded that although LLRs do not predict systemic allergic reactions, a subgroup (41.7%) of LLR patients experience a higher frequency of systemic allergic reactions during their immunotherapy course. Similarly to a previous study [28], this association occurred irrespective of whether a dose adjustment protocol was used for LLRs.

Dosing during peak pollen seasons

Although there are conflicting data from prospective, single-centre studies, surveillance data have suggested an increased risk for severe and life-threatening SCIT reactions during peak pollen seasons [3[•]]. The most recent AAAAI/ACAAI Surveillance Study [10^{••}] of SCIT found that dose adjustment during pollen seasons was associated with fewer WAO grade 3 or 4 systemic allergic reactions ($P < 0.001$). The AIT practice parameter states that 'SCIT given during periods when the patient is exposed to increased levels of allergens to which they are highly sensitive might be associated with an increased risk of systemic reactions' [23]. Dose adjustments are therefore recommended.

Dosing errors

Dosing errors account for a significant number of anaphylactic reactions to AIT. Amin *et al.* [22] reported that dosing errors occurred in 25% of near-fatal reactions. In a retrospective survey of practising allergists, 58% reported at least one event when a patient had been given an injection meant for another patient, and 74% reported at least one incorrect dose administration given to their patients over a 5-year span. The effect on patients ranged from local reactions to one fatality [29].

A report of the frequency of AIT administration errors in a practice found these to occur between 0.1 and 0.2%. The rate depended on the reporting mechanism. The two common situations that increased error rates were atypical dosing protocols and bottle changes [30].

Concomitant medications

Beta-blockers are thought to impair responses to beta-agonist agents like epinephrine and potentially

aggravate anaphylaxis, thus contributing to more severe and treatment-refractory SCIT reactions. Surveillance studies have reported fatalities in patients who were receiving SCIT whilst taking beta-blockers, although other studies have not confirmed an increased risk [3[•],23]. It is important to note that in a case of anaphylaxis, the relative contraindication extends not only to unselective but also to relatively selective beta-adrenergic blockers, as there is concern not only with the beta-adrenergic effect on smooth muscle in the lungs but also with the beta-adrenergic effect on the cardiovascular system [4].

There are some special circumstances in patients requiring VIT, in which withdrawal of beta-blockers may put the patient at risk. The AIT Practice Parameter recommends that 'concomitant use of beta-blockers and AIT should be carefully considered from an individualised risk/benefit standpoint'. Of note, individuals have successfully undertaken VIT alongside treatment with beta-blockers [31]. In such circumstances, glucagon must be readily available to treat refractory anaphylaxis.

Concomitant treatment with angiotensin-converting enzyme (ACE) inhibitors in some studies has been associated with more severe systemic allergic reactions during VIT [32] and with the highest risk for VIT failure [33]. However, other studies have failed to show a correlation between ACE inhibitor therapy and a higher incidence of anaphylaxis, either during VIT or during other types of immunotherapy [34]. A recent study [35] did not find any evidence of an ACE inhibitor-mediated increase of VIT-related systemic allergic reactions, supporting the continued use of these drugs throughout VIT.

Dose of allergen

Of the reported fatalities, some have occurred during up dosing, others during the maintenance phase as well as with the initial dose of SCIT, and even with a lower dose than the previous injection [3[•]]. In one survey, 58% of near-fatal reactions occurred in patients receiving maintenance doses [22]. It has been speculated that a greater incidence of systemic allergic reactions in maintenance vials may be because of the higher doses of allergen administered [3[•],36]. However, as it is impossible to predict when the risk is higher, clinicians should be vigilant at all times.

Immunotherapy schedules

Previous SCIT studies have demonstrated a higher risk of systemic allergic reactions with rush buildup for aeroallergens; however, there has been less

consensus regarding the risk of systemic allergic reactions with cluster regimens [23,37]. Feng *et al.* [38] performed a meta-analysis of the cluster SCIT studies for allergic rhinitis. There were no differences in the incidence of either local adverse reaction or systemic adverse reaction between the cluster group and control group. In the most recent AAAAI and ACAAI Surveillance Study [10¹¹] of SCIT, a lower target dose during cluster buildup before transitioning to maintenance was associated with a lower risk of WAO grade 3 systemic allergic reactions ($P=0.07$).

In contrast to aeroallergens, rush protocols for administration of stinging Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions [23].

Ultrarush SLIT schedules for aerollergens have been used in some studies. These have been well tolerated in both adults and children and no cases of anaphylaxis were observed [39–41].

Degree of sensitivity

The degree of allergen sensitivity has been considered a risk factor for anaphylactic reactions occurring during AIT [42]. In a retrospective review of 16 375 SCIT injections, 20 patients experienced 46 systemic reactions. All severe reactions occurred within 30 min. The estimated odds of systemic reaction were almost six times higher for patients with more than 33% 3–4+ positive skin tests. For each additional 4+ skin test, the estimated odds for systemic reaction increased by 17%. It was concluded that skin test patterns demonstrating a greater number of larger skin test responses to inhalant skin testing are associated with significantly elevated risk for systemic reaction in patients receiving SCIT [43]. Thus, dose adjustments should be considered in such patients.

MANAGEMENT

Most systemic reactions including severe ones occur within 30 min after an injection. However, fatal reactions can begin later than 30 min after injection, and systemic reactions can occur in rare instances more than 2 h after the injection is given [4]. In two prospective studies [44,45], 10–23% of anaphylactic reactions to SCIT were biphasic. The second phase of these reactions was mild and did not require treatment with additional epinephrine.

Following the report of the fatalities in 1986, a mandatory 2-h postinjection waiting period was applied in the UK. However, this led to a reduction in the use of immunotherapy for years until a 1-h standard observation period (which is now the

current practice) was accepted [46]. In North America, a postinjection observation period of 30 min is recommended [23].

Recognition and prompt management of anaphylaxis with intramuscular administration of epinephrine are important to prevent fatalities. A delay in the administration of epinephrine is considered a risk factor for poor outcomes amongst patients experiencing anaphylaxis and in some studies [3¹,47] it is a risk factor for biphasic reaction. It is also important that the patient recognizes the early manifestations of an anaphylactic episode and should be told to report any symptoms immediately [4].

It is worth noting that some of the fatalities occurred when SCIT was administered at home [6–8]. The Practice Parameter states that AIT ‘should be administered only by healthcare professionals trained in the recognition and treatment of anaphylaxis, only in healthcare facilities with the proper equipment for the treatment of anaphylaxis, and in clinics with policies and procedures that minimize the risk of anaphylaxis’. The applicability of this statement to SLIT, however, is uncertain.

Premedication with a nonsedating H1-antihistamine is suggested for selected patients, including those experiencing recurrent LLRs or mild systemic allergic reactions to prior injections [48–50]. However, there is insufficient evidence to conclude that pretreatment with H1-antihistamines can effectively prevent severe near-fatal or fatal anaphylactic reactions [23].

The use of omalizumab, anti-IgE antibody therapy has been evaluated in several trials as a possible addition to conventional SCIT to improve safety. In one study [51], the use of omalizumab 9 weeks before starting ragweed AIT improved the safety of rush SCIT by reducing systemic allergic reactions up to five-fold. In a double-blind, placebo-controlled trial of 248 allergic asthmatic patients whose symptoms were not controlled by inhaled corticosteroids, use of omalizumab was associated with fewer systemic allergic reactions to AIT and enabled more patients to achieve the target maintenance dose [52].

Several case reports suggest that in patients who experienced a systemic allergic reaction following a bee or wasp venom sting and who failed to tolerate VIT, co-administration of omalizumab was able to prevent anaphylaxis during VIT [53]. A case report of omalizumab mitigating anaphylaxis during ultrarush honey bee VIT in monoclonal mast cell activation syndrome [54] has also been published. However, in some cases, premedication with omalizumab has not been successful [55].

Another potential use of omalizumab is as pretreatment with oral immunotherapy (OIT). Phase 1

data have demonstrated that rush OIT to multiple foods with 16 weeks of treatment with omalizumab could allow fast desensitization in individuals with multiple food allergies [56].

CONCLUSION

Given the actual mechanism of immunotherapy, concern regarding the potential of AIT-inducing anaphylaxis is likely to remain always. However, there is currently an increased drive to produce immunotherapy products that are less allergenic whilst retaining the potential for developing tolerance. Different routes such as epicutaneous, intralymphatic, and OIT are also being studied.

In the meantime, clinicians should follow the recommendations about the use of AIT and aim to minimize to the best of their abilities any possible potential risk factors. AIT should always be administered in appropriately equipped facilities, in which adrenaline and resuscitation support are available.

Although SLIT appears to be less implicated in causing anaphylaxis than SCIT, it is important to administer the first dose under medical supervision as it is currently a common practice in many countries. Patients should be educated regarding the symptoms of anaphylaxis and should be advised to seek medical help early.

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Conflicts of interest

M.A.C. has received consultancy and lecture fees from ALK, Stallergenes, Merck, Allergopharma, and HAL Allergy. M.M. has no conflicts of interest.

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