

30 Adverse Effects Associated with Sublingual Immunotherapy

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HISTORICAL PERSPECTIVE

Allergen-specific immunotherapy is a biological response modifier that affects the response to allergen at the earliest steps of allergic diseases. For this reason, immunotherapy is currently a cornerstone in the management of allergic respiratory diseases and in Hymenoptera venom allergy. Since the beginning of the 20th century, allergenic vaccines were administered subcutaneously (SCIT, subcutaneous immunotherapy). The favorable clinical results rapidly resulted in the widespread use of SCIT, with this being the only form of allergen immunotherapy for many decades. Some clinicians occasionally tried routes other than subcutaneous (1-3). Since SCIT is well established in clinical practice, alternatives to SCIT generally were of limited interest (4).

In 1986, the British Committee for the Safety of Medicines officially reported 26 fatalities associated with SCIT (5). As a consequence, the risk-benefit ratio of immunotherapy was more critically questioned. The result was revision of the indications and implementation of additional safety measures, making the treatment impractical in some countries. The safety concerns with SCIT and resulting inconvenience stimulated the search for safer IT modalities, and the noninjection routes gained new interest. Although some of the adverse events (AEs) with SCIT can be avoided, others occur without explanation (6,7), contributing to the growth in interest of noninjection routes deemed to be safer. The first controlled trial with sublingual immunotherapy (SLIT) was published in 1986 (8). The earliest studies with SLIT were conflicting but an increasing number of positive studies were subsequently published. SLIT was mentioned in immunotherapy guidelines 10 years after the first SLIT trial (9), and in some subsequent guidelines (10,11). SLIT was categorized as a reasonable alternative to SCIT. Currently, SLIT is routinely used in several European countries, where standardized extracts for the relevant allergens are available. There is no FDA-approved SLIT allergen extract/vaccine in the United States and therefore SLIT is not an approved treatment.

THE SAFETY OF IMMUNOTHERAPY: GENERAL ASPECTS

A detailed description of the AEs possibly, probably, or certainly related to a treatment is provided by carefully reporting the experience in clinical trials or collecting reports from experience after approval. SCIT may cause a wide variety of AEs, ranging from a local wheal and flare reaction to systemic side effects such as asthma, generalized urticaria, anaphylaxis and, very rarely, death. The majority of the AEs are immediate (i.e., within 30 minutes) and therefore are presumed to be due to specific IgE, but delayed reactions also occur. AEs due to SCIT have been classified according to a system introduced in Europe in 1993 and updated in 2006 (12): local (large if >10 cm), mild systemic, moderate systemic, and severe systemic (usually requiring epinephrine). With the injection route, the rate of systemic reactions depends on the administration schedule, the type of allergen, and the survey method. The occurrence of systemic AEs with SCIT is approximately 0.05% to 0.6% of doses administered (13). Near fatal and fatal events are very rare with appropriate administration (14), but the risk of severe AEs and fatalities (approximately 1 per 2.5 million injections) persists even with the best clinical practice. Reporting of AEs for SCIT is sometimes incomplete. For example, no

information is provided about AEs in approximately 20% of the published clinical trials (15). In the remaining 80% of studies, AEs occur on average in 14% of patients, with limited details provided. A survey in 2004 reported that human error remains a major cause of incorrect dosing with SCIT, but human error may not be the cause of most serious SCIT reactions (7,8,16).

AE rates are reported in the majority of the SLIT studies since this treatment was developed to minimize AEs and the prevalence and incidence of AEs were more closely monitored. An AE classification system similar to SCIT is often used: local reactions in the mouth or digestive tract, mild systemic, moderate systemic, and severe systemic. Many of the AEs with SLIT involve the digestive system at various levels: itching, swelling, burning of the lips, oral mucosa or tongue; nausea; diarrhea; and abdominal pain. Some studies report that up to 50% of treated subjects experience oral or gastrointestinal reactions. The mechanisms of AEs with SLIT are not known, but the amount of allergen and possibly the number of allergens administered play an important role. When the allergen vaccine is immediately swallowed (oral route), there are few side effects involving the mouth, whereas abdominal pain and nausea are frequent. But when the dose is held under the tongue and expectorated, oral reactions are more common and abdominal complaints are less frequent. SLIT is self managed at home by the patient and the severity of AEs is usually mild; therefore, the frequency of SLIT AEs is probably underestimated.

DATA FROM THE RANDOMIZED DOUBLE-BLIND CLINICAL TRIALS

There are 49 randomized double-blind, controlled clinical trials with SLIT (4,17,18). No life-threatening AE or fatality has been described in clinical trials, but three severe AEs have been reported in clinical experience (19–21). Ten of 46 published trials report no AE.

The most frequently described AE in children and adults is the immediate onset of oral/sublingual itching after dosing (ranging from 0–40%), followed in frequency by abdominal pain, nausea, and/or diarrhea. These AEs are usually, but not always, described as mild and self-limited and do not require dose adjustment or medical treatment. Systemic AEs (e.g., asthma, rhinitis, urticaria, angioedema) or severe abdominal complaints are reported in less than 3% of patients (22–26). SLIT was used in 14 pediatric studies, including children from 3 to 17 years of age. All of those studies report an acceptable safety profile and four studies report no side effects. Local oral side effects are the most frequent in children as well. The occurrence of nausea, abdominal pain, and oral symptoms was 20% in the active group and 2% in controls when high-dose SLIT was employed (23). Three cases of moderately severe urticaria were described by Tari et al. (22). Bufe et al. (27), Hirsch et al. (28), and Pajno et al. (29) reported one moderate asthma exacerbation in the active groups. A published randomized SLIT trial with cat vaccine reported no AEs (30).

The largest published SLIT trial involved more than 600 patients (31), with three doses of allergen. AEs were reported by 54% of patients. Almost all of these events were mild/moderate and self-limited, but one episode of uvular edema was judged as a serious AE. Only 2% of the participants withdrew for AEs probably or possibly related to SLIT. A randomized controlled trial in 2006 was designed specifically to assess safety as well as efficacy of SLIT in subjects with asthma (32). The occurrence of asthma AEs was not different with SLIT compared with placebo in the 114 subjects studied. Mild, local discomfort occurred in 53% of the SLIT subjects and in none of the placebo-treated individuals; no severe AE occurred. Another controlled dose finding study of safety (33) was conducted in 48 grass-allergic patients outside the pollen season. They received SLIT for 28-day periods at progressively increasing doses, up to 200 µg Phl p 5 or approximately 20 to 40 times the amount given with maintenance SCIT. The overall incidence of all AEs was 74%, all of mild or moderate intensity. The most frequently reported events were irritation of the throat and oral itching.

SLIT has been utilized also in diseases other than respiratory allergy. Enrique et al. (34) reported successful treatment of hazelnut-induced allergy with SLIT. Local AEs were reported with 7% and systemic AEs with 0.2% of the doses, and no AE was severe or required SLIT discontinuation. However, in a randomized controlled study with dust mite–SLIT for atopic dermatitis, treatment lead to intolerable worsening of the skin lesions in 2 out of 24 children and SLIT was discontinued (35).

DATA FROM SYSTEMATIC REVIEWS OF THE LITERATURE

André et al. (36) examined the safety of SLIT in eight trials performed with vaccines from a single manufacturer. These studies involved 690 subjects (347 active + 343 placebo), with 218 children aged 5 to 16 years (103 active + 115 placebo). The majority of AEs were local (82%) and the systemic AEs did not differ in active and placebo groups. The only differences were the oral and gastrointestinal AEs that were more frequent in SLIT patients, although mild in severity. The rates of AEs and dropouts were similar in adults and children.

A 2006 review (17) of the available studies on SLIT (including nonrandomized and observational ones) reported the following major findings. In 41 studies with information on the total number of AEs, 1047 AEs in a total of 386,149 doses were identified (2.7 reactions per 1000 doses). There were 529 AEs per 4378 patients (12%) in 49 studies with information on the number of patients treated. In the trials that specified the severity of reaction, the occurrence of severe AEs was 0.56 per 1000 doses. Overall, 14 serious AEs probably related to the treatment were reported.

DATA FROM THE POSTMARKETING SURVEYS

The data on the safety derived from postmarketing surveys are of relevance. First, AEs occur more often in a more diverse population of patients. Second, these data reflect patients' perception of AEs in an uncontrolled setting since SLIT is self-administered at home (Table 1).

Di Rienzo et al. (37) followed 268 children between 2 and 15 years of age for 3 years. The overall rate of systemic AEs was 3% of the patients and 1/12,000 doses, with no discontinuation. Only one (urticaria) of the AEs was judged of moderate severity and required oral antihistamine therapy. Another survey was performed in adults (38), with 198 patients observed for about three years. Side effects occurred in 7.5% of patients and 0.52/1000 doses administered. Four urticaria and two gastrointestinal AEs were of moderate intensity.

Table 1 Summary of the Postmarketing Surveys

First author (ref)	N patients	Age range	Follow-up	Allergens	Cumulative dose/yr	AE % patients	AE/1000 doses
Di Rienzo (37)	268	2–15 yr	3 yr	54% mites 25% grass 6% Parietaria 16% mixed	200 µg Der 1 39 µg group 5 24 µg Par j 1	3	0.083
Lombardi (38)	198	Adults	3 yr	35% mites 38% grass 23% Parietaria 4% others	104,000 AU for all allergens	7.5	0.5
Pajno (39)	354	5–15 yr	3–4 yr	42% mites 20% Parietaria 11% grass 7% olive 20% mixed	120 µg Der 1 30 µg Par j 1 72 µg group 5 432 µg Ole e1	6	0.15
Fiocchi (40)	65	3–7 yr	1 yr	64% mites 17% grass 12% trees 7% Parietaria	36,000 IR for all allergens	15	Not stated
Drachenberg (41)	159	6–60 yr	<1 yr	16% mites 37% grass 12% trees 35% other/mix	Not stated	6.3	Not stated
Agostinis (42)	36	3–5 yr	2 yr	mites 19 grasses 17	90,000 AU for both allergens	5	0.07
Di Rienzo (43)	128	3–5 yr	2 yr	62% mites 22% grass 12% Parietaria 4% others	174 µg Der 1 39 µg group 5 24 µg Par j 1	5.6	0.2

AEs were controlled by a temporary dose adjustment, and in no case was the SLIT discontinued. In another survey of 354 asthmatic children of 5 to 12 years of age (39), both the sublingual-swallow and the sublingual-spit modalities were considered. The occurrence of AE was 6% of treated patients and 0.15/1000 doses. Nonspecific reactions, such as headache and fatigue, were observed in 4% of patients. Fiocchi et al. (40), with a high-dose (up to 40,000 IR) SLIT regimen, reported at least one AE in 11 of 65 children, aged from 3 to 10 years. All the events were mild (oral/intestinal) except one severe AE with vomiting (39). Drachenberg et al. (41) reported eight local and four systemic AEs (3 rhinitis, 1 exanthema) in 6.3% of 159 patients.

SCIT is generally not recommended in children younger than five years because the systemic side effects are more difficult to recognize in small children. There are two postmarketing surveys of SLIT performed in children between three and five years of age. The first, in 36 subjects, reported AE in 5% of patients and a rate of 0.071/1000 doses. These events were gastrointestinal and mild (42). The other survey (43) involved 128 children and reported AEs in 5.6% of patients (0.2/1000 doses). Two AEs were local and mild and the remaining (nausea, diarrhea) were moderate.

Finally, in 2006 and 2007, three cases of anaphylaxis were first reported with SLIT (19–22). In one case, the diagnosis of anaphylaxis was not made by a health professional, no epinephrine was needed, and the SLIT used was a mixture of six different allergens, some of which were nonstandardized (19). In another case, anaphylaxis with a standardized latex extract occurred at the maximum recommended dose with an ultrarush procedure (20). In the third case, a mixture of dust mites plus five grasses plus four cereals was used. The symptoms were severe oral and gastrointestinal complaints, but criteria for severe anaphylaxis were not met and epinephrine was not necessary (21).

ADVERSE EVENTS, ALLERGEN DOSE, AND INDUCTION REGIMEN

The relationship between allergen dose and AEs with SLIT is not clearly evident from the controlled trials published during the last 20 years. This may be due to a relatively small sample size in many of the studies. The limited evidence of a dose relationship is particularly true for systemic AEs due to their limited frequency. A review of the published studies (44) evaluated the occurrence of AEs according to the dose, expressed as the ratio between SLIT and the equivalent SCIT. This review concluded that local or oral side effects are more frequent with "low" doses of allergen (less than 50 times the corresponding SCIT dose) than with higher doses. Refuting this point are the results of two randomized controlled studies of several hundred adult subjects (32,33). These trials demonstrate that local AEs are dose dependent. Gastrointestinal complaints (nausea, stomachache, and vomiting) also occur more frequently with higher doses of vaccine.

The inconsistent relationship of dose and AE with SLIT has resulted in the proposal that a slow up dosing phase, or buildup, may not be necessary. One trial of differing induction regimens demonstrated that AEs were not related to the duration of the buildup (45). Subsequent reports with ultrarush (less than 2 hours) up dosing show that the rapid increase of SLIT doses does not increase AEs (46,47). Preliminary experiences with the no-up dosing regimen (initiating SLIT with the maintenance dosage) support the feasibility of this regimen (48). A randomized trial compared the safety of the traditional up dosing regimen with the no-up dosing (49) regimen in 135 patients and found no difference in AEs rate between the two groups. Four large randomized trials with grass extracts were performed with the no-up dosing regimen (31–33,50), and their results in term of safety were as favorable as those of the studies with the traditional buildup protocol.

CLINICAL IMPLICATIONS

The overall safety of SLIT is confirmed by clinical trials, postmarketing surveillance, and 20 years of clinical use. The following statements summarize the published SLIT literature in the opinion of the authors (Table 2).

Table 2 SLIT: Side Effect

Local	
Oral itching/swelling	Relatively frequent; usually self-resolve
Stomachache	after the first doses without treatment;
Nausea/vomiting	if persist reduce the dose and treat
Systemic	
Urticaria/angioedema	Rare; give symptomatic treatment
Rhinitis	and reduce the dose; if persist,
Asthma	stop SLIT
Anaphylaxis	Exceptional; treat properly and stop SLIT

The occurrence and severity of AE do not differ between children (even younger than 5 years of age) and adults.

No fatality with SLIT has been reported, indicating a very low risk.

Severe uncontrolled asthma is not a relative contraindication for SLIT as with SCIT.

Anaphylaxis rarely occurs and, in two of the three cases, a mixture of more than four allergens was utilized. This suggests that SLIT may be safer with administration of a limited number of relevant allergens, the typical practice in Europe. One case of anaphylaxis occurred with an ultrarush SLIT protocol for latex allergy, suggesting that latex SLIT may have unique risk. If anaphylaxis occurs, SLIT usually should be discontinued since SLIT is administered at home without immediate access to treatment.

The severity of the large majority of the AEs reported is mild. Most AEs involve the mouth (burning or itching) or the gastrointestinal tract (abdominal pain, nausea) and usually resolve within a few days without intervention.

In case of persisting or moderately severe local AEs, a temporary dose reduction and concomitant antihistamine therapy are considered. If an AE persists and remains troublesome, SLIT should be discontinued.

Systemic AEs, such as urticaria, rhinitis, or asthma, require treatment and temporary dose reduction and likely should result in discontinuation of SLIT.

No-updosing regimens, though convenient, likely increase the occurrence of AEs.

SALIENT POINTS

- SLIT is marketed and used in current clinical practice in many European countries. Detailed data on its safety are available in clinical trials and postmarketing surveys.
- The literature consistently shows that the side effects of SLIT are mostly local (oral itching/burning, stomachache) and mild and very rarely lead to treatment discontinuation.
- Systemic AEs (rhinitis, asthma, urticaria) have been occasionally reported.
- The rate of AEs is not increased in very young children (below the age of 5 years).
- Only three cases of severe systemic reactions (one ascertained anaphylaxis) have been reported, with ultrarush latex SLIT and with mixtures of multiple allergens. These circumstances may require special caution.
- The use of no-induction (no up-dosing) regimens is well tolerated and does not seem to increase the risk.

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