

Sublingual and oral immunotherapy

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Allergen-specific immunotherapy (IT) or allergen vaccination is the practice of administering increasing amounts of allergens (allergenic extract) to allergic patients to achieve a hyposensitization that will reduce (ideally abolish) symptoms during the natural exposure to the allergens. IT first was used in an empirical way as subcutaneous injections (SCITs) at the beginning of the past century [1]. This kind of treatment immediately proved effective in controlling symptoms of hay fever, and its use increased around the world. During the past century, investigators sporadically proposed and investigated other modalities of administration involving the administration of allergenic extract by way of gastrointestinal, nasal, or bronchial routes (Table 1). Oral administration of pollens first was suggested in 1900 [2], and clinical attempts were described a few years later [3,4]. In the subsequent years, other routes of administration were proposed, such as the bronchial route during the 1950s [5,6] and the nasal route during the 1970s [7,8]. The nasal administration of allergens was studied extensively. The oral route underwent rigorous controlled trials at the beginning of the 1980s [9–11]. In 1986, the British Committee for the Safety of Medicines [12] documented several deaths caused by SCIT and raised serious concerns about the safety and the risk–benefit ratio of SCIT. At that time, cheap and effective drugs (eg, nasal and inhaled steroids) had become available. It subsequently was demonstrated that, in most cases, life-threatening events were caused by avoidable human errors (wrong dose, improper prescription, incorrect administration)

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

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Table 1

Historical and early attempts with noninjection routes of immunotherapy

Author	Year	Journal	Article title
Curtis	1900	Med News (NY)	The immunizing cure of hayfever
Noon	1911	Lancet	Prophylactic inoculation against hay fever
Dunbar	1913	J Hyg	The present state of knowledge of hayfever
Black	1927	J Lab Clin Med	The oral administration of pollen
Zaler	1939	J Allergy	Oral ragweed pollen therapy
Feinberg	1940	JAMA	Oral pollen therapy in ragweed pollenosis
Black	1950	J Allergy	Treatment of respiratory allergy in children by oral administration of pollens
Herxheimer	1951	Int Arch Allergy App Immunol	Bronchial hypersensitization and hyposensitization in man
Swineford	1955	J Allergy Clin Immunol	Treatment of pollen hayfever and asthma by aerosols of pollens
Taylor	1972	Clin Allergy	Local nasal desensitization in allergic rhinitis
Scadding	1986	Clin Allergy	Low dose sublingual therapy in patients with allergic rhinitis due to dust mite

[13–15]. The interest in noninjection routes of IT rapidly increased [16], and the sublingual route was introduced [17]. Within the past 15 years, more than 50 controlled trials with noninjection routes have been published in peer-reviewed journals. The primary aim for administering allergens locally was to minimize or abrogate the risk for severe adverse events [16].

In 1998, a panel of experts from the World Health Organization extensively reviewed the literature and concluded that sublingual IT (SLIT) and local nasal IT are viable alternatives to the injection route and that their use in adults in clinical practice is justified [18]. The pure oral and bronchial routes were not recommended. These conclusions were confirmed in a position paper by the European Academy of Allergology and Clinical Immunology (EAACI) [19]. In 2001, the Allergenic Rhinitis and its Impact on Asthma (ARIA) document [20] extended the indication for SLIT use to children.

General aspects

The non-SCIT routes have various names: alternative, nonparenteral, non-injection, or local routes. The most proper terms are “local” and “noninjection,” which are equivalent, whereas the word “alternative” has been abandoned, because it might generate confusion with other unconventional medicines, such as homeopathy or acupuncture [21].

For allergenic extracts that are administered by way of the gastrointestinal tract, it is important to distinguish between pure oral IT (OIT) and SLIT, because these two terms generally are considered to be interchangeable. In OIT, the allergen, which is prepared as an aqueous solution, a tablet, or a gastroresistant capsule, immediately is swallowed with water or fruit juice. In SLIT, the extract is kept under the tongue for 1 to 2 minutes and then swallowed; this route is also

named the sublingual–swallow route. In some studies, the allergen was kept under the tongue and then spat out: this modality was called the sublingual–spit route. Only the sublingual–swallow route is used; the acronym SLIT indicates the sublingual–swallow modality [22].

In rigorous, well-controlled studies, OIT performed poorly or was effective only in high doses (with consequent side effects), whereas SLIT showed an incontrovertible clinical efficacy. It can be hypothesized that contact with the oral mucosa has a critical role in the action of these forms of IT. It was believed that sublingual administration allowed a prompt absorption of the allergen. This latter hypothesis has been excluded in pharmacokinetic studies performed in humans (discussed later in this article).

Oral immunotherapy

OIT represented the starting point for the subsequent use of SLIT. The rationale for giving the allergen orally is that the gastrointestinal tract has an abundant mucosal immune system (gut-associated lymphoid tissue), and effective antigen presentation is expected [23–26]. The earliest rigorous studies of OIT performed in the 1980s reported controversial or negative results and seemed to bring OIT into disfavor [9–11]. In subsequent trials performed by Scandinavian investigators, higher doses of allergen provided some favorable results and renewed the interest in oral administration.

Nine double-blind, placebo-controlled (DBPC) trials of OIT (Table 2) were performed with various allergens and conducted in a rigorous fashion [27–35]. The trials mainly evaluated the effects of OIT on rhinitis (symptoms and drug intake), and most of the trials were conducted in pediatric patients. Only three studies showed a statistically significant improvement of rhinitis symptoms [29,31,32]. In a dust-mite study, the clinical improvement of rhinitis could be

Table 2

Double-blind, placebo-controlled studies with oral immunotherapy

Reference	Age range (y)	Allergen	Duration	No. of patients taking A/P	Extract	Disease
Cooper, 1984 [27]	5–15	Grass	4 mo	22/22	Aqueous drops	R
Taudorf, 1985 [28]	11–44	Grass	6 mo	25/27	Enteric-coated tabs	R
Moller, 1986 [29]	9–17	Birch	10 mo	14/16	Enteric-coated tabs	R
Mosbech, 1987 [31]	15–38	Grass	12 mo	24/27	Enteric-coated tabs	R
Taudorf, 1987 [30]	16–47	Birch	18 mo	18/21	Enteric-coated tabs	R
Oppenheimer, 1994 [33]	3–13	Mite	3 y	10/8	Aqueous drops	R/A
Giovane, 1994 [32]	7–15	Mites	6 mo	8/7	Aqueous drops	R/A
Van Deusen, 1997 [34]	19–49	Ragweed	14 wk	12/11	Capsules	R
Litwin, 1997 [35]	21–50	Ragweed	4 mo	20/21	Capsules	R

Abbreviations: A, asthma; A/P, active treatment/placebo; R, rhinitis; tabs, tablets.

detected only after 2 years of treatment, and improvement of asthma symptoms became significant only at 3 years [32]. In almost all studies, many side effects were reported, although they were not life threatening. The side effects were mainly gastrointestinal (nausea, vomiting, stomachache, sublingual itching) and seemed to be dose dependant, because their frequency increased as the dose of the allergen increased [30]. Because it was hypothesized that the allergen was destroyed by gastric juices, the use of gastroresistant capsules was proposed to avoid the degradation. This pharmaceutical form did not enhance the performance of OIT [29,34,35]. Overall, the measurable clinical efficacy of OIT was marginal and could be achieved only with high doses.

OIT showed immunologic effects resembling those provoked by SCIT (eg, increase in levels of IgG subclasses, reduction of specific reactivity at the target organs) [32,36]; however, for all of the aforementioned reasons (eg, low efficacy, need for high dosage, costs), the clinical use of OIT is no longer recommended [18–20], and clinical trials with OIT were abandoned beginning in the early 1990s.

Clinical efficacy of sublingual immunotherapy

As mentioned previously, the original rationale for sublingual administration of IT was to achieve a prompt and rapid absorption of the allergen extract and avoid possible gastrointestinal degradation. Although it was demonstrated that no direct absorption through the sublingual mucosa occurs, SLIT proved to be effective since the first attempts made in 1986. In 1998, the World Health Organization (based on four studies), and the EAACI and European Society for Paediatric Allergology and Clinical Immunology (considering six studies) concluded that SLIT is a viable alternative to SCIT [18,19]. A total of 27 DBPC randomized trials (Table 3), a meta-analysis, and several postmarketing surveys have examined the efficacy of SLIT [22,37]. Most of these studies were performed in allergic rhinitis, and eight studies included only pediatric patients.

All of the studies [38–64] except three [42,53,59] substantially confirmed the clinical efficacy of SLIT in rhinitis induced by common allergens, such as grass, mites, birch, and parietaria pollen. Studies of olive, cypress, and mixed-trees extracts also have reported positive results. In all of the studies, the primary outcome variable was symptom score, which various studies combined with drug intake. In some studies, other objective parameters, such as the specific nasal or conjunctival reactivity, peak expiratory flow rate, or immunologic changes, were assessed and showed a measurable objective effect. Overall, the magnitude of the clinical efficacy ranged from an approximate 20% reduction to a more than 60% reduction of symptoms or medication scores. Two studies with mite extracts [42,53] failed to demonstrate a significant difference between placebo and SLIT despite a trend toward improvement that was seen in the active-treatment groups. SLIT and SCIT generally are less effective in mite-allergic patients than in patients with pollinosis. In mite-allergic patients, positive results were seen for

Table 3

Summary of the double-blind, placebo-controlled studies of sublingual immunotherapy

Reference	Age range (y)	Patients A/P	Allergen	Duration	Cumulative dose	Disease
Tari, 1990 [38]	5–12	30/28	Mites	18 mo	365 STU	R/A
Sabbah, 1994 [39]	13–51	19/29	Grasses	17 wk	4500 IR	R
Feliziani, 1995 [40]	14–48	18/16	Grasses	3.5 mo	25 BU	R
Troise, 1995 [41]	17–60	15/16	<i>Parietaria</i>	10 mo	105 BU	R
Hirsch, 1997 [42]	6–16	15/15	Mites	1 y	570-g Der p1	R/A
Passalacqua, 1998 [47]	15–46	10/9	Mites (monoid)	2 y	10,000 AU	R
Vourdas, 1998 [45]	7–17	33/31	Olive	2 y	4-mg Ole e 1	R/A
Clavel, 1998 [43]	8–55	62/28	Grasses	6 mo	28 µg Phl p 5	R/A
Horak, 1998 [44]	16–48	18/16	Birch	4 mo	250 STU	R
Hordijk 1998 [46]	18–45	30/27	Grasses	6 mo	100,000 BU	R/A
Bousquet, 1999 [49]	15–37	15/15	Mites	2 y	25-mg Der p 1	A
Passalacqua, 1999 [48]	15–42	15/15	<i>Parietaria</i>	8 mo	16-mg Par j 1	R/A
Pradalier, 1999 [51]	6–25	59/61	Grasses	4 mo	5000 STU	R/A
La Rosa, 1999 [52]	6–14	20/21	<i>Parietaria</i>	6 mo	4000 STU	R/A
Purello, 1999 [50]	14–50	14/16	<i>Parietaria</i>	8 mo	12-mg Par j 1	R/A
Pajno, 2000 [54]	8–15	12/12	Mites	2 y	2.4-mg Der p 1	A
Guez, 2000 [53]	6–51	24/18	Mites	2 y	2.2-mg Der p 1	R
Caffarelli, 2000 [55]	4–14	24/20	Grasses	3 mo	32,000 AU	R/A
Ariano, 2001 [56]	19–50	10/10	Cypress	8 mo	250,000 RU	R/A
Bahceciler, 2001 [57]	7–15	8/7	Mites	6 mo	2000 IR	R/A
Voltoni, 2001 [58]	15–52	24/13	Trees	24 mo	4000 IR	R
Lima, 2002 [59]	16–48	24/22	Grasses	18 mo	16-mg Phl p 5	R
Mortemousse, 2003 [60]	6–60	26/19	Mites	24 mo	2.2-mg Der p 1	C
Andrè, 2003 [61]	6–55	48/51	Ragweed	7 mo	variable	R
Ippoliti, 2003 [62]	5–12	47/39	Mites	6 mo	12 µg Der p1	R/A
Pajno, 2003 [63]	8–14	15/15	<i>Parietaria</i>	13 mo	23 µg Par j1	R/A/C
Wutrich, 2003 [64]	6–13	11/11	Grasses	2 y	not available	R/A

Abbreviations: A, asthma; A/P, active/placebo; C, conjunctivitis; R, rhinitis.

treatments of long duration [47,49,54,60]. One study of grass pollen SLIT and placebo, despite no significant difference in clinical score, showed a clear-cut difference between the two treatment groups as assessed by patient self-evaluation [59]. This study also demonstrated a systemic immunologic effect (reduction of the late cutaneous response and increase in IgG4 levels).

Wilson et al evaluated the efficacy of SLIT in allergic rhinitis in a meta-analysis [65]. The analysis included 22 randomized, placebo-controlled trials, four of which were performed in children. A total of 979 patients participated in the studies. The meta-analysis concluded that SLIT significantly differs from placebo in the ability to reduce symptoms and the need for medications in patients with allergic rhinitis, and the overall safety of SLIT was satisfactory. According to evidence-based medicine criteria, the efficacy of SLIT in rhinitis is graded as 1a, and the strength of recommendation is A [66].

The studies devoted to asthma are few, and a meta-analysis is not possible [45,49–52,54,63]. The results of the single studies are encouraging. They documented a reduction in the number of days with asthma symptoms, use of β_2 -agonists, intake of systemic steroids, and clinical symptoms. Andr  et al [61] evaluated the efficacy of SLIT with a ragweed extract, which was given to 99 patients for 6 months, and found a lower occurrence of asthma in the active-treatment group. The magnitude of the efficacy was partly dose dependent. Ippoliti et al [62] evaluated the effects of SLIT in 86 children with asthma and rhinoconjunctivitis caused by mites and found that after 6 months of treatment, asthma and rhinitis symptoms significantly improved and the forced expiratory volume in 1 second changed significantly. One study documented a measurable effect of SLIT on quality of life [49]. In an uncontrolled, not randomized, retrospective study involving 288 children who were treated with SLIT [67], complete remission was obtained in approximately 80% of patients, accompanied by significant changes in objective parameters, such as rhinomanometry. Cirila et al [68] demonstrated a reduction of the priming effect caused by tree allergy in patients who were sensitized to birch or hazel and grass pollen and were treated with combined SLIT and SCIT. In an open-label, controlled study, SLIT with a grass extract reduced the nonspecific bronchial hyperresponsiveness to methacholine, which was measured outside of the pollen season [69]. The effect of SLIT on nonspecific bronchial hyperresponsiveness was confirmed in a randomized, controlled, open-label trial involving more than 500 patients [70]. In a randomized, double-blind, placebo-controlled study involving 30 children with parietaria-induced asthma, Pajno et al [71] found that SLIT abrogated seasonal bronchial hyperresponsiveness.

One DBPC study evaluated the effects of SLIT on allergic conjunctivitis [60]. Sixty patients with perennial conjunctivitis caused by mites were treated for 24 months. A significant increase in the threshold dose at conjunctival provocation and a significant clinical efficacy were seen. The use of SLIT was proposed for latex allergy. Patriarca et al [72] described conducted a preliminary, nonrandomized, open-label study involving 12 patients with an ultra-rush SLIT. The treatment proved to be effective in desensitizing the natural exposure to rubber latex.

Safety issues of sublingual immunotherapy

The primary rationale for SLIT (and other noninjection routes) is to minimize or abolish the risk for adverse events. With SCIT, the rate of systemic reactions is variable and depends on the administration schedule, allergen, and survey method. The rate of systemic reactions with SCIT ranges between 0.5% and 2.9% [73,74], although higher figures were reported in children [75]. Approximately 20% of DBPC clinical trials of SCIT provide no information about side effects [76], and in the remaining studies, side effects are reported to occur in a mean 14% of patients. On administration of SCIT, the overall occurrence of systemic

reactions is estimated to range from 0.05% to 0.6% [77], and near-fatal events are rare when SCIT is administered correctly [78]. Although the risk for fatalities is estimated to be less than 1 death per 2 million injections, the risk for severe systemic side effects is real, although low.

A completely different scenario is observed with SLIT. Since its introduction in 1986, no life-threatening adverse event or fatality has been described in the literature or in clinical practice. The overall occurrence of side effects as derived from the postmarketing study is 0.1 to 0.5 per 1000 doses (discussed later in this article). This incidence is much lower than that reported for SCIT.

The most frequently reported side effects are local and involve the site of administration: oral or sublingual itching after taking the dose, stomachache, and nausea. These events are described as mild and self-resolving, and they can be managed by a temporary reduction of the dose. In published clinical trials, discontinuation of SLIT because of a side effect rarely was required. The occurrence of side effects seems to be low in pediatric patients, in whom the treatment was tolerated optimally. In one study, three cases of asthma were reported [38], whereas in another study, one subject dropped out because of adverse events [63]. One trial reported a high rate of gastrointestinal adverse events [52], but the amount of allergen was 375-fold the amount administered in a standard SCIT course. These facts, and other data from the studies, confirm the impression that the frequency and intensity of side effects are partly dose related. Systemic side effects (eg, headache, constipation, rhinitis, asthma, urticaria) occurred sporadically in randomized trials, and their overall occurrence did not differ among the placebo and active-treatment groups.

Andr  et al [79] performed a retrospective review of SLIT in eight trials that were performed with extracts from a single manufacturer. The analysis involved 690 subjects (347 received active treatment, and 343 received placebo), of which 218 were children (103 received active treatment, and 115 received placebo). The systemic side effects were mild, and their occurrence did not differ in the active-treatment and placebo groups. Only the oral and gastrointestinal side effects were found to be significantly more frequent than in the active-treatment group than in the placebo group, but the effects were of mild intensity.

Although the information on safety in controlled trials is important, it must be taken into account that the populations in clinical studies strictly are selected, the administration of SLIT usually is supervised, and all side effects are recorded. The situation is different in clinical practice, in which patients often self-manage SLIT. More realistic data concerning safety can be obtained by postmarketing surveillance studies. An early study reported that the incidence of side effects was low: Oral itching represented approximately 50% of the untoward effects, followed by rhinorrhea and constipation [80]. Urticaria and asthma were rare. More than 90% of the effects were mild and did not require medical treatment.

Di Rienzo et al [81] followed 268 children between 2 and 15 years of age who received SLIT for up to 3 years. The overall rate of systemic side effects was 3% in these patients and occurred with 1 in 12 doses; no discontinuation was needed, however. Of the eight side effects, only one case of urticaria was judged of

moderate severity and required a single dose of an oral antihistamine. Another large pharmacosurveillance study was performed in 198 patients who were observed for approximately 3 years [82]. Side effects occurred in 7.5% of patients and with 0.52 in 1.00 doses. Four urticaria cases and two gastrointestinal complaints were judged of moderate intensity. Side effects were controlled by a temporary dose adjustment, and no cases required discontinuation of treatment.

An increased risk for adverse events could be expected in patients with oral allergy syndrome. It has been suggested that the administration of a relatively large amount of a purified cross-reacting protein could provoke severe local reactions. A parallel-group, controlled study involving 30 patients with oral allergy syndrome did not confirm that hypothesis [83]. It has been shown that no change in oral mucosal tryptase occurs after the administration of SLIT in children, even patients with oral itching [84]. In a case report, a course of SLIT with an extract of kiwi fruit was beneficial in a woman with severe adverse reactions to kiwi fruit [85].

The data from the randomized, controlled trials and the pharmacosurveillance studies seem to provide good documentation of the safety of SLIT. This support is why the ARIA document stated that SLIT can be administered safely to adults and children [20].

Comparison of sublingual immunotherapy and subcutaneous injection

One of the most controversial and unresolved issues in the clinical use of SLIT is its efficacy and safety when compared with those of SCIT. Because SCIT has been used for a century, a large body of evidence, especially on its long-term effect, is available. SLIT has been administered for the past 15 years, and comparative data are still lacking.

The first aspects to be considered when comparing the two routes of IT are the magnitude of the clinical efficacy and the safety. In the case of specific IT, it is difficult to directly compare the two routes, because clinical studies are time consuming and expensive, a correct selection of patients is difficult, and a placebo arm is necessary to establish a correct and rigorous study design. Because two different ways of administration are being compared, the double-blind, double-dummy design is the more appropriate method [86].

Several attempts to compare SCIT and SLIT have been made (Table 4). In an open-label and not randomized study, Ongari et al [87] showed that the two routes had similar efficacy in 20 patients with grass allergy and that both treatments were significantly more effective than pharmacologic treatment alone. Other investigators studied 20 patients with allergy caused by *Alternaria tenuis* for 12 months and found a significant clinical improvement in SLIT and SCIT recipients [88]. Another study assessed the clinical efficacy of SLIT, SCIT, and local nasal IT in 43 patients with rhinitis caused by mites: Only the immunologic changes, which were significant for SCIT, were emphasized [89]. Nevertheless, the investigators acknowledged that SLIT was tolerated well. In an open com-

Table 4

Summary of the studies directly comparing sublingual immunotherapy with subcutaneous injection

Reference	Design	Patients	Allergen	Main results
Ongari [87]	Open, controlled	5 controls 8 SLIT 7 SCIT	Grass	Treatments equally effective on symptoms
Bernardis [88]	Open, controlled	12 SLIT 11 SCIT	<i>Alternaria</i>	Symptoms and drug intake with both treatments
Piazza [89]	Open, controlled	17 SCIT 14 SLIT 12 Nasal IT 14 controls	Mite	Symptoms with all treatments IgE and IgG4 only with SCIT
Mungan [90]	Open, placebo-controlled, randomized	15 SLIT 11 SCIT 10 PLA	Mite	Rhinitis symptoms with both treatments Asthma symptoms only with SCIT
Quirino [91]	Double-blind, double-dummy, randomized, controlled	10 SLIT 10 SCIT	Grass	Equally effective SLIT better tolerated
Kinchi [92]	Double-blind, double-dummy, randomized, placebo-controlled	21 SCIT 18 SLIT 19 PLA	Birch	Rate of symptoms: 50% with SLIT and 66% with SCIT versus baseline Both treatments better than placebo No side effects greater than grade 2 with SLIT

Abbreviation: PLA, placebo.

parison study involving mite-allergic patients who were treated with SLIT or SCIT, the symptom score for asthma and rhinitis were considered separately [90]. This study demonstrated that the clinical improvement was more rapid and of greater magnitude with SCIT than with SLIT, especially for asthma symptoms; however, rhinitis symptoms also were controlled with SLIT. This latter study is heavily biased by the fact that the groups were not homogeneous for asthma scores at baseline.

The aforementioned studies provide incomplete information because of the inadequate study design and methodologic biases. Only two double-blind, double-dummy studies have been published. The first one involved 20 patients with grass pollen allergy who were treated for 8 months [91]. SLIT and SCIT had equivalent clinical efficacy (incidence of symptoms and drug intake), but SLIT overall was better tolerated. This study was well designed, but the absence of a placebo arm made the results inconclusive. A randomized, double-blind, double-dummy, placebo-controlled study from 2004 compared the efficacy of SLIT, SCIT, and placebo in 71 patients with birch pollen allergy who were followed for three consecutive pollen seasons (the study included a baseline evaluation) [92]. Clinical scores, medication intake, side effects, and quality of life were evaluated. No significant difference between SLIT and SCIT in terms of symptom scores

and drug intake was found, and the overall disease severity was reduced by 50% in the SLIT group and by 66% in the SCIT group. Both active treatments proved superior to placebo. SCIT seemed to be slightly more effective, but SLIT displayed a superior safety profile (no effects from grades 3–4 with SLIT versus one grade-4 side effects and five grade-3 side effects with SCIT).

Another important aspect of the comparison between SLIT and SCIT is long-lasting efficacy, which has been well demonstrated for SCIT [93] but not for SLIT. In a prospective, parallel-group, controlled study involving 60 children (mean age, 8.5 years) with allergic asthma or rhinitis caused by mite, 35 children underwent a 4- to 5-year course of SLIT with a standardized extract, and 25 children (control group) received only drug therapy [94]. The patients were evaluated at baseline, the end of SLIT, and 4 to 5 years later. In the SLIT group, a significant difference for the presence of asthma ($P < 0.001$), compared with baseline values, was documented, even 5 years after discontinuation, whereas no difference was observed in the control group. Based on these results, it can be expected that SLIT can exert a long-lasting effect that is similar to that of SCIT.

The superiority of SCIT versus SLIT also was claimed because SCIT was shown to prevent the onset of new skin sensitizations [95–97]; however, data showing that SLIT also results in such prevention recently became available. In a randomized, open-label study performed for 3 years in more than 500 patients [71], new sensitizations occurred in 38% of control patients and in only 6% of the SLIT recipients.

Immunology and pharmacokinetics of sublingual immunotherapy

The mechanisms of action of SCIT have been described [98,99]. SCIT down-regulates the production of cytokines and mediators and decreases the activation and recruitment of effector cells [100,101] by acting on the T helper cell type 1–T helper cell type 2 (Th1–Th2) balance [102,103]. SLIT has been studied mainly from a clinical point of view to assess its efficacy and safety. Few observations concerning its mechanisms of action have been elucidated. In early experiments, SLIT reduced the *in vitro* proliferative response of T lymphocytes from atopic subjects [104], and this finding also was observed with local nasal IT [105]. *In vivo*, SLIT reduced the influx of inflammatory cells after specific antigen challenge of the nose [48] and conjunctiva [47]. In those cases, the reduction of the inflammatory infiltrate paralleled the clinical efficacy and the reduction of the epithelial expression of the intercellular adhesion molecule 1 (ICAM-1). An open-label study involving 10 children confirmed that SLIT could reduce ICAM-1 expression on nasal epithelial cells and decrease methacholine responsiveness [106]. Concerning immunoglobulins (specific IgE and IgG4), their modifications with SLIT are sometimes similar to those seen with SCIT, but usually less relevant [51,52,54,59]. The effect of SLIT on the late-phase cutaneous response to allergens is similar to that observed with SCIT [63]. In one study involving children, a significant decrease of serum eosinophilic ca-

tonic protein and IL-13 was shown [62]. This latter finding is in agreement with the hypothesis that SLIT had an effect on the Th1–Th2 balance, because IL-13 is a typical Th2 cytokine.

After a century of use, the absorption and fate of the allergenic extracts injected subcutaneously in humans still are not known. The pharmacokinetics is of greater relevance when the allergens are administered by way of the gastrointestinal tract. Clinical studies showed that the allergen that is swallowed immediately (oral route) performs poorly, whereas the allergen that is administered through the sublingual route is effective. Some data have shown that the allergen is degraded almost completely in the duodenum in humans [107,108], and this finding could explain why gastroresistant capsules do not work. In rats and rabbits, the allergen partially is absorbed directly by the oral mucosa [109]. This latter finding is in agreement with the increased permeability of nasal epithelium to macromolecules that has been observed in allergic subjects [110].

The pharmacokinetics of local routes was investigated in humans with a dedicated experimental model involving a ^{123}I -radiolabeled purified allergen (Par j 1) (Fig. 1) [111]. After oral, sublingual, or intranasal administration of the radiolabeled allergen, sequential scintiscans, plasma radioactivity, and plasma chromatographies were evaluated at different times. Based on the plasma radioactivity profile, no direct absorption of the allergen through the mucosae could be detected. The allergen was retained for up to 40 hours at the mucosal level in the nose and mouth. Gastrointestinal absorption was present, but only peptide fragments could be detected in the bloodstream. If a modified allergen

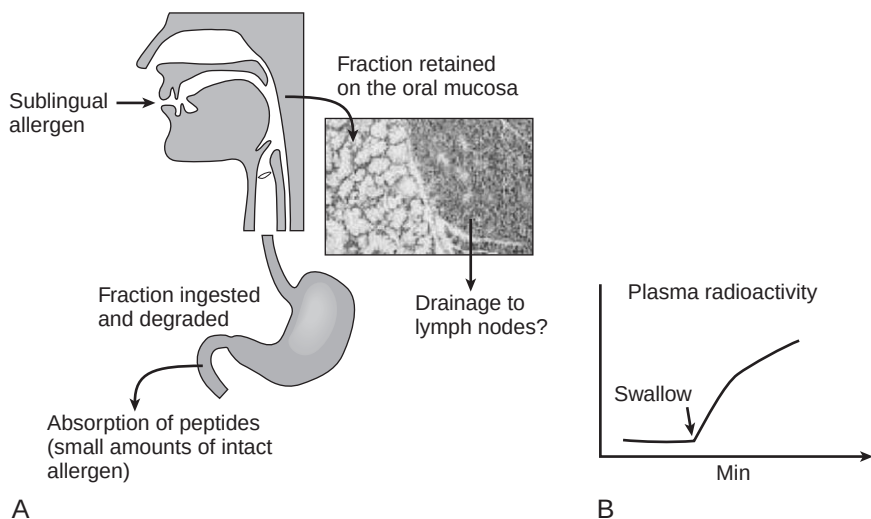


Fig. 1. (A) Overall pharmacokinetics of sublingual immunotherapy. (B) Behavior of radioactivity in the blood after sublingual administration.

(monomeric allergoid) was used, it could be detected in unmodified, trace amounts in plasma [112]. The sublingual pharmacokinetics did not differ between allergic and healthy subjects or between a laboratory-made solution and the commercial preparation. No significant difference in terms of pharmacokinetics existed between the sublingual–swallow and the sublingual–spit routes [113], but with the latter modality about 30% of the extract was lost. These data suggest that (1) the contact of the allergen with the oral mucosa is critical, and (2) the allergen is not absorbed directly in the mouth (see Fig. 1).

Practical aspects, adherence, and costs

In Europe, extracts for SLIT are prepared and commercialized as a patient-named product by several manufacturers. These extracts are standardized biologically or immunologically and are labeled in different units, such as allergen units (AU), index of reactivity (IR), biological units (BU), and standard units (STU). For many extracts, the content of the major allergens is also available in micrograms. SLIT is prepared as soluble tablets or drops to be kept under the tongue for 1 to 2 minutes and then swallowed (sublingual–swallow mode). For practical reasons, SLIT is preferably given in the morning with fasting, although this recommendation is not mandatory. Similar to SCIT, SLIT involves an escalating-dose phase and a maintenance phase, in which the maximum dose is administered once weekly, every other day, or daily. The escalating-dose phase usually requires about 4 to 6 weeks, and the extract is prepared in separate vials (or in separate blisters of tablets) at increasing concentrations. Administration schedule, duration of escalating-dose phase, and frequency of administration differ slightly from one manufacturer to another. SLIT is administered preseasonally (before the season and then discontinued at the beginning of the season), preseasonally and seasonally (before the season and throughout the season), or continuously. The first two routes are used for pollen allergy, whereas continuous treatments are the choice for perennial allergens. The amount of allergen given during a course of SLIT is always higher than in an equivalent course of SCIT, which is why the treatment often is called high-dose SLIT.

Based on the safety profile and mild side effects, it has been proposed to simplify or to speed up the escalating-dose phase. The rationale behind this proposal is to make the treatment more patient friendly and to avoid the mistakes that may occur when vials or blisters of different potency have to be used. In principle, a slow incremental increase of SLIT doses might not be necessary, and the escalating-dose phase can be omitted. A study involving four parallel groups with different escalating regimens showed that starting immediately with the highest dose (100-fold with respect to the traditional schedule) does not modify significantly the safety profile of the treatment [114]. In another study, a similar 1-day, ultra-rush dosing with a Cypress extract was used without side effects [115].

SLIT is self-managed at home by patients much like most oral medications, and similar to other treatments, the adherence is critical for a successful outcome. Adherence is defined as the degree to which a patient's behavior coincides with the physician's recommendations for treatment. With SLIT, adherence always has been regarded as a weak point, because the treatment is self-administered; however, in principle, adherence with SCIT is optimal, because the injections are given at scheduled times by the physician. In the few studies available, the rate of spontaneous discontinuation of SCIT ranges between 10% and 34%, mainly because of side effects or inconvenience [116–118]. The authors attempted to systematically evaluate adherence to SLIT in a real-life setting [119]. Consecutive patients treated with SLIT by tablets for allergy to mites or pollens underwent random telephone interviews and were asked to count the remaining tablets at that moment. With a simple calculation, it was possible to establish the exact number of tablets taken versus the number of tablets expected at a given time. After 1 year of observation, the data from 89 patients showed that the adherence rate was around 93% for pollen IT and 95% for mite IT. This result confirms that SLIT affords a satisfactory adherence. In one of the aforementioned studies, adherence was assessed by measuring the volume of the extract remaining in the returned vials, and in 72% of patients, the compliance rate was greater than 80% [71].

Because the amount of allergen given with SLIT is higher than the amount given with SCIT, the cost of SLIT is higher. The higher cost is counterbalanced by the absence of the costs for injections and associated visits to the hospital or doctor's office.

Unresolved questions and future developments

Positive results from clinical trials have led to the official approval of SLIT for routine clinical use [18–20]. Because the studies only have been conducted in the past 15 years, several points still need to be clarified [120]. These controversial points represent the subject of further investigation.

Dose

Based on the literature, SLIT is effective with doses of extract that are between 3 and 375 times greater than the doses used with SCIT. This dose range is wide, and there is no proof that one dose performs better than another. It is not known whether the clinical efficacy is dose dependent, because variable results were reported with high and low doses. Only one study, which used a single batch of extract, has shown that the efficacy increases as the dose increases [61]. It is clear that troublesome, although not severe, gastrointestinal symptoms are more frequent with the highest doses. Dosing studies, possibly using extracts with known content of allergens, urgently are needed.

Preventive effect

The prevention of the onset of new skin sensitization has been demonstrated for SLIT [71]. SCIT can prevent the onset of asthma in patients with rhinitis, modifying the natural history of the allergic disease [121]; such an effect has not been yet demonstrated with SLIT, however, because of the fact that SLIT is a new treatment, and studies on prevention require long follow-up periods and large sample size.

Use in children

The optimal safety profile of SLIT would make it suitable for use in pediatric patients [122], especially if a preventive effect could be demonstrated. There are too few studies involving pediatric patients, and the results are not definitely conclusive. The safety of SLIT seems to be good in young children (age, <5 years), but a rigorous safety analysis in younger children is lacking.

Mechanisms of action

Most clinical trials of SLIT have been designed to confirm efficacy and safety. Only a few data on the mechanism of action were studied. The most recent data suggested that the Th1–Th2 balance is effected [62] and that the increase in nasal tryptase levels after specific allergen challenge is prevented [123]. Overall, the data and clinical results suggest that SLIT and SCIT do not differ greatly from each other. A detailed definition of the mechanisms of action of SLIT is mandatory, however, and probably will become a major research endeavor.

Summary

As frequently happens in scientific research, empirical attempts can lead (even for the wrong reasons) to the development of effective approaches. For noninjection routes, the use of OIT opened the way to SLIT. OIT did not prove to be sufficiently effective for clinical use, but SLIT immediately did. The amount of data produced in less than 15 years with SLIT is impressive, and in the space of 8 years, a skeptical position held by the allergy community [16] has turned into official acceptance of the treatment for clinical use [20]. This change is exemplified by the tangible changes in the opinion of the medical community that considers SLIT to be a more acceptable treatment [124–127].

SLIT represents a significant advance in allergy treatment because of the safety and the acceptance. The clinical efficacy of SLIT in asthma and rhinitis is supported by numerous controlled trials, and the efficacy of SLIT in rhinitis, compared with placebo, has been confirmed by a meta-analysis. Other studies have added information on SLIT's duration of effect, ability to prevent new

sensitizations, and adherence rate. Despite these findings, more studies are needed to clarify the mechanisms of action, preventive effect, and optimal dose.

The indications for SLIT are the same as for SCIT, although self-administration requires careful instructions to patients and detailed follow-up. The prescription must be made only by a specialist after a detailed diagnosis has been established and after the expected cost–benefit ratio has been evaluated carefully.

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