

The safety of sublingual-swallow immunotherapy: an analysis of published studies

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Summary

Background As the main target of sublingual immunotherapy (SLIT) is to reduce at most the occurrence of adverse events (AE), safety represents a critical issue. This aspect deserves particular mention when a higher dose of allergen extract than traditional subcutaneous immunotherapy (SCIT) is required to be effective: that may be up to 500 times that employed for SCIT.

Objective All published controlled studies concerning SLIT-swallow were analysed to evaluate AE rates.

Methods Studies were subdivided in two groups: (i) studies using low allergen dose (LAD), i.e. ranging from 1 to 50 times the dose commonly administered with SCIT, and (ii) studies with high allergen dose (HAD), i.e. ranging from 50 to 500 times the dose administered with SCIT.

Results Twenty-five studies were altogether analysed: 13 studies belonged to the low-dose group, 12 belonged to the high-dose group. We considered all patients with at least one AE. Local reactions were significantly more frequent in the LAD group than in the HAD group ($P < 0.0001$), while there was no difference in the rate of systemic reactions. Severe systemic reactions were never reported.

Conclusion This study represents the first analysis of the safety of SLIT concerning the allergen dose employed in the treatment. There is evidence that AE occurrence is substantially not dose-dependent. This fact highlights two main clinical aspects: the elevated tolerability of SLIT in general and the safety of HAD regimen.

Keywords high allergen dose, low allergen dose, safety, sublingual immunotherapy

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Introduction

Allergen-specific immunotherapy represents the only validated causal treatment of allergic disorders that is capable of both improving symptoms [1, 2] and modifying the natural course of allergy [3]. There is evidence that specific immunotherapy is effective in patients with allergic rhinitis and mild form of asthma, as it has been stated in a recent WHO position paper [1].

As the traditional subcutaneous route of administration subcutaneous immunotherapy (SCIT) showed the risk of serious adverse reactions, sublingual immunotherapy (SLIT) has been investigated and developed [4].

The rationale of SLIT is that oral administration of high-dose allergen extract may reduce and prevent IgE responses [5]. Methodologically, the allergen extract is kept under the tongue a few minutes and then swallowed: this is the so-called 'sublingual-swallow'. A different method may be used, the

sublingual-spit, which consists in spitting out the allergen after having kept it under the tongue. At present, this last method is rarely used.

SLIT efficacy has been evaluated in the WHO position paper [1], in the EAACI/ESPACI document [6], and in the ARIA document [7]. All the published studies but three showed the clinical efficacy of SLIT both on rhinitis and asthma symptoms [4, 5]. The efficacy for rhinitis has recently been confirmed by a meta-analysis Cochrane review [8].

As the main target of SLIT is to reduce at most the occurrence of adverse events (AE), safety represents a critical issue. This aspect deserves particular mention because doses of allergen extracts up to 500 times higher than traditional SCIT are required to be effective.

The safety of SCIT in 488 adults and children with rhinitis and asthma was re-evaluated in a recent multi-centre study [9], which reported that 3.7% of patients experienced a systemic reaction and that a higher ratio of reactions was found among asthmatic and house dust mite allergic patients. An accompanying Editorial article underlined the relevance of safety aspects of SCIT [10].

Thus, we aimed at evaluating this issue by a systematic review of all the controlled studies concerning patients treated with SLIT-swallow.

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Table 1. Demographic features and study characteristics

Reference	Ratio SLIT/SCIT	Author	Allergen	Potency (mL)	Age	Active	Placebo	Total sample	Cumulative dose	No. of doses in active
High allergen dose										
[19]	50	Sabbah et al.	Grasses	100 IR	13–43	29	29	58	4,500 IR	2.227
[20]	70	Bahceciler et al.	Mites	100 IR	7.8–18	8	7	15	7,000 IR	744
[21]	150	Pradalier et al.	Grasses	100 IR	8–50	63	63	126	11,000 IR	7.623
[22]	200	Andre et al.	Ragweed	100 IR	18–53	53	53	106	23,000 IR	13.356
[23]		Bousquet et al.	Mites	300 IR	7–36	42	43	85	104,000 IR	15.288
[24]		Guez et al.	Mites	300 IR	12–51	36	36	72	90,000 IR	11.592
[25]		Tonnel et al.	Mites	100 IR	12–38	15	17	32	69,000 IR	7.305
[26]	257	Grosclaude et al.	Grasses	300 IR	5–45	47	16	63	18,000 IR	3.572
[27]	300	Vourdas et al.	Olive	300 IR	8–17	34	32	66	60,000 IR	7.582
[28]	375	La Rosa et al.	Parietaria	300 IR	6–14	20	21	41	150,000 IR	10.460
[29]		Mortemousque et al.	Mites	300 IR	6–60	30	30	60	90,000 IR	9.660
[30]	500	Clavel et al.	Grasses	300 IR	9–55	68	58	126	40,700 IR	10.540
Subtotal						445	405	850		99.949
Low allergen dose										
[31]	1	Horack et al.	Birch	500 STU	18–38	20	21	41	21,300 STU	1.362
[40]		Casanovas et al.	Olive	10 HEP	18–47	9	6	15	19.4 HEP	540
[32]	3	Voltolini et al.	Trees	100 BU	17–63	15	15	30	819 BU	885
[33]		Ippoliti et al.	Mites	10 BU	5–12	47	39	86	180 BU	4.371
[34]	4	Pajno et al.	Parietaria	10 BU	8–14	15	15	30	338 BU	2.400
[35]	5	Ariano et al.	Cypress	10,000 URAST	22–48	10	10	20	250,000 URAST	1.400
[36]		Hirsch et al.	Mites	11.9 mcg Der p1	6–15	15	15	30	570 mcg Der p1	2.598
[37]		Tari et al.	Mites	5 BU	5–12	30	28	58	720 BU	6.210
[38]	7	Passalacqua et al.	Parietaria	10 BU	22–47	15	15	30	256 BU	1.845
[34]	10	Hordijk et al.	Grasses	9,500 BU	18–45	27	30	57	780,000 BU	2.758
[17]	10	Bufe et al.	Grasses	10,000 AU	6.4–12.6	56	47	103	2,625,000 AU	59.976
[39]	20	Troise et al.	Parietaria	5 BU	18–60	15	16	31	105 BU	2.415
	40–50	Torres Lima et al.	Grasses	100 mcg Phl p5	21–53	28	28	56	10.8–16.2 mg Phl p5	11.844
Subtotal						302	285	587		98.604
Total						747	690	1.437		198.553

Materials and methods

To evaluate the relationship between allergen dose (SLIT/SCIT ratio) and frequency of AE, we analysed all published studies on SLIT.

The considered parameters were (i) the number and the type of AE per patient, (ii) the percentage of patients with AE, and (iii) the number of AE per number of SLIT doses. Only AE that were considered likely to be linked to SLIT were evaluated. We performed a systematic review of studies reported on Medline from 1986 to May 2004; the search terms were SLIT, swallow, and safety.

We evaluated published studies on the basis of inclusion and exclusion criteria. Inclusion criteria were double-blind, placebo-controlled (DBPC) studies, demonstration of successful effects, SLIT–swallow procedure, and use of native allergen extracts. Exclusion criteria were studies performed with other methodologies, use of modified allergens, and absence of safety data.

We reviewed 30 papers published, but excluded five of them as three trials were SLIT–spit and two used modified allergen extracts [11–15]. Three studies did not report the number of patients with AE, but had the AE per number of doses and were included in this kind of analysis [16–18]. Thus, 25 DBPC SLIT–swallow trials reporting side effects were analysed [16–40].

Table 2. Local reactions evaluated concerning the allergen dose

	Local reactions			
	High allergen dose		Low allergen dose	
	Active	Placebo	Active	Placebo
Sample (No. patients)	445	405	302	285
Buccolingual	159	15	417	36
Gastrointestinal	50	10	6	1
Total	209	25	423	37
Reaction per patient	0.47	0.06	1.4	0.13
$P < 0.0001$				

As there is no standardized unity to measure allergen extracts, we considered the ratio between SCIT and SLIT allergen dose as suggested in a consensus document [7]. Therefore, we subdivided these studies into two groups: (i) studies using low allergen dose (LAD), i.e. ranging from 1 to 50 times the dose administered with SCIT and (ii) studies with high allergen dose (HAD), i.e. ranging from 50 to 500 times the dose administered with SCIT.

Table 3. Systemic reactions evaluated concerning the allergen dose

	Systemic reactions			
	High allergen dose		Low allergen dose	
	Active	Placebo	Active	Placebo
Sample (No. patients)	445	405	302	285
Ocular itching	3	1	8	3
Cutaneous	11	8	5	3
Respiratory reactions	43	33	40	16
Others (headache, dizziness, tiredness)	10	12	7	7
Total	67	54	60	29
Reaction per patient	0.15	0.13	0.20	0.10
	NS			

NS, non-significant.

Table 4. Number of patients with AE as ratio of number of SLIT doses

	High allergen dose			Low allergen dose			Total
	Active	Placebo	Total	Active	Placebo	Total	
Number of patients	445	405	850	191	180	371	1,221
Number of administered doses*	99,949	97,331	197,280	24,026	22,951	46,977	244,257
Number of patients with AE*	114	58	172	34	15	49	221
	NS						
% of patients with AE*	25.6%	14.3%	20.2%	17.8%	8.3%	13.2%	18.1%
	NS						
Number of patients with AE*/10,000 doses	11.4	6	8.7	14.2	6.5	10.4	9
	NS						

*Data available in 22 studies. AE, adverse events; SLIT, sublingual immunotherapy; NS, non-significant.

AE were defined as local or systemic according to position papers [1, 6, 7]. Local reactions were oral itching and/or swelling, and gastroenteric complaints. Systemic reactions were cutaneous symptoms (urticaria, itching), ocular symptoms

(redness, itching, tearing), nasal symptoms (itching, sneezing, rhinorrhea, obstruction), and asthma symptoms (cough, wheezing, dyspnea, tightness of chest). The rates of AE in the different groups were compared by the chi square test.

Results

Twenty-five studies were altogether analysed: 13 concerned LAD and 12 HAD, as reported in Table 1. Analytic details of these trials are reported here. LAD group concerned 587 patients: 302 treated with allergen extract and 285 with placebo. HAD group included 850 patients: 445 actively treated and 405 assuming placebo. Totally, 1437 patients were evaluated, receiving an overall number of 198,553 active allergen doses.

We considered all patients with at least one AE.

Nine hundred and four AE were reported: 694 local and 210 systemic reactions. No anaphylactic shock was reported. Patients treated with allergen extracts showed 759 AE: 632 local and 127 systemic, whereas the placebo group showed 145 AE: 62 local and 83 systemic.

Table 2 shows local reactions in HAD and LAD groups: the LAD group had significantly more local reactions (mainly buccolingual) than the HAD group ($P < 0.0001$).

Table 3 shows systemic reactions in the two groups: there was no significant difference between the LAD and the HAD group.

Table 4 reports the ratio between the number of patients with AE (available in 22 studies) and the number of doses

administered: HAD group received more doses than LAD. Although the absolute number of patients with AE was higher in the HAD than in the LAD group, normalizing the number per 10,000 doses there was no difference between the two groups. Table 5 reports the ratio between the number of AE and the number of doses administered: there were significantly more total AE and local reactions in the LAD group, while the difference was not significant concerning systemic reactions. Figure 1 depicts the correlation between the number of AE per number of doses and the ratio SLIT/SCIT defining low and high allergen dosage in the 25 studies (reported with their respective data in Table 6): no linear, curvilinear or polynomial correlation was obtained, which indicates a lack of association between AE and SLIT allergen dose.

Discussion

This study is the first analysis of the safety of SLIT considering the allergen doses employed in the treatment. We know that the main attempt of SLIT is to reduce the risk

Table 5. Adverse events (AE) as ratio of number of sublingual immunotherapy doses

	High allergen dose			Low allergen dose			Total
	Active	Placebo	Total	Active	Placebo	Total	
Number of patients	445	405	850	302	285	587	1,437
Number of administered doses	99,949	97,331	197,280	98,604	88,196	186,800	384,080
Number of AE	276	79	355	483	66	549	904
	$P < 0.0001$						
Number of AE /10,000 doses	27.6	8.1	18	49	7.5	29.4	23.5
	$P < 0.0001$						
Number of LR /10,000 doses	20.9	2.6	11.9	42.9	4.2	24.6	18.1
	$P < 0.0001$						
Number of SR /10,000 doses	6.7	5.5	6.1	6.1	3.3	4.8	5.5
	NS						

LR, local reaction; SR, systemic reaction.

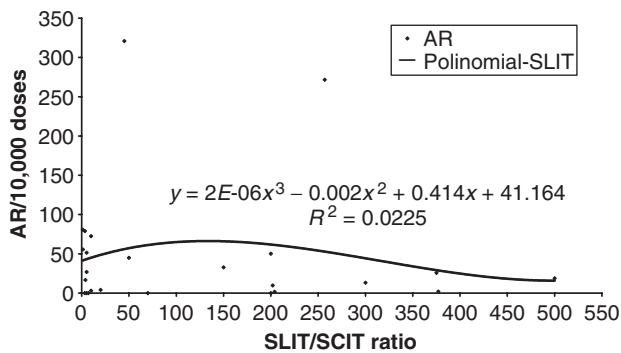


Fig. 1. Lack of correlation between adverse events (AE) and magnitude of sublingual immunotherapy (SLIT) doses. Regression curve obtained by interpolating the points corresponding to the incidence of AE occurred for each dose expressed as SLIT to subcutaneous immunotherapy (SCIT) ratio.

Table 6. Ratio AE/number of SLIT doses and ratio SLIT/SCIT defining low and high allergen doses in the 25 studies included in the analysis

Author	Reference	AE/10,000 doses	Ratio SLIT/SCIT
Horack	[31]	80.8	1
Casanovas	[40]	55.6	1.2
Ippoliti	[33]	0.0	3
Voltolini	[32]	79.1	3
Pajno	[18]	16.7	4
Ariano	[35]	0.0	5
Hirsch	[36]	26.9	5
Tari	[37]	51.5	5
Passalacqua	[38]	0.0	7
Bufe	[17]	3	10
Hordijk	[34]	72.5	10
Troise	[39]	4.1	20
TorresLima	[16]	320.8	40–50
Sabbah	[19]	44.9	50
Bahceciler	[20]	0.0	70
Pradalier	[21]	32.8	150
André	[22]	50.2	200
Tonnel	[25]	0.0	200
Bousquet	[23]	9.8	200
Guez	[24]	1.7	200
Grosclaude	[26]	27.6	257
Vourdas	[27]	13.2	300
La Rosa	[28]	25.8	375
Mortemousque	[29]	1.9	375
Clavel	[30]	19.0	500

AE, adverse events; SLIT, sublingual immunotherapy; SCIT, subcutaneous immunotherapy.

for serious reactions; therefore, careful assessment of this issue in clinical trials is deserved.

First of all, we can confirm that serious reactions have never been reported. This point is particularly crucial because SLIT, unlike SCIT, has never induced severe systemic reactions during a period of about 15 years.

Globally, the number of AE was about five times higher in actively than in placebo-treated patients, with local reaction representing the most commonly reported AE (77% of AE). In particular, oral itching is the most frequent local reaction, occurring quickly after assuming SLIT. Such a reaction was reported as mild and self-remitting in all studies. Gastro-

intestinal symptoms are less usual: about one-third of oral reactions.

In our analysis, local reactions were significantly more common in patients treated with LAD SLIT, while there was no difference between LAD and HAD studies according to systemic reactions, mainly represented by respiratory symptoms. Also, when examined by the ratio between the number of AE and the number of SLIT doses, LAD treatment caused significantly more local and, as a consequence of their prevalence, total AE.

It is difficult to explain why low doses are associated with more frequent local reactions: one may hypothesize that a lower amount of allergen molecules may interact more efficiently with the specific IgE in the oral mucosa, as occurs by natural exposure in subjects with the so-called oral allergy syndrome, who react to the limited allergen load present in fresh fruits and vegetables. On the other hand, it is possible that the reporting of local reactions has a variable level of accuracy in the different studies. For example, the trial by TorresLima et al. [16], classifiable among LAD studies, contributed a relevant quote of the overall local reactions, while other studies dealing with HAD SLIT may not have reported all local reactions because of their negligible clinical importance.

The data obtained with the present analysis highlight three main clinical aspects: the elevated tolerability of SLIT, the fact that AE are substantially not dose dependent, and the safety of HAD regimen. This last issue deserves mention, as it is well known that both the effectiveness and the safety of immunotherapy by the classical subcutaneous route are dose-dependent [1]; thus, high SLIT doses may be considered safe and effective.

Our analysis confirms a previous review evaluating the safety in controlled trials using allergen extracts produced by the same manufacturer [41]. This review concerned 690 patients (347 active and 343 placebo), 218 of them were children (103 active and 115 placebo). Most reactions were slight. Apart from local reactions, such as oral and gastrointestinal, active- and placebo-treated patients showed similar frequency of AE. Finally, this review reported that reactions were superimposable in children and adults.

Three recent post-marketing surveillance studies provided information more adherent to the common clinical practice, as in real life, patients are less stringently selected and followed than in controlled trials. The first study reported a limited incidence of AE [42]. About 50% of reactions consisted of oral itching and 90% of all reactions were mild and self-resolving. The second study dealt with the paediatric population by evaluating 268 children assuming SLIT for up to 3 years [43]. Systemic reactions affected 3% of children (1/12,000 doses) and no child discontinued SLIT. The third study concerned an adult population of 98 patients [44] and reported reactions in 7.5% of patients: 0.52/1000 doses.

Comparing safety in SLIT and SCIT, systemic reactions occur in a range between 0.85 and 46.7%, depending on the administration schedule [45]. The most recent study on SCIT reported an occurrence rate of 3.7% [9], and a recent review estimated an average occurrence of systemic reactions in 24% of patients treated with SCIT [10], while our analysis on SLIT shows a rate of systemic reactions per patient of 0.13 for HAD and 0.18 for LAD.

In conclusion, revising the data reported by controlled studies, safety of SLIT has been adequately considered. The analysis of these trials demonstrates that local reactions are quite common, with higher rate for LAD, but mild and self-resolving, and that systemic reactions occur more rarely and are not dose - dependent. Therefore, this analysis confirms the statements of consensus documents [1, 7] that SLIT is safe and may be prescribed even using HAD in both adults and children.

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