

Safety of Sublingual-Swallow Immunotherapy in Children and Adults

C. André C. Vatrinet S. Galvain F. Carat H. Sicard

Scientific and Medical Department, Stallergènes SA, Antony, France

Key Words

Immunotherapy, sublingual-swallow · Asthma ·
Rhinoconjunctivitis · Mites · Pollen

Abstract

Background: Immunotherapy is an established treatment of allergic diseases. The safety of this treatment, particularly when administered without direct medical surveillance, as in the case of the sublingual-swallow route needs to be established. The aim of this paper is to review the safety of the sublingual-swallow immunotherapy as reported in eight double-blind, placebo-controlled trials carried out in France, Italy and Greece.

Methods: Six hundred and ninety subjects, 472 adults and 218 children, took part in trials of specific immunotherapy (SIT) for the treatment of rhinoconjunctivitis and/or asthma. Three hundred and forty-seven patients received SIT and 343 patients received placebo. Treatment with specific immunotherapy with allergen extracts or placebo was administered using the sublingual-swallow technique. The allergens administered were grass, ambrosia, parietaria and olive pollens, and mites. The daily dose taken during maintenance therapy ranged from 100 to 300 IR (index of reactivity) and cumulative doses

ranged from 4,500 to 104,000 IR. Treatment duration ranged from 4 months to 2 years. Adverse events reported either spontaneously by the patient or on direct questioning by the investigator were analysed. **Results:** One hundred and forty-five unusual events were reported in the subjects receiving active SIT and 79 in those receiving placebo ($p < 0.001$). Of these 85 were children aged 15 years or less (50 received active SIT, 35 placebo) and 139 were adults (95 received SIT, 44 placebo). Unusual events involving the buccal cavity (61 SIT, 13 placebo) and the gastro-intestinal tract (47 SIT, 15 placebo) were significantly more frequent in the SIT-treated patients ($p < 0.001$). Wheezing (9 SIT, 21 placebo) was more frequent in the placebo-treated patients ($p < 0.05$). There were no differences in the frequency of unusual events between adults and children and in the frequency of events involving other body systems. No event was reported as serious. Two events reported as laryngeal oedema were not considered to be accurate descriptions. **Conclusions:** No serious adverse event was reported in the studies monitored, confirming the good safety profile of the sublingual-swallow method both in children and adults with rhinitis or moderate asthma.

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Introduction

Specific immunotherapy (SIT), allergen avoidance and allergen elimination are the only treatments of respiratory allergic disease that deal with its causation. When SIT is administered at sufficient doses, using standardised allergenic extracts, this type of parenteral treatment has been demonstrated to be effective in rhinoconjunctivitis and allergic asthma [1].

The occurrence of adverse events, such as reactivation of the disease, but also, more exceptionally, anaphylaxis and death (induced by anaphylaxis or bronchospasm), led the Committee on the Safety of Medicines in 1986 to recommend that desensitising vaccines administered by injection 'should be used only where facilities for full cardiorespiratory resuscitation are immediately available, and patients should be kept under medical observation for at least two hours after treatment', so that the procedure has almost totally disappeared from clinical practice in Great Britain [2]. However, parenteral SIT is a treatment modality used in the rest of Europe and in the United States.

In addition to parenteral SIT, non-parenteral forms of SIT have also been used (oral, sublingual, nasal and bronchial). These alternative therapeutic regimens, particularly the sublingual-swallow route, had not been sufficiently validated and, in 1993, a Position Paper published by the European Academy of Allergology and Clinical Immunology recommended that this treatment should only be used in double-blind placebo-controlled clinical trials [3].

However, following studies conducted since then [4–7], the WHO has recently recognised the efficacy and safety of this type of treatment, at least for adult allergic rhinitis [8]. Several questions remain unanswered: the efficacy in children, as only a limited number of published studies have been devoted to this age group, and the safety of this treatment regimen in children, as drug administration is performed at home, in the absence of medical supervision. One of the published studies reported an excessive number of adverse events in children [6]. The objective of the present paper is to review the adverse events observed in adults, but also in children, in the course of 8 double-blind placebo-controlled trials devoted to sublingual-swallow SIT conducted by Stallergènes SA.

Materials and Methods

Subjects and Protocols

The results of 8 double-blind placebo-controlled clinical trials are reported. Most trials have been published as complete papers [5, 9–13], one is in press [14] and one in preparation for publication [15] but already presented in abstract form [16, 17]. The data are also on file at the Stallergènes company.

A total of 690 subjects were studied: 347 treated with an allergenic extract presented in the form of drops or sublingual tablets and 343 treated with the corresponding placebo. There were 218 children under the age of 16 years (103 active treatment and 115 placebo) and 472 adults (244 active treatment and 228 placebo).

For each of the eight trials, table 1 indicates the country in which the trial was conducted, the principal investigator, the name of the Ethics Committee approving the study, the type of allergen used, the disease treated (rhinoconjunctivitis, with and without associated

Table 1. Administrative and technical data concerning 8 double-blind placebo-controlled sublingual-swallow clinical trials

Country	Principal investigators	Ethics committees	Allergens	Indication	Formulations	Ages	Number of patients	Maximal daily dosages IR	Number of days of treatment/month	Duration of treatment months	Cumulative dosages IR	Major allergens/1 ml 100 IR
France	Sabbah	Angers	Grasses	RC	Drops	C + A	29 AE/29 P	100	15	4	4,500	Not done
France	Clavel	Lyon	Grasses	RC + AA	Drops	C + A	70 AE/66 P	300	30	8	40,700	Phl p 5, 6.4 µg
Greece	Papa-georgiou	Athens	Olive	AA	Drops	C	34 AE/32 P	300	30	12	60,000	Ole e 1, 13.5 µg
France	Bousquet	Paris	Mites	AA	Drops	C + A	42 AE/43 P	300	13	25	104,000	Der p 1, 8 µg– Der f 1, 14 µg
France	Guez	Bordeaux	Mites	RC	Drops	C + A	36 AE/36 P	300	13	24	90,000	Der p 1, 9.6 µg– Der f 1, 7.5 µg
France	Pradaliér	Paris	Grasses	RC + AA	Drops + tablets	C + A	63 AE/63 P	100	30	4	11,000	Phl p 5, 8.5 µg
France	Perrin-Fayolle	Lyon	Ragweed	RC + AA	Drops + tablets	C + A	53 AE/53 P	300	13	7	25,000	Amb a 1, 160 µg
Italy	Canonica	Genoa	Parietaria	AA	Drops	C	20 AC/21 P	300	13	24	150,000	Par j 1, 70 µg

RC = Rhinoconjunctivitis; AA = allergic asthma; A = adult; AE = allergenic extract; P = placebo; C = children.

asthma or allergic asthma alone), the number of subjects receiving active treatment or placebo, the pharmaceutical form used (drops or drops + tablets as maintenance treatment), the inclusion of adults and/or children, the duration of treatment, the maximum allergen concentration used and the cumulative dose of allergen. The results for these last two parameters are expressed in IR (index of reactivity), the biological unit developed by Stallergènes. An allergenic solution is considered to represent 100 IR when its concentration elicits a wheal with a geometrical mean diameter of 7 mm in 30 skin-prick-tested allergic patients. Table 1 also presents the major allergen content of 1 ml of each extract of 100 IR used. In each trial, the initial treatment with increasing doses lasted about 1 month and was followed by maintenance treatment at a fixed dose for 4–25 months. The cumulative dosage used was 50–375 times higher than with par-enteral immunotherapy.

At each trial visit, at 2-month intervals, after questioning the patients, the investigator recorded all adverse events and patients were asked about the occurrence of specific adverse events. Specific questions were asked about the occurrence of skin reactions (urticaria or deterioration of atopic dermatitis), buccal reactions (oedema and pruritus of the lips and mouth), gastrointestinal manifestations (abdominal pain, diarrhoea, vomiting), deterioration of symptoms of rhinitis or conjunctivitis, asthma attack, angio-oedema or anaphylaxis. Any other symptoms also had to be reported. Grading of the severity was done according to the EAACI position paper on immunother-

apy [3, 8]. Patients were free to discontinue the trial and investigators could withdraw patients. Details were recorded of patients withdrawn because of adverse events.

Statistical Analysis

The data were analysed by the χ^2 test at 5% test significance levels.

Results

Tables 2 and 3 present the results (in percentage of adverse events) for each study. Table 4 presents absolute numbers for the 8 clinical trials. The majority of events were classed as minor. Indeed the grading of the severity of reactions according to the EAACI position paper showed non-specific and mild systemic reactions and never non-life-threatening systemic reactions and anaphylactic shocks. Forty-two percent of subjects receiving active SIT treatment reported at least one adverse event compared to 23% who received placebo. There was no difference in the reporting of adverse events between actively treated adults (39%) and children (48%).

Table 2. Adverse events (in percentage) for each study in the paediatric patients

	Papageorgiou		Canonica		Bousquet		Perrin-Fayolle		Pradalier		Clavel		Sabbah		Guez	
	placebo	active	placebo	active	placebo	active	placebo	active	placebo	active	placebo	active	placebo	active	placebo	active
Skin			4						11	12	6				5	
Mouth	6	17	19	20	9	33			11	37	5		12		5	
Rhinitis				5					11	12			20			
Gastro-intestinal		2	4	40									12			
Wheezing			4								15	13			5	
Conjunctivitis		2	4	5						12						
Laryngeal oedema											6					
Aphthous ulcers									11							
Headache										12						
Muscle spasm																

Table 3. Adverse events (in percentage) for each study in the adult patients

	Papageorgiou		Canonica		Bousquet		Perrin-Fayolle		Pradalier		Clavel		Sabbah		Guez	
	placebo	active	placebo	active	placebo	active	placebo	active	placebo	active	placebo	active	placebo	active	placebo	active
Skin				6	9				3	7	2		8			4
Mouth					3		35		1	14	9		4	14		4
Rhinitis										5			12	23	4	
Gastro-intestinal				9	9	6	30	3	3		3		4			
Wheezing				6	3	4	3	7								
Conjunctivitis									1		1					
Laryngeal oedema							1									
Aphthous ulcers																
Headache				3		4		1								
Muscle spasm											1					

Table 4. Number and nature of adverse events reported

	Children		Adults		All subjects	
	placebo	active treatment	placebo	active treatment	placebo	active treatment
Skin	2	1	8	9	10	10
Mouth	10	21	3	40	13	61 ^b
Rhinitis	9	2	3	9	12	11
Gastro-intestinal	6	20	9	27	15	47 ^b
Wheezing	6	1	15	8	21 ^a	9
Conjunctivitis	1	3	1	0	2	3
Laryngeal oedema	0	1	0	1	0	2
Aphthous ulcers	1	0	0	1	1	1
Headache	0	1	4	0	4	1
Muscle spasm	0	0	1	0	1	0
Total	35	50	44	95	79	145 ^b

^a $p < 0.05$: significantly higher incidence in the placebo group; ^b $p < 0.001$: significantly higher incidence in the active treatment group.

Table 5. Number and nature of adverse events leading to dropping out of the clinical trial

	Children		Adults		All subjects	
	placebo	active treatment	placebo	active treatment	placebo	active treatment
Skin	0	1	3	0	3	1
Mouth	0	1	1	8	1	9
Rhinitis	0	0	1	0	1	0
Gastro-intestinal	1	4	2	5	3	9
Wheezing	0	0	3	1	3	1
Total	1	6	10	14	11	20

In the actively SIT-treated patients 58% of the adverse events occurred during the dose escalation phase, 33% during maintenance treatment and 9% during dose escalation and maintenance treatment. In the placebo-treated patients 34% of the adverse events occurred during the dose escalation phase, 58% during maintenance treatment and 8% during dose escalation and maintenance treatment. Adverse events involving the skin had the same frequency in both the active and placebo groups, the most common event being an acute episode of urticaria, which is not a surprising event in atopic patients. The frequency of exacerbations of the underlying symptoms treated, rhinitis and conjunctivitis, was also the same in both treatment groups. This probably corresponds to the natural course of the disease rather than to adverse events. The frequency of adverse events involving the buccal cavity and gastro-intestinal tract, the route of administration, was significantly greater in the actively treated group compared to the placebo group ($p < 0.001$). They also had

a similar incidence in adults and children. The frequency of episodes of asthma was significantly higher in the placebo-treated group ($p < 0.05$). One reported side effect occurring under active treatment, laryngeal oedema, was of more concern. This was reported in two cases, 1 child and 1 adult. In the case of the child the event was reported on two occasions. More detailed investigation revealed that the event was in fact an alteration in the tone of the voice immediately following administration of the drops. In view of the benign nature of the phenomenon, the investigator decided to continue the trial as planned. In the case of the adult, the patient presented with dysphagia, which was diagnosed as laryngeal oedema. The patient continued treatment for 8 weeks after this adverse event was first reported. This was not associated with any other effects. The patient was seen twice again before being subsequently lost to follow-up.

Table 5 indicates the reasons for dropping out of the clinical trials because of adverse events. Ten adults and

1 child dropped out of the trial while receiving placebo. Fourteen adults and 6 children dropped out of the trial while receiving active treatment. Apart from 1 adult with rhinitis (active treatment) and 4 adults with wheezing (3 active, 1 placebo), the reasons for dropping out were repeated buccal and abdominal complaints in both adults and children. Indeed, 15 patients presented a reaction twice, 1 patient 3 times, another one 4 times, and only 1 patient 10 times but on placebo treatment.

Discussion

This review of the 8 placebo-controlled clinical trials of sublingual administration of allergenic extracts provides confidence in the relative safety of this method. An unexpected large number of adverse events was reported. However, this figure must be modulated by the fact that, in most subjects, the reported symptoms were not repeated or occurred only once. The presence of an obvious nocebo effect, probably suggested by the adverse effect of the recording modalities, is all the more obvious in view of the fact that the frequency of adverse events was 23% in adults and children receiving placebo.

The majority of observed adverse events involved those organs (mouth and gut) in direct contact with the allergenic extracts administered according to the sublingual-swallow method. These adverse events were, therefore, not unexpected. Their development in approximately one third of patients resembles the local cutaneous adverse events (erythema of less than 5 cm in diameter) observed after injections and considered to be acceptable.

As unstable asthma is a contraindication to parenteral SIT and as deaths related to SIT are more frequent in asthmatics, it is logical to question the justification for sublingual SIT in asthmatic adults or children. The number of asthma attacks attributed to treatment in the 8 trials was significantly lower in the treated group. Analysis of the adverse events designed to assess the potential risks associated with the method in moderate asthma demonstrated the efficacy of this treatment to prevent asthma, as identical proportions of asthmatic patients were included in the placebo and active treatment groups in the studies reported.

Analysis of dropping out showed that the main causes were buccal phenomena and abdominal pain in both adults and children. In every case, dropping out was motivated by the repetition or intensity of the disorders. It is noteworthy that no dropping out, particularly in children,

was due to asthma, while two protocols were devoted to sublingual-swallow SIT for mild-to-moderate asthma in this age group.

In conclusion, prospective studies confirm the safety of sublingual-swallow specific immunotherapy, both in children and in adults, presenting with either rhinitis or mild-to-moderate asthma. No serious adverse event was reported in the studies monitored. Of the two cases of laryngeal oedema reported, neither was classified as severe. In the case of the child the actual symptom was a change in voice and treatment was continued. In the adult case, the reported symptom was dysphagia, which was not severe, but the case was lost to follow-up. These results must be placed in the context of the proven efficacy of this treatment suggesting that a greater number of patients, at least with rhinitis, would certainly benefit from treatment with sublingual immunotherapy, even in Great Britain [18]. These conclusions are also in agreement with other available trials [19–22] and with a postmarketing surveillance study on the safety of sublingual immunotherapy in paediatric patients [23].

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