

An update on the safety of specific immunotherapy

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Purpose of review

As allergen sublingual immunotherapy becomes more widely used in Europe and draws the attention of physicians of the USA, it is important to compare and contrast the safety aspects of this therapy versus allergen subcutaneous immunotherapy.

Recent findings

There are reports of severe systemic reactions associated with sublingual immunotherapy, but no fatalities. There are various studies of systemic reactions, including those that result in death, associated with subcutaneous immunotherapy over its nearly 100-year worldwide experience. Local reactions are common to both forms of the treatment.

Summary

If both forms of therapy are equally effective, a cost (including safety aspects) – benefit analysis of sublingual immunotherapy versus subcutaneous immunotherapy is necessary to determine how best to incorporate both forms of specific immunotherapy into the management of allergic patients. Adherence to published guidelines will reduce the likelihood of adverse reactions.

Keywords

adverse reactions, safety, subcutaneous immunotherapy, sublingual immunotherapy

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Introduction

Specific allergen immunotherapy via the subcutaneous route of delivery is an immune modulating form of therapy for allergic rhinitis, allergic asthma and Hymenoptera hypersensitivity. Due to safety concerns, the British Committee for the Safety of Medicines established restrictive regulations on the administration of subcutaneous immunotherapy (SCIT) in Great Britain, based on a report of 26 fatalities associated with SCIT from 1957 to 1986. This ruling sharply curtailed the use of SCIT in England. During the same year as this 1986 ruling, the first controlled trial of an alternative delivery of allergen vaccines, sublingual immunotherapy (SLIT), was published. This review will focus on the safety characteristics of these two forms of immunotherapy as reported in clinical trials, postmarketing surveys and questionnaires.

Subcutaneous immunotherapy

Historically, immunotherapy is the subcutaneous administration of an allergen vaccine, beginning with a very dilute concentration and gradually increasing the dose on a weekly or bi-weekly basis (build-up phase), finally reaching a maintenance dose that is continued for 5 years or more. SCIT is effective to treat allergic rhinitis, allergic asthma and Hymenoptera hypersensitivity. Unlike

pharmacotherapy, SCIT targets the underlying cause of the disease and has proven long-term benefits. Because immunotherapy targets individuals with severe disease, administration of these allergen vaccines can cause adverse, allergic reactions and even death.

Adverse reactions to subcutaneous immunotherapy

Studies have evaluated adverse reactions, seeking to determine the frequency, type, severity and risk factors associated with SCIT. Local swelling at the site of an allergen vaccine injection is common and does not require specific therapy or adjustment in dosing. However, systemic reactions involving organ-specific systems distant from the injection site can be potentially serious, ranging from rhinorrhea to severe asthma and anaphylactic shock. The adverse reaction rate depends on a variety of factors, including degree of allergic sensitivity, the dose schedule, the allergen vaccine and formulation and the presence of asthma (Table 1).

A study of 1410 Hymenoptera allergic patients on 3 years of Food and Drug administration (FDA)-standardized venom immunotherapy showed that 171 of these patients experienced 327 systemic reactions, 28 of which were classified as severe, nonfatal [1]. The incidence of skin involvement (pruritus, urticaria or angioedema) was similar with mild, moderate or severe systemic reactions. Historic and diagnostic criteria failed to predict which

Table 1 Risk factors associated with adverse reactions to subcutaneous immunotherapy

Asthma, especially unstable or severe	Highly allergic patients
Concomitant beta blocker use	In-season exacerbated respiratory disease
Accelerated dosing schedules (e.g. rush)	High dose allergen
Injectons from new vials	Dosing errors

patient would experience a systemic reaction. The study concluded that treatment of this potentially life-threatening condition with a standardized SCIT vaccine is associated with a low incidence of adverse reactions, most of which are not serious.

A review of 38 SCIT studies, using inhalant allergens, found that the reaction rates increase as the immunotherapy schedule is accelerated and when high or optimal dose regimens (associated with efficacy) are used in highly sensitive patients [2]. The rate of systemic reactions per injection ranged from 0.05 to 3.2% in studies using a conventional schedule. Maintenance injections were associated with fewer systemic reactions than those given during the build-up period.

A study of 419 patients receiving over 9000 doses of standardized aluminum hydroxide-adsorbed grass pollen or *Dermatophagoides pteronyssinus*, using a conventional dosing schedule, demonstrated systemic reactions in 4.8% of patients ($n=20$), 84% ($n=352$) of whom had asthma [3]. Reactions occurred more often during the build-up phase ($P < 0.05$) and none were life threatening. In another study, data were collected in 4578 patients receiving SCIT over 1 year in a multiple physician office group located in Atlanta, Georgia [4]. The reaction rate was one per 1600 patient visits, or one per 47 patients, when receiving full concentration maintenance injections. This rate was significantly higher during the build-up phase, one per 32 patients. Twelve cases were severe involving hypotension or respiratory distress. Twenty-eight of the 98 patients with systemic reactions had the onset of their reaction more than 30 min after the injection, none involving hypotension.

There were 115 systemic reactions (5.2% of patients and 0.06% of injections) from 1981 to 1990 and 26 systemic reactions over the next decade (1.08% of patients and 0.01% of injections) in a report from Europe on nonfatal reactions to SCIT in 4600 patients [5]. This was a retrospective study in patients receiving alum hydroxide adsorbed vaccines from various manufacturers. The latter period, 1991–2000, was associated with fewer systemic reactions, particularly those manifested as asthma and urticaria. In neither period were there any fatalities. A study of 423 patients, receiving 2 years of SCIT, reported 53 systemic reactions in 18 patients, although 40% (21 reactions) would not have

occurred if those five patients experiencing multiple reactions had been discontinued from immunotherapy after their third systemic reaction [6].

Fatalities

Fatal reactions to SCIT have been reported and the likelihood of a fatal reaction is estimated at 1 in 2–2.5 million doses administered. The Committee on Allergen Standardization of the AAAAI collected information on 46 deaths due to immunotherapy ($n=40$) and skin testing ($n=6$) from 1945 to 1984 [7]. The data were analyzable in 24 deaths associated with immunotherapy. An error in administration of the vaccine was documented in three fatalities and was suspected in one other. The time for onset of the reaction was less than 30 min in 15 of 24, more than 30 min in 2 of 24 and not reported in 4 of 24 patients. The patient was receiving injections as part of the build-up schedule in 61% of cases.

Two additional surveys by the AAAAI found similar results, one from 1985 to 1989 and the other from 1990 to 2001, both with 17 fatalities. Asthmatic patients accounted for more than 75% of the cases, half were on build-up therapy, and more than 80% had onset of symptoms within 30 min of their injections. An extension of the 1990–2001 survey focused on reports of near-fatal reactions, defined as severe respiratory compromise, hypotension, or both requiring emergency epinephrine treatment [8]. Maintenance dosing was involved in 58%, reactions during the height of the allergy season in 46%, dosing errors occurred in 25% and there was a history of a previous systemic reaction in 9% of cases.

Sublingual immunotherapy

SLIT is administered as soluble tablets or drops under the tongue where it is held for 1–2 min and then swallowed. Currently SLIT is not approved by the FDA for use in the USA, but it has become the standard-of-care in some parts of Europe.

Initiating sublingual immunotherapy

Unlike SCIT protocols, where treatment begins with serial increasing doses over several months, SLIT has been initiated without this build-up or up dosing regimen [9,10^{*}]. However, reactions have been noted on the first dose when high-dose allergen treatment is used. Throat swelling occurred in two out of five patients initiated on a high dose of a five-grass pollen vaccine [11]. In another study, a 10-day incremental schedule was tolerated; however, severe lip edema and blisters occurred in the group initiated on high-dose therapy [12^{*}].

Local reactions to sublingual immunotherapy

Frequently reported side effects from SLIT include oral itching and irritation and range from 0 to 100% of cases

[13,14,15[•]]. Most of these remit with ongoing treatment. Patients will experience abdominal pain, nausea or diarrhea less commonly. In a placebo-controlled study using a three-grass pollen vaccine in 127 allergic rhinitis patients, the principle events were mouth and throat irritation, occurring in 69% of the actively treated versus 40% in the placebo group [16[•]]. Three of the nine patients interrupting their treatment because of adverse events were on the grass pollen SLIT. No serious events were noted. The absence of any local reaction in a study raises the question of possible underreporting and, in turn, underestimation of the adverse event potential of this form of therapy [14].

Systemic reactions to sublingual immunotherapy

Sixty-six SLIT studies involving 4378 patients were reviewed [17]. There were no serious life-threatening reactions reported. Adverse events occurred at a rate of 2.7 reactions per 1000 doses, affecting 12% of patients. Severity scales were not consistently defined with only three studies using the European Academy of Allergology and Clinical Immunology recommended grading scale for anaphylaxis: grade 1 – nonspecific, grade 2 – mild-systemic reactions, grade 3 – nonlife-threatening systemic reactions including urticaria and grade 4 – anaphylactic shock. Adverse reactions accounted for withdrawal from study participation in 3% of patients on SLIT versus 1.4% placebo. Grade 2 reactions (mostly rhinoconjunctivitis) occurred in 15 patients on SLIT, 14 on SCIT and 11 on placebo in a 2-year placebo-controlled trial of birch-induced rhinoconjunctivitis [18]. Five cases of grade 3 and one grade 4 reaction were reported in the SCIT group. There was one grade 3 reaction in the placebo group and no grade 3 or 4 reactions in the SLIT group.

A rapidly dissolving, grass tablet for SLIT, Grazax, containing approximately 15 µg of the major allergen of *Phleum pratense*, was studied in a double-blind, placebo-controlled trial in rhinoconjunctivitis patients in 55 centers in eight countries [19,20,21^{••}]. Eight hundred and eighty-five patients were randomized to the initial dose finding study. They were immediately started on the once daily maintenance dose tablets for 8 weeks prior to and during the grass pollen season [19]. Adverse events, judged by the investigators to be probably or possibly related to treatment, occurred in 66% on Grazax versus 26% on placebo. Twenty-six withdrew because of adverse events, all, but three, were on active drugs. Six hundred and thirty-four patients were randomized in a follow-up double-blind, placebo-controlled study starting 16 weeks prior to the grass season and continuing through the 8-week season [20]. The placebo was matched for taste and smell but did not contain histamine or other active ingredients. Forty-six percent of actively treated patients experienced oral pruritus versus 4% on placebo.

Reactions led to study withdrawal in 4% of patients in the active group, and all were treated with study reliever medication or analgesics; none required epinephrine.

Dahl *et al.* [21^{••}] reported on 351 of these same patients who continued on grass allergen tablets or placebo for an average of 22 months. No differences occurred between the treatment and placebo groups in adverse events during the second year of the trial. There were no serious adverse events and unlike the first year there was no predominance of local reactions (four events of oral pruritus reported).

More severe systemic reactions to sublingual immunotherapy

A severe systemic reaction associated with SLIT was first reported in the USA in 2006 [22]. A 31-year-old woman with allergic rhinitis and mild intermittent asthma was treated with a mixed vaccine containing *Alternaria tenuis*, cat, dog, and various pollens. On the third day, within minutes of self-administering six drops under the tongue, she experienced marked generalized pruritus, angioedema of her hands and feet, dyspnea, wheezing and dizziness. She responded to an antihistamine, albuterol and oral glucocorticoid. She was not examined during the reaction and decided to discontinue SLIT. The first European report of a severe systemic reaction involved an 11-year-old female with asthma and allergic rhinitis receiving a mixture of house dust mites in the morning and a seasonal pollen mixture in the night [23[•]]. One month into maintenance therapy, during the peak pollen season, within 3 min of administering the pollen drops, she developed lip swelling accompanied thereafter by chest pain, high fever, nausea and abdominal pain. She was successfully treated in the emergency room.

In another case, a 16-year-old female, with perennial allergic rhinitis and intermittent asthma, took six times the normal dose of house dust mite vaccine and within 5 min had generalized pruritus, flushing and diffuse urticaria [24^{••}]. She experienced respiratory and cardiovascular complications (blood pressure 70/40 mmHg) and was shifted to the emergency room where she became unconscious, without pulse and blood pressure. She was treated in an ICU and recovered over a 24-h period. Two additional patients experienced adverse reactions following the first dose of Grazax: (1) a 13-year-old male with rhinoconjunctivitis, within 15 min after dosing, noted tongue and eye swelling and generalized urticaria; he was treated with antihistamines; and (2) a 27-year-old female with asthma and allergic rhinitis, within minutes of dosing, developed asthma, generalized pruritus, faintness and abdominal cramps; she treated herself with an antihistamine and inhaled corticosteroid/long-acting β agonist and finally improved when she was given

Table 2 Recent studies of sublingual immunotherapy in children

Study	Subjects/# active SLIT	Age range (yrs)	Allergen used	Duration SLIT	Adverse events
Valovirta <i>et al.</i> [28]	88/65	5–15	tree mix	10–20 months (average 17 months)	oral reactions 43% versus 25% placebo; one withdrew due to abdominal pain
Ibanez <i>et al.</i> [29 [•]]	60/45	5–12	grass (<i>Phleum pratense</i>)	28 days	810 versus 18 events on placebo, abdominal pain in 8 pts. (none placebo), two withdrew (active)
Pham-Thi <i>et al.</i> [30 ^{••}]	111/55	5–15	mites	18 months	71% versus 66% placebo, oral and abdominal reactions more frequent in active group; one withdrew each group
Pajno <i>et al.</i> [31 [•]]	56/28	5–16	mites, in atopic dermatitis patients	18 months	active group only – one oral angioedema, three oral itching, resolved spontaneously; two withdrew
Roder <i>et al.</i> [32 [•]]	168/108	6–18	grass mix	2 years	only local reactions different, 39% versus 17% placebo; withdrew nine active, five placebo
Bufe <i>et al.</i> [33]	252/126	5–16	Grass (<i>Phleum pratense</i>)	6 months	no serious events; two withdrew

SLIT, sublingual immunotherapy.

epinephrine at her doctor's office where her blood pressure at presentation was 90/50 mmHg (de Groot H, personal communication).

Although two of the three published case reports above involve patients receiving multiple allergen SCIT, most studies evaluating the safety and efficacy of SLIT use single allergen vaccines. Lombardi *et al.* [25[•]] performed a postmarketing survey of patients on single versus multiple allergen SLIT to address whether multiple allergen vaccines are more likely to lead to adverse reactions. Eighty-three patients on multiple allergen therapy and 76 patients on single allergen treatment were evaluated for 3 months. The side effects did not differ between the groups.

Pediatric aspects

SLIT is particularly attractive for children because of its pain-free delivery. A study of 268 children in Italy, 2–15 years old, treated with one or at most two noncross reacting allergens for 3 months to 7 years (mean of 34 months) was associated with no serious reactions [26]. Systemic side effects occurred in eight patients (3% of patients, 0.083/1000 doses), one of which required treatment, an antihistamine for urticaria. An earlier double-blind, placebo-controlled study in 58 patients, under 12-years-old, using standardized dust mite SLIT reported 17 severe reactions among the 30 patients in the active group (defined as severe asthma, nasal symptoms or severe eye symptoms) [27]. The findings from other studies of SLIT in children show that treatment is tolerated with only the occasional patient withdrawing from treatment due to adverse events [28,29[•],30^{••},31[•],32[•],33] (Table 2).

Beyond respiratory allergens

SLIT with latex has reduced sensitivity to latex. Latex vaccine administered three times per week in 10 latex-allergic children with congenital malformations requiring

multiple surgeries resulted in two minor reactions, oral itching and minimal angioedema, that resolved spontaneously [34]. A placebo-controlled trial of 35 latex-sensitive patients, 18 assigned to liquid latex for 1 year, the rest assigned to placebo, reported oral itching and burning in two patients in the latex group and a third had lip angioedema [35[•]]. One patient in the placebo group reported an asthma episode. Using a similar 4-day induction schedule, Antico *et al.* [36] reported a patient with a severe systemic reaction 20 min after the maximum dose on the fourth day. This 36-year-old woman was successfully treated in the emergency room.

Inducing oral tolerance to foods in food allergic individuals has been partially successful with SLIT and oral immunotherapy (the food is swallowed, not held in the mouth as is done with SLIT), but falls outside the scope of this review. However, a number of studies with egg and milk have shown that patients can tolerate larger amounts of food protein after completing a gradual up dosing schedule [37–39]. A proof-of-concept trial in Hymenoptera inducing large local reaction in patients was performed using honeybee venom SLIT at five times the standard SCIT dose [40[•]]. This double-blind, placebo-controlled trial enrolled 30 patients with such reactions to honeybee stings. No side effects were noted in this 6-month trial.

Preventing adverse reactions

National and international guidelines have been introduced in the past several years to improve both the efficacy and safety of allergen immunotherapy [41^{••},42[•],43]. Careful adherence to guidelines and coordination of doctor, staff and patient roles are crucial to minimize adverse reactions, especially associated with SCIT. The safety measures to reduce the risk of an adverse reaction to immunotherapy are as follows:

- (1) Proper patient selection
- (2) Special attention to asthmatics, highly allergic patients
- (3) Awareness of clinical status on treatment days, postpone dose if unstable
- (4) Monitor patient for new medication usage, particularly, β blockers
- (5) Careful dosing – right patient, right dose
- (6) Consider dose adjustments during allergy season
- (7) Compliance with treatment schedules
- (8) Make dose adjustments for newly prepared vaccines
- (9) Early recognition and treatment of adverse reactions
- (10) Consider discontinuing therapy in repeat reactors
- (11) Remain vigilant – reactions can occur after years of maintenance therapy and more than 30 min after dosing

Many of the SCIT guidelines apply to SLIT, but additional recommendations are necessary for a therapy that is primarily given at home. For example, compliance with self-administration of allergen vaccine is an issue unique to SLIT. This issue was addressed in a 3 month study of 71 children receiving SLIT therapy. Eighty-five percent used more than 75% of their doses [44^{*}]. As illustrated earlier by the severe systemic reaction case associated with an overdose, compliance with specific doses administered may be more critical than the daily schedule of SLIT administration.

In high-risk immunotherapy situations, pretreatment with omalizumab is capable of reducing adverse events from SCIT. Starting omalizumab, prior to rush ragweed SCIT, produced a five-fold reduction in risk of anaphylaxis [45]. The same study using omalizumab prior to SLIT has not been undertaken.

Conclusion

The long history of SCIT's use has provided ample opportunity to identify adverse responses to allergic injections. Through careful adherence to new guidelines, the 20–50 year old statistics of adverse reactions should no longer be as relevant to today's practice of SCIT. Since 1990, a number of studies have borne this out. Additional data on SLIT are necessary to identify the optimal dose, treatment regimens using single allergens versus a combination of allergens and the preferred treatment schedule. Until a more standardized approach to treatment is established, it is difficult to fairly evaluate its safety profile. As long as patients can be relied upon to dose themselves correctly, preliminary evidence suggests that SLIT has a safety advantage over SCIT. Whether patients should be allowed to self-administer SLIT vaccines at home will depend on results of future studies.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 594–595).

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