

The Safety of Allergen Specific Sublingual Immunotherapy

Giovanni Passalacqua, Laura Guerra, Enrico Compalati and Giorgio Walter Canonica*

Allergy and Respiratory Diseases, Department of Internal Medicine, University of Genoa, Italy

Abstract: Sublingual immunotherapy (SLIT) was proposed for clinical practice about 20 years ago with the main aim of improving the safety and of avoiding the side effects. More than 30 randomized controlled trials have been published so far, in addition to several post marketing surveys. Thus, the literature provides a solid documentation of the safety profile of this treatment.

Concerning the randomized controlled trials, the more frequently reported side effect of SLIT is the oral itching or swelling, followed by gastrointestinal complaints. These side effects are invariably described as mild and easily managed by temporarily adjusting the dose. Systemic relevant adverse events (asthma, urticaria, angioedema) occur sporadically, with their rate not being different from the placebo groups. Moreover, the safety profile seems not to differ in adults and children.

More interestingly, the post marketing surveys consistently showed that the occurrence of all side effects is less than 20% of patients and less than 1 per 1,000 doses, thus being quite insignificant compared to subcutaneous immunotherapy. The most recent surveys showed that the rate of adverse events does not increase in children below the age of 5 years, being traditionally considered as a prudential limit for injection IT. Finally, it seems that the occurrence of some adverse events, at variance with injection route, does not depend strictly on the dose of allergen administered.

INTRODUCTION

Allergen-specific immunotherapy (IT) is the practice of administering to allergic subjects increasing amounts of an allergen to achieve a "hyposensitization" towards the allergen, thus improving symptoms and reducing the need for medications when exposure to the allergen occurs. It is now recognized that IT is a biological response modifier and a cornerstone of the management of allergic diseases. Since the earliest attempts at the beginning of the 20th century [1], allergenic extracts were administered subcutaneously (SCIT). The good clinical results rapidly favored the widespread use of SCIT that remained for many decades the only type of allergen immunotherapy. On the other hand, some attempts to apply immunotherapy by routes different from the injection were sporadically made [2-5]. In the middle 1970's the nasal immunotherapy (LNIT) began to be intensively investigated and at the beginning of the 80's also the oral route (allergen immediately swallowed) also received considerable interest [6].

In 1986, the British Committee for the Safety of Medicines officially reported 26 fatalities provoked by SCIT [7] and the cost/benefit ratio of IT began to be questioned. This fact also stimulated the search for safer IT modalities, possibly with different routes of administration. Of note, the first study with sublingual immunotherapy (SLIT) was published just in 1986 [8].

Although it was shown [9, 10] that severe events with SCIT were often caused by avoidable errors (incorrect administration, dose errors), the importance of non-injection routes continued to grow [11]. Indeed, the oral and the

bronchial immunotherapy were shown to have a limited efficacy with many side effects [12] and were almost completely abandoned, whereas LNIT and SLIT were officially accepted as viable alternatives to SCIT [13, 14, 15]. Currently, SLIT is routinely used in several European countries, where standardized extracts for the most important allergens are available. The present review summarizes the data on the safety of SLIT currently available in literature. For this purpose, double blind randomized, placebo controlled trials, post-marketing surveys and other relevant clinical studies concerning safety, published until May 2006 were searched in MedLine.

THE SAFETY OF IMMUNOTHERAPY: CLINICAL CONSIDERATIONS

It is well known that the subcutaneous injection of allergens can provoke a wide variety of side effects, ranging from a local wheal and flare reaction, to subcutaneous nodules, to systemic side effects such as asthma or generalized urticaria sometimes resulting in fatal anaphylaxis. The majority of these reactions are immediate (i.e. within 30 minutes) and therefore are supposed to be reaginic in nature but delayed reactions are also described. With the injection route, the rate of systemic reactions depends on the administration schedule, the allergen and the survey method. In previous studies, the occurrence of systemic reactions was reported to range between 0.5% and 2.9% of patients [16, 17]. In one study in children with severe asthma, the occurrence of anaphylaxis was reported to be up to 5.6% [18]. The occurrence of systemic reactions with SCIT is in general about 0.05-0.6% of doses administered [19] that is, 10 to 100 times greater than with SLIT. Near fatal events are rare, when SCIT is correctly prescribed and applied [20] but the risk of severe adverse events is real [9] and some fatalities have been reported with SCIT. As a general impression, the quality of reporting of AE for SCIT is poor. In about 20% of the published clinical trials, no information was provided about the side effects

*Address correspondence to this author at the Allergy & Respiratory Diseases, Department of Internal Medicine, Pad. Maragliano, L.go, R. Benzi 10, 16132 Genoa, Italy; Tel: +39 0103538908; Fax: +39 0103538904; E-mail: canonica@unige.it

[21] and in the remaining studies, side effects were reported to occur on average in 14% of patients, with no or few details. The adverse events due to SCIT have a special classification [13, 22]: local (large if >10 cm), mild systemic (rhinitis or asthma responding adequately to antihistamines or bronchodilators), moderate systemic (urticaria/angioedema, moderate asthma) and severe (anaphylactic shock, laryngeal edema, severe asthma). Of note, it is acknowledged from recent surveys that human errors still remain the major cause of side effects [23].

In the case of SLIT, recently introduced with the rationale of improving safety, a detailed description of the AE is available in almost all studies. With SLIT, many of the untoward effects involve the digestive system at various levels: itching, swelling, burning of the lip or oral mucosa or tongue, nausea, diarrhea, abdominal pain. The mechanisms are not known but the amount of allergen administered and the contact with the mucosa play an important role. In fact, when the allergen is immediately swallowed (oral route), there are no side effects involving the mouth, whereas stomachache and nausea are frequent [24-26]. On the contrary, with SLIT, problems with the oral mucosa are common. Concerning the severity of side effects, the classification above mentioned is also applied to SLIT, with the difference that local side effects are oral rather than cutaneous.

DATA FROM THE RANDOMIZED CLINICAL TRIALS

Presently, 36 randomized double blind and controlled clinical trials with SLIT are available [27-62] (Table 1). The first important datum from the literature is that no life-threatening adverse event or fatality has ever been described since the introduction of SLIT in the clinical practice. The side effects are described in detail in almost all the studies published.

The most frequently reported side effects in children and adults are the immediate onset of oral/sublingual itching after taking the dose. This effect is followed in frequency by stomachache, rhinitis, nausea and diarrhea. These events are invariably described as mild and self-resolving without dose adjustment. In the remaining cases, the moderate side effects could be easily managed by a temporary reduction of the dose given. Considering in detail, moderately severe systemic AE were described in few studies [27, 42, 48, 54, 55], mainly asthma, generalized urticaria or troublesome gastrointestinal complaints, but these effects were overall rare. One study with very high doses (375 times the amount administered in a standard SCIT) reported a noticeably high rate of gastrointestinal AE [41], but such rate was also remarkably high with lower doses [57]. In 12 out of 36 studies, no side effect at all was reported.

SLIT was used in 12 pediatric studies (Table 1). All those studies agreed on the good safety profile of the treatment and 4 studies reported no side effects. Also in children, local oral side effects were frequent. In the study using a very high dose [41], the occurrence of nausea, stomachache and oral symptoms was 20% in the active group and 2% in controls. Three cases of moderate urticaria were described by Tari [27] and one by Bufe [55], Hirsch [31] and Pajno [52] reported one moderate asthma in the active group.

Andre *et al.* examined the safety of SLIT in 8 trials performed with vaccines from a single manufacturer [63]. These studies involved 690 subjects (347 active + 343 placebo) with 218 children (103 active + 115 placebo). The large majority of events were mild and their occurrence did not differ in active and placebo groups. The only differences were the oral and gastrointestinal side effects that were more frequent in SLIT patients, although mild. The rate of side effects and dropouts was similar in adults and children.

DATA FROM THE POST MARKETING SURVEYS (TABLE 2)

The information on safety from post-marketing surveillance surveys is of great relevance, because it is obtained in relatively unselected patients. Moreover, since SLIT is self-managed at home by patients themselves, post marketing studies in real-life probably better reflect the common clinical practice.

Di Rienzo *et al.* [64] followed-up 268 children aged between 2 and 15 years, receiving SLIT up to 3 years. The overall incidence of systemic side effects was 3% of the patients and 1/12,000 doses and no discontinuation of the SLIT was needed. Of 8 side effects described, only one presenting urticaria was judged of moderate severity and required a single dose of oral antihistamine. Another pharmacosurveillance study was performed in adults [65], with 198 patients observed for about 3 years. Side effects occurred in 7.5% of patients and 0.52/1,000 doses were administered. Four urticaria and 2 gastrointestinal complaints were judged of moderate intensity. Also in this study, side effects were controlled by a temporary dose adjustment and in no case was the treatment discontinued. In another survey in children [66], both the sublingual-swallow and the sublingual-spit modalities were considered. The occurrence of side effects was 6% of patients and 0.15 per 1,000 doses. In this latter study, nonspecific reactions as headache and tiredness were observed in 4% of patients, but they could not be attributed to SLIT. Fiocchi *et al.*, with a very high dose regimen reported at least one adverse event in 11 of 65 children. All the events were mild (oral or intestinal) but one presenting with severe vomiting. There was no difference between the children below 5 years of age and those being older [67]. Draichenberg *et al.* [68], in a cohort of 159 patients reported 8 local and 4 systemic AE (3 rhinitis, 1 exanthema) with an overall rate of 6.3% of patients, but no detail on doses was given.

The age below 5 years is considered a relative contraindication for SCIT, because the possible side effects are more severe and difficult to treat in small children. On the other hand, the good safety profile of SLIT has suggested its possible use also under the age of 5 years without particular problems. There were two recent post-marketing surveys performed in very young children (between 3 and 5 years of age). The first one was conducted in 36 subjects: side effects were reported to occur in 5% of patients and at a rate of 0.071 per 1,000 doses. The side effects were gastrointestinal and invariably mild [69]. Another survey [70] involved 128 young children and reported side effects in 5.6% of patients (0.2 per 1,000 doses); two side effects were local and mild and the remaining (nausea, diarrhea) were moderate.

Table 1. Randomized Controlled Trials with SLIT

Author, Year, Ref.	Age Range	Patients A/P *	Allergen	Duration	Cumulative Dose **	Adverse Events Described
Tari, 1990 [27]	5-12 Years	30/28	Mites	18 mths	365 STU	3 urticaria, 4 abdominal pain only in SLIT group, all moderate
Sabbah, 1994 [28]	13-51 Years	19/29	Grasses	17 wks	4.500 IR	Mild side effects in 10 SLIT patients and 7 placebo patients. Of these, 4 oral itching in SLIT and 1 in placebo. No significant difference
Feliziani, 1995 [29]	14-48 Years	18/16	Grasses	3.5 mths	25 BU	None
Troise, 1995 [30]	17-60 Years	15/16	Wall pellitory	10 mths	105 BU	1 mild oral itching in SLIT and placebo group
Hirsch, 1997 [31]	6-16 Years	15/15	Mites	1 yrs	570 mcg Der p1	5 mild oral itching in SLIT and 1 in placebo 1 mild asthma in SLIT, unlikely related to treatment
Passalacqua, 1998 [36]	15-46 Years	10/9	Mites	2 yrs	10.000 AU	None
Vourdas, 1998 [34]	7-17 Years	33/31	Olive	2 yrs	4 mg Olive major allergen (Ole e 1)	8 mild oral itching in SLIT group and 2 in placebo
Clavel, 1998 [32]	8-55 Years	62/28	Grasses	6 mths	28 mcg Phl p 5	SLIT: 18 mild ; placebo: 10 mild. Difference only in oral itching; 9 SLIT and 3 placebo
Horak, 1998 [33]	16-48 Years	18/16	Birch	4 mths	250 STU	Mild side effects in 7 SLIT and 5 placebo patients. No difference at all
Hordijk, 1998 [35]	18-45 Years	30/27	Grasses	6 mths	300.000 BU	45 mild adverse events (20 in the SLIT and 25 in the placebo group) in 27 patients. No difference at all. 20% of AE were moderate
Bousquet, 1999 [38]	15-37 Years	15/15	Mites	2 yrs	104,000 IR 4.2 mg Der p 1	15 mild AE in the SLIT group and 14 mild AE in the placebos. No difference at all
Passalacqua, 1999 [37]	15-42 Years	15/15	Wall pellitory	8 mths	265 BU 16 mcg Par j 1	2 mild oral itching in SLIT group
Pradaliere, 1999 [40]	6-25 Years	59/61	Grasses	4 mths	11,000 IR .935 mg Phl p5	30 mild AE in the SLIT group and 22 mild AE in the placebo in 25 and 13 patients, respectively. No overall difference. Mild oral itching: 9 SLIT, 1 placebo; Rhinitis: 4 SLIT, 0 placebo
La Rosa, 1999 [41]	6-14 Years	20/21	Wall pellitory	6 mths	75,000 IR 52.5 mg Par j1	Abdominal pain: 19 SLIT and 1 PLAC. All other side effects identical in the 2 groups
Purello, 1999 [39]	14-50 Years	14/16	Wall pellitory	8 mths	12 mcg Par j1	None
Pajno, 2000 [43]	8-15 Years	12/12	Mites	2 yrs	360 mcg Der p1	Tiredness : 4 SLIT - 1 PLA. Oral itching: 2 SLIT, 0 placebo ; all mild. 1 moderate asthma in placebo group
Guez, 2000 [42]	6-51 Years	24/18	Mites	2 yrs	90,000 IR 2,2 mg Der p 1	2 mild oral itching in SLIT group ; 1 mild asthma in placebo group
Caffarelli, 2000 [44]	4-14 Years	24/20	Grasses	3 mths	37.000 AU	None
Ariano, 2001 [45]	19-50 Years	10/10	Cypress	8 mths	250.000 RU	None
Bahceciler, 2001 [46]	7-15 Years	8/7	Mites	6 mths	7.000 IR 0.56 mg Der p1	None
Voltolini, 2001 [47]	15-52 Years	24/13	Trees	24 mths	250,000 RU	None
Lima, 2002 [48]	16-48 Years	24/22	Grasses	18 mths	0.9 mg Phl p 5 per month	80% of AE in the SLIT group were mild oral itching. No other difference between groups
Mortemousque, 2003 [49]	6-60 Years	26/19	Mites	24 mths	90,000 IR 2.2 mg Der p 1	Only local mild reactions (mouth itching) in the active group.
Andre, 2003 [50]	6-55 Years	48/51	Ragweed	7 mths	Variable	37 local side effects in SLIT Systemic AE identical in the 2 groups
Ippoliti, 2003 [51]	5-12 Years	47/39	Mites	6 mths	57 mcg Der p1	None
Pajno, 2003 [52]	8-14 Years	15/15	Wall pellitory	13 mths	23 mcg Par j1	3 tiredness + 1 oral itching in SLIT; 2 tiredness in placebo
Wuhrich, 2003 [53]	6-13 Years	11/11	Grasses	2 yrs	138 mcg group 5 allergens per year	None
Tonnel, 2004 [54]	7-45 Years	15/17	Mites	2 yrs	1.28 mg Der p1	1 lip itching and 1 gastric pain in SLIT; 1 asthma in placebo

(Table 1) contd.....

Author, Year, Ref.	Age Range	Patients A/P *	Allergen	Duration	Cumulative Dose **	Adverse Events Described
Bufe, 2004 [55]	6-13 Years	68/74	Grasses	3 yrs	2,650,000 AU 9.6 mg Phlp5	17 mild oral itching and 1 urticaria in SLIT
Smith, 2004 [56]	18-60 Years	45 1 yr, 46 2 yr 46 pla	Grasses	1 yr 2 yrs	6.2 mg Lol p 1, 3.6 mg Dac g 1 / year	1 st yr: minor side effects in 85/121 SLIT patients and 26/59 placebo patients. P <0.05 only for oral itching 2 nd yr: minor side effects in 17/48 SLIT and 15/103 placebo with no difference. 3 SLIT patients with moderate events and 1 placebo patient with a severe event
Rolinck-Werninghaus, 2004 [57]	3-14 Years	39/38	Grasses	3 yrs	188 mcg group 1 allergens	Mild local reactions or rhinitis: 45% of SLIT and 20% of placebo patients. No difference in other AE
Bowen, 2004 [58]	6-52 Years	36/40	Ragweed	4 mths	Cumulative: 10 to 30 mg Amb a 1	Only mild itching in the SLIT group. No overall difference between groups
Dahl, 2006 [59]	18-64 Years	61/32	Grass	6 mths	Cumulat. 2.7 mg Phl p 5	Overall incidence of adverse events equal in SLIT and placebo patients. Mild oral itching: 53% SLIT patients and 5% placebo
Niu, 2006 [60]	6-12 Years	49/48	Mites	6 mths	Cumulat 1.7 mg Der p / 3 mg Der f	Overall incidence of adverse events: 6 SLIT and / placebo patients. Serious adverse events: 1 SLIT and 4 placebo
Passalacqua, 2006 [61]	14-56 Years	28/28	Mites	2 yrs	Allergoid	None
Durham, 2006 [62]	18-60 Years	815	Grasses	4 mths	2,500 SQ 0.06 mg Ph p5/4mths; 25,000 SQ 0.6mg Ph p5/4mths; 75,000 SQ 1.8 mg Ph p5/4 mths	Mild local side effects in 60% of active and placebo recipients. 2% withdrew for side effects. 1 serious side effect in the 25,000 SQ group

*Active/Placebo.

**BU= Biological Units, IR= Index of Reactivity, SQ= Standardized Quality Units, AU= Allergenic Units; RU= Rast Units.

CLINICAL IMPLICATIONS

The optimal safety profile of SLIT is now well ascertained and generally accepted [71]. Also the post-marketing survey in children further confirms that the treatment is well tolerated even below the age of 5 years. For these reasons, it has been proposed that a slow up-dosing phase would not be necessary, in order to make the treatment more patient-friendly and convenient to manage. Indeed, there have been some reports with ultra rush (less than 2 hours) up dosing showing that the rapid increase of the doses does not lead to an increase of side effects [72, 73]. Subsequently, preliminary experiences with the no-updosing (i.e. starting the SLIT with the maintenance dosage) confirmed the feasibility of this administration [74, 75]. The most recent large randomized trials [59, 62] were all performed with the no-updosing regimen and their results in terms of safety were as favorable as those of the studies with the traditional route. A randomized trial compared the safety of the traditional up dosing regimen with the no-updosing [76] in 135 patients and found no difference in adverse events rate between the two groups. A controlled dose finding study of safety [77] involved 48 grass-allergic patients outside pollen season. They received SLIT for 28-day periods at progressively increasing doses, being up to 200 mcg Phl p 5 allergen that is about 40 times the amount given with one injection. The overall incidence of side effects was 74%, all being of mild or moderate intensity. The most frequently reported events were irritation of the throat and oral itching.

Regarding the adjustment of the dose, taking into consideration the published controlled trials, the relation between dosage and side effects is not completely defined, although local effects (oral itching) seem to be dose-dependent [77] whereas the systemic effects are too few to provide clear information. A recent review of the published studies [78] evaluated the occurrence of side effects according to the dose expressed as the ratio between SLIT and an equivalent SCIT treatment. This review concluded that local side effects are even more frequent with "low" doses of allergen (less than 50 times the corresponding SCIT), than with the higher ones. On the other hand, gastrointestinal complaints (nausea, stomachache and vomiting) are dose related. The overall occurrence of all adverse events seemed not to be related to the dose as compared to SCIT (Fig. 1).

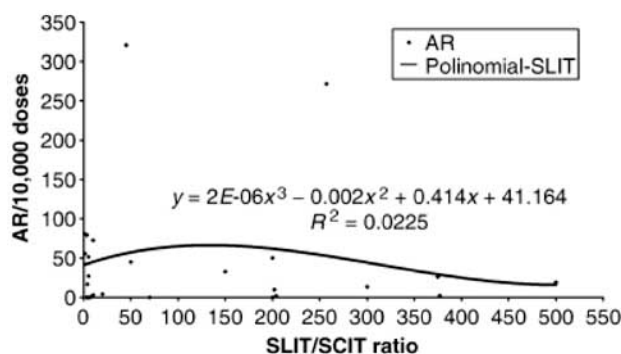
In principle, SLIT could be at particular risk in those patients suffering from oral allergy syndrome, because the administration to the oral mucosa of a cross-reacting allergen could provoke severe reactions. So far there is a single controlled study, performed in 30 patients with oral allergy syndrome, which did not confirm that hypothesis [79]. On the contrary, in a case report it was shown that a course of SLIT with an extract of kiwi fruit was able to reduce the oral symptoms [80].

Finally, it was initially believed that SLIT allows a prompt and rapid absorption of the extract through the sublingual mucosa, thus raising concerns about the safety. The recent pharmacokinetics studies [81, 82] performed in hu-

Table 2. Adverse Events (AE) Reported in the Post Marketing Surveys

Author, Ref.	Number of Pats	Age Range	Average Follow-Up	Allergens	Cumulative Dose Per Year	Adverse Events (% of Patients)	Adverse Events (Per 1,000 Doses)
Di Rienzo [64]	268	2-15 years	3 years	54% mites 25% grass 6% wall pellitory 16% mixed	200 mcg Der 1 39 mcg group 5 24 mcg Par j 1	3 %	0.083/1,000
Lombardi [65]	198	> 14 years	3 years	35% mites 38% grass 23% wall pellitory 4% others	104,000 AU for all allergens	7.5 %	0.5/1,000
Pajno [66]	354	5-15 years	3-4 years	42% mites 20% wall pellitory 11% grass 7% olive 20% mixed	120 mcg Der 1 30 mcg Par j 1 72 mcg group 5 432 mcg Ole e 1	6 %	0.15/1,000
Fiocchi [67]	61	3-7 years	8 months	68% mites 8% wall pellitory 18% grass 6% other	Mean cumulative 36.000±2,000 IR	18%	Not stated
Drachenberg [68]	159	6-60 years	< 1 year	16% mites 37% grass 12% trees 35% other/mix	Not stated	6.3%	Not Stated
Agostinis [69]	36	3-5 years	2 years	House dust mites 19 Grasses 17	90,000 AU for both allergens	5 %	0.07/1,000
Di Rienzo [70]	128	3-5 years	2 years	62% mites 22% grass 12% wall pellitory, 4% others	174 mcg Der 1 39 mcg group 5 24 mcg Par j 1	5.6%	0.2/1,000

mans with radiolabeled allergens, have consistently shown that no relevant passage of the allergen through sublingual mucosa occurs. This excludes the risks due to a rapid absorption of the extract.

**Fig. (1).** Lack of correlation between adverse reactions (AR) and SLIT doses expressed as SLIT to SCIT ratio [78].

CONCLUSIONS

The treatment of respiratory allergy is based on: allergen avoidance, pharmacological treatment and immunotherapy.

Immunotherapy is the unique allergen-oriented treatment, which affects the immune response to allergens. SLIT may be regarded as an advance in immunotherapy, since it offers an additional option and an alternative to SCIT. Its efficacy has been repeatedly proven in meta analysis studies [83, 84] and there are also data on its long-lasting action [85] and prevention effect on the onset of asthma [86].

The results of clinical studies and post-marketing studies conducted in real life confirm that self administration does not represent a problem for safety. It is true that the prescription must be made only by specialists, after a detailed diagnosis has been established and the expected benefit/cost ratio has been carefully evaluated. Moreover, since the treatment is self-managed by the patient, a correct and detailed information and education must be considered mandatory. According to the most extensive review available [71], only 17 serious adverse events (mainly asthma) were reported in 20 years, and only two cases of anaphylaxis were recently described [87, 88].

After several years of partially justified skepticism, in the very recent years there has been a gradual change in the general opinion [89, 90] and SLIT has become a well accepted modality of immunotherapy. It is reasonable to expect that the good safety profile of the treatment would allow to ex-

pand indications and to find more convenient administration modalities.

ACKNOWLEDGEMENTS

This article was partially supported by ARMIA (Associazione Ricerca Malattie Immunologiche e Allergiche).

REFERENCES

- Noon L. Prophylactic inoculation against hay fever. *Lancet* 1911; i: 1572-1573.
- Black JH. The oral administration of pollen. *J Lab Clin Med* 1927; 12: 1156.
- Herxheimer H. Bronchial hypersensitization and hyposensitization in man. *Int Arch Allergy Appl Immunol* 1951; 40: 40-57.
- Taylor G, Shivalkar PR. Local nasal desensitization in allergic rhinitis. *Clin Allergy* 1972; 2: 125-126.
- Taudorf E, Weeke B. Orally administered grass pollen. *Allergy* 1983; 38: 561-564.
- Passalacqua G, Berardi M, Baena-Cagnani CE, Canonica GW. Oral and sublingual immunotherapy in pediatric patients. *Curr Opin Allergy Immunol* 2003; 3: 139-145.
- Committee on the safety of medicines. CSM update. Desensitizing vaccines. *Br Med J* 1986; 293: 948.
- Scadding K, Brostoff J. Low dose sublingual therapy in patients with allergic rhinitis due to dust mite. *Clin Allergy* 1986; 16: 483-491.
- Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy and skin testing. *J Allergy Clin Immunol* 1987; 79: 660-677.
- Reid MJ, Lockey RF, Turkeltaub PC, Platt-Mills TAE. Survey of fatalities from skin testing and immunotherapy. *J Allergy Clin Immunol* 1993; 92: 6-15.
- Malling HJ, Weeke B. EAACI Immunotherapy position paper. *Allergy* 1993; 48 (suppl 44): S64.
- Canonica GW, Passalacqua G. Non injection routes for immunotherapy. *J Allergy Clin Immunol* 2003; 111: 437-448.
- Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy : therapeutical vaccines for allergic diseases. World Health Organization Position Paper. *Allergy* 1998 ; 53(Suppl 54).
- Malling HJ. EAACI Position Paper on local immunotherapy. *Allergy* 1998; 53: 933-944.
- Bousquet J, Van Cauwenberge P. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108(suppl 5): S146-S150.
- Tinkelman DG, Cole WQ, Tunno J. Immunotherapy: a one-year prospective study to evaluate risk factors of systemic reactions. *J Allergy Clin Immunol* 1995; 95: 8-14.
- Lin MS, Tanner E, Lynn J, Friday GA. Nonfatal systemic reactions induced by skin testing and immunotherapy. *Ann Allergy* 1993; 71: 557-562.
- Ostergaard PA, Kaad PH, Kristensen T. A prospective study on the safety of immunotherapy in children with severe asthma. *Allergy* 1986; 41: 588-593.
- Stewart GE, Lockey RF. Systemic reactions from allergen immunotherapy. *J Allergy Clin Immunol* 1992; 90: 567-578.
- Lockey RF, Nikoara-Kasti GL, Theodoropoulos DS, Bukantz SC. Systemic reactions and fatalities associated with allergen immunotherapy. *Ann Allergy Asthma Immunol* 2001; 87 (1 suppl): S46-S55.
- Malling HJ. Immunotherapy as an effective tool in allergy treatment. *Allergy* 1998; 53: 461-472.
- Muller U, Mosbech H. Immunotherapy with hymenoptera venom. Position Paper. *Allergy* 1993; 48(suppl 14): 9-35.
- Aaronson DW, Gandhi TK. Incorrect allergy injections: allergists' experiences and recommendations for prevention. *J Allergy Clin Immunol* 2004; 113: 1117-1121.
- Moller C, Dreborg S, Lanner A, Bjorksten B. Oral immunotherapy of children with rhinoconjunctivitis due to birch pollen allergy. *Allergy* 1986; 41: 271-279.
- Taudorf E, Laursen CL, Lanner A, *et al.* Oral immunotherapy to birch pollen hay fever. *J Allergy Clin Immunol* 1987; 80: 153-161.
- Mosbech H, Dreborg S, Madsen F, *et al.* High dose grass pollen tablets used for hyposensitization in hay fever patients. A one year double blind placebo controlled study. *Allergy* 1987; 42: 451-455.
- Tari MG, Mancino M, Monti G. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double blind study. *Allergol Immunopathol* 1990; 18: 277-284.
- Sabbah A, Hassoun S, Le Sellin J, Andre C, Sicard H. A double blind placebo controlled trial by the sublingual route of immunotherapy with a standardized grass pollen extract. *Allergy* 1994; 49: 309-313.
- Feliziani V, Lattuada G, Parmiani S, Dall'Aglia PP. Safety and efficacy of sublingual rush immunotherapy with grass allergen extracts. A double blind study. *Allergol Immunopathol* 1995; 23: 173-178.
- Troise C, Voltolini S, Canessa A, Pecora S, Negrini AC. Sublingual immunotherapy in parietaria pollen induced rhinitis: a double blind study. *J Invest Allergol Clin Immunol* 1995; 5: 25-30.
- Hirsch T, Sahn M, Leupold W. Double blind placebo controlled study of sublingual immunotherapy with house dust mite extracts in children. *Pediatr Allergy Immunol* 1997; 8: 21-27.
- Clavel R, Bousquet J, Andre' C. Clinical efficacy of sublingual swallow immunotherapy: a double blind placebo controlled trial of a standardized five grass pollen extract in rhinitis. *Allergy* 1998; 53: 493-498.
- Horak F, Stubner UE, Berger U, Marks B, Toth J, Jager S. Immunotherapy with sublingual birch pollen extract: a short term double blind study. *J Invest Allergol Clin Immunol* 1998; 8: 165-171.
- Vourdas D, Syrigou E, Potamianou P, *et al.* Double blind placebo controlled evaluation of sublingual immunotherapy with a standardized olive tree pollen extract in pediatric patients with allergic rhinoconjunctivitis and mild asthma due to olive tree pollen sensitization. *Allergy* 1998; 53: 662-671.
- Hordijk GJ, Antwelink JB, Luwema RA. Sublingual immunotherapy with a standardized grass pollen extract: a double blind placebo controlled study. *Allergol Immunopathol* 1998; 26: 234-240.
- Passalacqua G, Albano M, Fregonese L, *et al.* Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite induced rhinoconjunctivitis. *Lancet* 1998; 351: 629-632.
- Passalacqua G, Albano M, Riccio AM, *et al.* Clinical and immunological effects of a rush sublingual immunotherapy to parietaria species: a double blind placebo controlled trial. *J Allergy Clin Immunol* 1999; 104: 964-968.
- Bousquet J, Scheinmann P, Guinépain MT, *et al.* Sublingual swallow immunotherapy (SLIT) in patients with asthma due to house dust mites: a double blind placebo controlled study. *Allergy* 1999; 54: 249-260.
- Purello D'Ambrosio F, Gangemi S, Isola S, *et al.* Sublingual immunotherapy: a double blind placebo controlled trial with Parietaria judaica extract standardized in mass units in patients with rhinoconjunctivitis, asthma or both. *Allergy* 1999; 54: 968-973.
- Pradaliere A, Basset D, Claudel A, *et al.* Sublingual swallow immunotherapy (SLIT) with a standardized five grass pollen extract (drops and sublingual tablets) versus placebo in seasonal rhinitis. *Allergy* 1999; 54: 819-828.
- La Rosa M, Ranno C, Andre' C, *et al.* Double blind placebo controlled evaluation of sublingual swallow immunotherapy with standardized parietaria judaica extract in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 1999; 104: 425-432.
- Guez S, Vatrinet C, Fadel R, Andre' C. House dust mite sublingual swallow immunotherapy in perennial rhinitis: a double blind placebo controlled study. *Allergy* 2000; 55: 369-375.
- Pajno GB, Morabito L, Barberio G, Parmiani S. Clinical and immunological effects of longterm sublingual immunotherapy in asthmatic children sensitized to mite: a double blind study. *Allergy* 2000; 55: 842-849.
- Caffarelli C, Sensi LG, Marcucci F, Cavagni C. Preseasonal. local allergoid immunotherapy to grass pollen in children: a double-blind, placebo-controlled, randomized trial. *Allergy* 2000; 55: 1142-1147.
- Ariano R, Spadolini I, Panzani RC. Efficacy of sublingual specific immunotherapy in Cupressaceae allergy using an extract of Cupressus arizonica. A double blind study. *Allergol Immunopathol (Madr)* 2001; 29: 238-244.
- Bahceciler NN, Isik U, Barlan IB, Basaran N. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. *Pediatr Pulmonol* 2001; 32: 49-55.
- Voltolini S, Modena P, Minale P, *et al.* Sublingual immunotherapy in tree pollen allergy. Double blind, placebo controlled study with a

- biologically standardized extract of tree pollen (alder, birch and hazel) administered by a rush schedule. *Allergol Immunopathol* 2001; 29: 103-110.
- [48] Lima MT, Wilson D, Pitkin L, *et al.* Grass pollen sublingual immunotherapy for seasonal rhinoconjunctivitis : a randomized controlled trial. *Clin Exp Allergy* 2002; 32: 507-514.
- [49] Mortemousque B, Bertel F, De Casamayor J, Verin P, Colin J. House-dust mite sublingual-swallow immunotherapy in perennial conjunctivitis: a double-blind, placebo-controlled study. *Clin Exp Allergy* 2003; 33: 464-469.
- [50] André C, Perrin-Fayolle M, Grosclaude M, *et al.* A double blind placebo controlled evaluation of SLIT with a standardized ragweed extract in patients with seasonal rhinitis. *Int Arch Allergy Immunol* 2003; 131: 111-118.
- [51] Ippoliti F, De Sanctis W, Volterrani A, *et al.* Immunomodulation during sublingual therapy in allergic children. *Pediatr Allergy Immunol* 2003; 14: 216-221.
- [52] Pajno G, Vita D, Caminiti D, Parmiani S, Barberio G. Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to Parietaria pollen treated with inhaled fluticasone propionate. *Clin Exp Allergy* 2003; 33(12): 1641-7.
- [53] Wuthrich B, Bucher Ch, Jorg W, *et al.* Double-blind, placebo-controlled study with sublingual immunotherapy in children with seasonal allergic rhinitis to grass pollen. *J Investig Allergol Clin Immunol* 2003; 13(3): 145-8.
- [54] Tonnel AB, Scherpereel A, Douay B, *et al.* Allergic rhinitis due to house dust mites: evaluation of the efficacy of specific sublingual immunotherapy. *Allergy* 2004; 59(5): 491-7.
- [55] Bufe A, Ziegler-Kirbach E, Stoeckmann E, *et al.* Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. *Allergy* 2004; 59: 498-504.
- [56] Smith H, White P, Annala I, Poole J, Andre C, Frew A. Randomized controlled trial of high-dose sublingual immunotherapy to treat seasonal allergic rhinitis. *J Allergy Clin Immunol* 2004; 114: 831-7.
- [57] Rolinck-Werninghaus C, Wolf H, Liebke C, *et al.* A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy* 2004; 59: 1285-1293.
- [58] Bowen T, Greenbaum J, Charbonneau Y, *et al.* Canadian trial of sublingual swallow immunotherapy for ragweed rhinoconjunctivitis. *Ann Allergy Asthma Immunol* 2004; 93: 425-30.
- [59] Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy* 2006; 61: 185-901.
- [60] Niu CK, Chen WY, Huang JL, Lue KH, Wang JY. Efficacy of sublingual immunotherapy with high-dose mite extracts in asthma: A multi-center, double-blind, randomized, and placebo-controlled study in Taiwan. *Respir Med* 2006; 100(8): 1374-83.
- [61] Passalacqua G, Pasquali M, Ariano R, *et al.* Randomized double blind controlled study with sublingual carbamylated allergoid in mild rhinitis due to mites. *Allergy* 2006; 61(Suppl 81): 20-3.
- [62] Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass-allergen tablets: a randomised controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006; 117(4): 802-9.
- [63] André C, Vatrinet C, Galvain S, Carat F, Sicard H. Safety of sublingual swallow immunotherapy in children and adults. *Int Arch Allergy Immunol* 2000; 121: 229-234.
- [64] Di Rienzo V, Pagani A, Parmiani S, Passalacqua G, Canonica GW. Post-marketing surveillance study on the safety of sublingual immunotherapy in children. *Allergy* 1999; 54: 1110-1113.
- [65] Lombardi C, Gargioni S, Melchiorre A, *et al.* Safety of sublingual immunotherapy in adults: a post marketing surveillance study. *Allergy* 2001; 56: 889-892.
- [66] Pajno GB, Peroni DG, Vita D, Pietrobelli A, Parmiani S, Boner AL. Safety of Sublingual immunotherapy in children with asthma. *Paediatr Drugs* 2003; 5: 777-81.
- [67] Fiocchi A, Pajno G, La Grutta S, *et al.* Safety of SLI T in children aged 3 TO 7 years. *Ann Allergy Asthma Immunol* 2005; 95(3): 254-8.
- [68] Drachenberg KJ, Urban E, Proll S, Woroniecki SR. Sublingual specific immunotherapy for adults and children: a post marketing survey. *Allergo Immunopathol* 2004; 32: 76-81.
- [69] Agostinis F, Tellarini L, Falagiani P, Canonica GW, Passalacqua G. Safety of SLIT in very young children. *Allergy* 2004; 60(1): 133.
- [70] Di Rienzo V, Minelli M, Musarra A, *et al.* Post-marketing survey on the safety of sublingual immunotherapy in children below the age of 5 years. *Clin Exp Allergy* 2005; 35: 560-4.
- [71] Cox LS, Linnemann DL, Nolte H, Weldon D, Finegold I, Nelson HS. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol* 2006; 117(5): 1021-35.
- [72] Rossi R, Monasterolo RE. A pilot study of feasibility of ultra-rush (20-25 minutes) sublingual-swallow immunotherapy in 679 patients (699 sessions) with allergic rhinitis and/or asthma. *Int J Immunopathol Pharmacol* 2005; 18(2): 277-85.
- [73] Tripodi S, Di Rienzo Businco A, Benincori N, Scala G, Pingitore G. Safety and tolerability of ultra-rush induction, less than one hour, of sublingual immunotherapy in children. *Int Arch Allergy Immunol* 2005; 139(2): 149-152.
- [74] Grosclaude M, Bouillot P, Alt R, *et al.* Safety of various dosage regimens during induction of sublingual immunotherapy. *Int Arch Allergy Immunol* 2002; 129: 248-253.
- [75] Guerra L, Compalati E, Rogkakou A, Pecora S, Passalacqua G, Canonica GW. Randomized open comparison of the safety of SLIT in a no up dosing and traditional up dosing schedule in patients with parietaria allergy. *Allergol Immunopathol* 2006; 34: 82-83.
- [76] Rodriguez F, Boquete M, Ibanez MD, de la Torre-Martinez F, Tabar AI. Once daily sublingual immunotherapy without up dosing-a new treatment schedule. *Int Arch Allergy Immunol* 2006; 140: 321-326.
- [77] Kleine-Tebbe J, Ribel M, Herold DA. Safety of a SQ-standardised grass allergen tablet for sublingual immunotherapy: a randomized, placebo-controlled trial. *Allergy* 2006; 61(2): 181-4.
- [78] Gidaro GB, Frati F, Sensi L, Marcucci F, Incorvaia C, Ciprandi G. The safety of sublingual-swallow immunotherapy: an analysis of published studies. *Clin Exp Allergy* 2005; 35(5): 565-71.
- [79] Lombardi C, Canonica GW, Passalacqua G. Sublingual immunotherapy is clinically safe in patients with oral allergy syndrome. *Allergy* 2000; 55: 677-678.
- [80] Mempel M, Rakoski J, Ring J, Ollert M. Severe anaphylaxis to kiwi fruit: Immunologic changes related to successful sublingual allergen immunotherapy. *J Allergy Clin Immunol* 2003; 111: 1406-1409.
- [81] Bagnasco M, Mariani G, Passalacqua G, *et al.* Absorption and distribution kinetics of the mayor Parietaria allergen administered by noninjectable routes to healthy human beings. *J Allergy Clin Immunol* 1997; 100: 121-129.
- [82] Bagnasco M, Passalacqua G, Villa G, *et al.* Pharmacokinetics of an allergen and a monomeric allergoid for oromucosal immunotherapy in allergic volunteers. *Clin Exp Allergy* 2001; 31: 54-60.
- [83] Wilson DR, Torres LI, Durham SR. Sublingual immunotherapy for allergic rhinitis (Cochrane review). *Cochrane Database Syst Rev* 2003; 2: CD002893.
- [84] Penagos M, Tarantini E, Compalati E, *et al.* Efficacy of sublingual immunotherapy for rhinitis. Meta analysis in pediatric patients. *Ann Allergy Asthma Immunol* 2006; 97(2): 141-8.
- [85] Di Rienzo V, Marcucci F, Puccinelli P, *et al.* Long lasting effect of sublingual immunotherapy in children with asthma due to house dust mites: a ten-year prospective study. *Clin Exp Allergy* 2003; 33: 206-210.
- [86] Novembre E, Galli E, Landi F, *et al.* Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2004; 114: 851-7.
- [87] Dunskey EH, Goldstein FM, Dvorin J, Belecanech GA. Anaphylaxis to sublingual immunotherapy. *Allergy* 2006; 61: 1235.
- [88] Antico A, Pagani M, Crema A. Anaphylaxis by latex sublingual immunotherapy. *Allergy* 2006; 61: 1236.
- [89] Bousquet J. Sublingual immunotherapy: from proven prevention to putative rapid relief of allergic symptoms. *Allergy* 2005; 60: 1-3.
- [90] Bieber T. Allergen-specific sublingual immunotherapy: less mystic, more scientific. *Allergy* 2006; 61(2): 149-50.