
CME review article

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Efficacy and safety of sublingual immunotherapy

Giovanni Passalacqua, MD*; Laura Guerra, MD*; Mercedes Pasquali, MD*; Carlo Lombardi, MD†; and Giorgio Walter Canonica, MD*

Objective: To review the available published data concerning the use of sublingual immunotherapy (SLIT) in respiratory allergy to primarily evaluate the clinical efficacy and safety of the treatment and to secondarily consider the mechanisms of action and any unresolved questions.

Data Sources: Articles in the medical literature (starting from 1986 up to November 2003) derived from searching the MEDLINE database with the keywords *sublingual immunotherapy*, *respiratory allergy*, *asthma*, and *rhinitis*. Sources included review articles, randomized controlled clinical trials, postmarketing surveillance studies, and relevant reports from meeting proceedings.

Study Selection: Articles concerning safety, efficacy, and mechanisms of SLIT published in English-language, peer-reviewed journals.

Results: SLIT proved effective and safe in adults and children. As with traditional subcutaneous immunotherapy, SLIT has long-lasting efficacy and a preventive effect on new sensitizations.

Conclusion: SLIT is a viable alternative to subcutaneous immunotherapy. Its use in pediatric patients seems to be particularly promising.

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INTRODUCTION

Allergen-specific immunotherapy, or allergen vaccination, is the practice of administering to allergic patients gradually increasing amounts of an allergen (so-called vaccine). The scope of immunotherapy is to achieve and to maintain a hyposensitization toward the allergen, thus improving symptoms and reducing the need for medications when exposure to the allergen occurs. Since the earliest attempts,¹ immunotherapy has been administered subcutaneously (SCIT). During the last century, however, other modalities of administration (gastrointestinal, nasal, and bronchial) have been proposed

and explored to improve the safety of the treatment.^{2–5} Those routes of administration were formerly named *alternative*, *nonparenteral*, *noninjection*, or *local* routes. Currently, it is agreed that the most proper and equivalent terms are *local* and *noninjection* routes.

In 1986, the British Committee for the Safety of Medicines⁶ reported 26 deaths caused by SCIT and raised serious concerns about the safety and the risk-benefit ratio of SCIT. Although it was subsequently shown^{7,8} that life-threatening events were often due to avoidable errors (wrong dose, improper prescription, incorrect administration), the interest in noninjection routes rapidly increased.⁹ Since the first report of a controlled study,¹⁰ the sublingual route appeared the most promising alternative to traditional SCIT.

In 1998, a panel of experts from the World Health Organization (WHO) performed an extensive review of the literature and concluded that sublingual immunotherapy (SLIT) was a viable alternative to the injection route and that its use

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

† Allergy Service, Department of Internal Medicine, S. Orsola Hospital, Brescia, Italy.

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in clinical practice in adults is justified.¹¹ These conclusions were then confirmed in a position paper by the European Academy of Allergology and Clinical Immunology (EAACI).¹² In 2001, the Position Paper “ARIA” (Allergic Rhinitis and its Impact on Asthma)¹³ confirmed and extended the indication of SLIT to children. Currently, SLIT is routinely used in many European countries, where a large clinical experience is therefore available.

This article reviews the available published data concerning the use of SLIT in respiratory allergy to primarily evaluate the clinical efficacy and safety of the treatment and to secondarily consider the mechanisms of action and any unresolved questions. We considered articles in the medical literature (starting from 1986 up to November 2003) derived from searching the MEDLINE database with the keywords *sublingual immunotherapy, respiratory allergy, asthma, and rhinitis*. Sources included review articles, randomized controlled clinical trials, postmarketing surveillance studies, and relevant reports from meeting proceedings. Articles concerning safety, efficacy, and mechanisms of SLIT published in English-language, peer-reviewed journals were chosen for inclusion in this review.

PRACTICAL ASPECTS

In European countries, there are several manufacturers that commercialize SLIT extracts, and the administration schedules and the amount of allergen(s) vary, depending on the manufacturer. The vaccines commercialized in Europe are standardized either biologically or immunologically. Similar to SCIT, the extracts are labeled in different units, such as allergen units (AU), index of reactivity (IR), biological units (BU), or standard units (STU). Recently, for many extracts, the content in micrograms of the major allergens has become available.

SLIT is given as soluble tablets or drops to be kept under the tongue for 1 to 2 minutes and then swallowed (*sublingual-swallow* mode), although some investigators have also used the *sublingual-spit* modality. SLIT can be administered pre-seasonally (stop at the beginning of the season), pre-seasonally (stop at the end of the season), or continuously. Preseasonal schedules are commonly chosen for pollen allergy, whereas for perennial allergens continuous treatments are preferred. The amount of allergen given during a

course of SLIT is higher than in an equivalent SCIT; therefore, the treatment is often termed *high-dose SLIT*.

Similar to SCIT, SLIT involves a build-up phase (with gradually increasing doses) and a maintenance phase, where the maximum dose is administered 1 to 3 times a week. The build-up phase usually lasts approximately 4 to 6 weeks, and the vaccine is prepared in separate vials (or in separate blisters of tablets) at increasing concentrations. Administration schedule, duration of build-up, and frequency of administration slightly vary from one manufacturer to another. Some examples of SLIT schedules are given in Tables 1 and 2. Accelerated build-up schedules have been proposed also for SLIT based on the good safety profile. The use of simplified schedules of administration is expected to benefit patients.

CLINICAL EFFICACY

Rhinitis

The first randomized trial with SLIT was published in 1986¹⁰; after 12 years, in 1998, the WHO position paper mentioned 4 studies and the EAACI/European Society for Paediatric Allergology and Clinical Immunology document published in the same year considered 6 studies. To date, 25 double-blind, placebo-controlled trials^{14–38} conducted with adequate methods have been published in peer-reviewed journals. Eight of them were conducted in pediatric patients only (Table 3).

All the studies but 3^{18,29,35} confirmed the clinical efficacy of SLIT in rhinitis induced by common allergens such as grass, mites, birch, and *Parietaria*. There are also single positive studies with olive, cypress, and mixed-tree extracts. In all the studies, as usual, the primary outcome variable for clinical efficacy was the symptom score combined with the drug intake score. In some studies, other objective parameters, such as specific nasal or conjunctival reactivity, peak expiratory flow rate, or immunological changes, were evaluated. Overall, the magnitude of the clinical efficacy ranged from an approximately 20% to a more than 60% reduction of symptoms and/or medication scores. It is true that some studies failed to demonstrate a difference between placebo and SLIT. Lima et al³⁵ found no significant clinical effect (symptom score and medication intake) in rhinitis due to grass, although the self-evaluation made by the patients was largely positive

Table 1. Example of a Standard Sublingual Immunotherapy Schedule with Tablets

	First blister: tablets, 25 AU	Second blister: tablets, 100 AU	Third blister: tablets, 300 AU	Fourth blister: tablets, 1,000 AU
Week 1	1 tablet every other day			
Week 2	1 tablet every other day			
Week 3		1 tablet every other day		
Week 4		1 tablet every other day		
Week 5			1 tablet every other day	
Week 6			2 tablet every other day	
Maintenance				1 tablet twice weekly

Abbreviation: AU, allergen units.

Table 2. Example of a Standard Sublingual Immunotherapy Schedule with Drops

	First vial: 0.1 IR/mL	Second vial: 1 IR/mL	Third vial: 10 IR/mL	Fourth vial: 100 IR/mL
Day 1	1 drop			
Day 2	2 drops			
Day 3	3 drops			
Day 4	4 drops			
Day 5	6 drops			
Day 6	8 drops			
Day 7	10 drops			
Days 8–14		The same as vial 1		
Days 15–21			The same as vial 2	
Days 22–28				The same as vial 3, up to 20 drops
Maintenance				20 drops 3 times a week

Abbreviation: IR, index of reactivity.

Table 3. Summary of the Randomized, Placebo-Controlled Studies with Sublingual Immunotherapy

Source, y	Age range, y	No. of active/placebo patients	Allergen	Duration	Cumulative dose	Disease
Tari et al, ¹⁴ 1990	5–12	30/28	Mites	18 mo	365 STU	R/A
Sabbah et al, ¹⁵ 1994	13–51	19/29	Grasses	17 wk	4,500 IR	R
Feliziani et al, ¹⁶ 1995	14–48	18/16	Grasses	3.5 mo	25 BU	R
Troise et al, ¹⁷ 1995	17–60	15/16	<i>Parietaria</i>	10 mo	105 BU	R
Hirsch et al, ¹⁸ 1997	6–16	15/15	Mites	1 y	570 μ g of Der p 1	R/A
Passalacqua et al, ²³ 1998	15–46	10/9	Mites (monoid)	2 y	10,000 AU	R
Vourdas et al, ²¹ 1998	7–17	33/31	Olive	2 y	4 mg of Ole e 1	R/A
Clavel et al, ¹⁹ 1998	8–55	62/28	Grasses	6 mo	28 μ g of Phl p 5	R/A
Horak et al, ²⁰ 1998	16–48	18/16	Birch	4 mo	250 STU	R
Hordijk et al, ²² 1998	18–45	30/27	Grasses	6 mo	300,000 BU	R/A
Bousquet et al, ²⁵ 1999	15–37	15/15	Mites	2 y	104,000 IR	A
Passalacqua et al, ²⁴ 1999	15–42	15/15	<i>Parietaria</i>	8 mo	4.2 mg of Der p 1 265 BU	R/A
Pradalier et al, ²⁷ 1999	6–25	59/61	Grasses	4 mo	16 μ g of Par j 1 11,000 IR	R/A
La Rosa et al, ²⁸ 1999	6–14	20/21	<i>Parietaria</i>	6 mo	0.935 mg of Phl p 5 75,000 IR	R/A
Purello-D'Ambrosia et al, ²⁶ 1999	14–50	14/16	<i>Parietaria</i>	8 mo	52.5 mg of Par j 1 200 BU	R/A
Pajno et al, ³⁰ 2000	8–15	12/12	Mites	2 y	12 μ g of Par j 1 360 μ g of Der p 1	A
Guez et al, ²⁹ 2000	6–51	24/18	Mites	2 y	90,000 IR 2.2 mg of Der p 1	R
Caffarelli et al, ³¹ 2000	4–14	24/20	Grasses	3 mo	37,000 AU	R/A
Ariano et al, ³² 2001	19–50	10/10	Cypress	8 mo	250,000 RU	R/A
Bahceciler et al, ³³ 2001	7–15	8/7	Mites	6 mo	7,000 IR 0.56 mg of Der p 1	R/A
Voltolini et al, ³⁴ 2001	15–52	24/13	Trees	24 mo	250,000 RU	R
Lima et al, ³⁵ 2002	16–48	24/22	Grasses	18 mo	0.9 mg of Phl p 5 per month	R
Mortemousque et al, ³⁶ 2003	6–60	26/19	Mites	24 mo	90,000 IR 2.2 mg of Der p 1	C
Andr� et al, ²⁷ 2003	6–55	48/51	Ragweed	7 mo	Variable	R
Ippoliti et al, ³⁸ 2003	5–12	47/39	Mites	6 mo	57 μ g of Der p 1	R/A

Abbreviations: A, asthma; AU, allergen units; BU, biological units; C, conjunctivitis; IR, index of reactivity; R, rhinitis; RU, radioallergosorbent assay test units; STU, standard units.

and a systemic immunological effect was also apparent. Also in 2 studies^{18,29} conducted with mite extracts, SLIT performed poorly: a trend toward clinical improvement was seen in the active groups, but it did not reach statistical significance. This fact is well known also for SCIT, which is usually less effective in mite allergic patients than in pollen sensitive ones. In mite allergic patients, the duration of the treatment seems to be crucial; in fact, those treatments that last at least 2 years gave positive results.^{23,25,30,36} Indeed, recently Wilson et al³⁹ tested the efficacy of SLIT in allergic rhinitis in a meta-analysis. Twenty-two randomized, placebo-controlled trials involving 979 patients were included, 4 of them performed in children. The meta-analysis concluded that SLIT significantly differs from placebo in reducing symptoms and need for medications in allergic rhinitis and that the safety is satisfactory overall. According to the evidence-based medicine criteria,⁴⁰ the efficacy of SLIT in rhinitis can be graded as 1a and consequently the strength of recommendation is A.

Asthma

As previously observed with SCIT, SLIT also seems to have an effect on asthma symptoms. Several recent studies²⁵⁻²⁷ documented a reduction in days with asthma symptoms, use of β_2 -agonists, intake of systemic steroids, and clinical symptoms. Andr   et al³⁷ evaluated the efficacy of SLIT with a ragweed extract given to 99 patients for 6 months and found a lower occurrence of asthma in the active group. This study noticed that the magnitude of the efficacy is, at least in part, dose dependent. Ippoliti et al³⁸ evaluated the effects of SLIT in 86 children with asthma and rhinoconjunctivitis due to mites and found, after 6 months of treatment, a significant improvement in asthma and rhinitis symptoms and a significant change in the forced expiratory volume in 1 second. To date, there is one study²⁵ that documents a measurable effect of SLIT on the quality of life of asthmatic patients. Finally, an open controlled study with a grass extract showed that SLIT significantly reduced the nonspecific bronchial hyperresponsiveness to methacholine measured out of the pollen season.⁴¹

Other Allergic Diseases

Interestingly, there is one recent study that evaluated the effects of SLIT on allergic conjunctivitis.³⁶ These authors studied 60 patients with perennial allergic conjunctivitis for 24 months and found a clearcut increase in the threshold dose for conjunctival provocation and a significant clinical efficacy over placebo starting from 12 months of treatment. Currently, attempts have been made to use SLIT also for latex allergy. Patriarca et al⁴² have recently reported the results of a nonrandomized open study with successful hyposensitization to latex in 12 patients by means of an ultrarush SLIT.

SLIT vs SCIT

When comparing 2 different routes of administration for a treatment, the gold standard method is the double-blind double-dummy. To date, two double-dummy studies published as full articles are available.^{43,44} The first one,⁴³ conducted in grass pollen allergic patients, showed that the clinical effi-

cacy of SLIT (symptoms and need for drugs) was equivalent to that of SCIT. The other study⁴⁴ showed that SLIT and SCIT were equally effective, although the safety and tolerability were superior with the noninjection route. Looking to the more recent literature, the only other study available is an open comparison,⁴⁵ again in mite allergic patients, showing that the clinical improvement was more prompt with the subcutaneous route, especially for asthma symptoms, although SLIT controlled rhinitis symptoms well. Indeed, this latter study is heavily biased by the fact that the groups were not homogeneous at baseline for asthma scores.

Other important factors in comparing the 2 treatments are the well-known special properties of immunotherapy (long-lasting efficacy after discontinuation, prevention of new skin sensitizations, prevention of asthma onset). These effects have so far been demonstrated only for SCIT. Nevertheless, the data published recently suggest that SLIT possesses the same properties as SCIT.

Long-Lasting Efficacy

One of the most relevant clinical characteristics of SCIT is its long-lasting effect after discontinuation.⁴⁶ Until last year, the proof of such an effect was lacking for SLIT, thus suggesting the superiority of SCIT. A prospective, parallel group, controlled study performed in 60 children (mean age, 8.5 years) with allergic asthma or rhinitis due to mite was recently published.⁴⁷ Thirty-five children underwent a 4- to 5-year course of SLIT with a standardized extract, and 25 (control group) received only drug therapy. The patients were evaluated at baseline, at the end of SLIT, and 4 to 5 years later. In the SLIT group, a significant difference vs baseline for the presence of asthma ($P < .001$) was documented even 5 years after discontinuation, whereas no difference was observed in the control group.

CLINICAL SAFETY

The primary rationale of SLIT (and of the other local 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, the allergen, and the survey method. In previous studies, the occurrence of systemic reactions was reported to range from 0.5% to 2.9% of patients.^{48,49} In one study of children with severe asthma, the occurrence of anaphylaxis was reported to be up to 5.6%.⁵⁰ Indeed, in approximately 20% of the published clinical trials with SCIT no information is provided about the adverse effects,⁵¹ and in the remaining studies adverse effects are reported to occur on average in 14% of patients. The occurrence of systemic reactions is in general approximately 0.05% to 0.6% of doses administered,⁵² but near-fatal events are rare when SCIT is correctly prescribed and given.⁵³ Nevertheless, the risk of severe adverse events is real,¹¹ and some fatalities have been reported.

The situation is completely different with SLIT. Since its introduction in 1986, no life-threatening adverse event or fatality has been described in the literature or clinical prac-

tice. Furthermore, the adverse effects are described in detail in all the studies published, and their occurrence is, on average, lower with respect to SCIT.

The most frequently reported adverse effect is the onset of oral or sublingual itching after taking the dose, followed by stomachache and nausea. These events are invariably described as mild and self-resolving, and they can be easily managed by a temporary reduction of the dose given. Of note, the occurrence of adverse effects was particularly low in the pediatric studies, where the treatment was optimally tolerated. Only in one early study¹⁴ were 3 cases of asthma reported. On the other hand, a recent trial reported a noticeably high rate of gastrointestinal adverse events,²⁸ but in this study the amount of allergen was as high as 375 times the amount administered in a standard SCIT course. This demonstrates that the frequency and intensity of adverse effects are at least in part dose related. Other systemic adverse effects, such as headache, constipation, rhinitis, asthma, and urticaria, were described only sporadically in the randomized trials, and their incidence did not differ from the placebo groups.

Andr  et al⁵⁴ reviewed the safety of SLIT in the trials performed with vaccines from a single manufacturer, involving 690 subjects (347 active and 343 placebo), with 218 children (103 active and 115 placebo). Most events were mild, and their occurrence did not differ in the active and placebo groups. The only differences were the oral and gastrointestinal adverse effects that were more frequent in SLIT patients, although mild. The occurrence of adverse effects and dropouts was similar in adults and children.

Probably the most valuable information came from the postmarketing surveillance studies, which were performed in a real-life setting and in relatively unselected patients, thus reflecting everyday clinical practice. Di Rienzo et al⁵⁵ followed up 268 children between the ages of 2 and 15 years who had been receiving SLIT for up to 3 years. The overall incidence of systemic adverse effects was 3% in the patients and 1 in 12,000 doses, and no discontinuation of SLIT was needed. Of 8 adverse effects described, only 1 (urticaria) was judged to be of moderate severity and required a single dose of oral antihistamine. The second pharmacosurveillance study was performed in adults,⁵⁶ with 198 patients observed for approximately 3 years. Adverse effects occurred in 7.5% of patients and in 0.52 of 1,000 doses administered. Four urticaria and 2 gastrointestinal complaints were judged to be of moderate intensity. Also in this study, adverse effects were controlled by a temporary dose adjustment, and in no case was the treatment discontinued.

In principle, SLIT could pose a particular risk for those patients with oral allergy syndrome, because administration to the oral mucosa of a cross-reacting allergen could provoke severe reactions. However, a controlled study performed in 30 patients with ascertained oral allergy syndrome did not confirm that hypothesis.⁵⁷ This agrees with the recent observation that administration of SLIT to children did not cause any change in the mucosal levels of tryptase and eosinophil

cationic protein (ECP), even in 1 patient who displayed oral itching after SLIT intake.⁵⁸ Finally, a recent case report showed that a course of SLIT with an extract of kiwi fruit was beneficial in a woman with severe adverse reactions to kiwi itself.⁵⁹

The good safety profile of SLIT should allow speeding the build-up phase. In fact, in a recent study, a 1-day ultrarush build-up with a Cypress extract was used without adverse effects.⁶⁰ In addition, with SLIT it seems to be unnecessary to perform a slow increase of the doses, since there is no risk for severe adverse events. Therefore, it is hypothesized that the build-up phase can even be omitted. A recent 4-parallel group study, with different build-up regimens, showed that starting with higher doses (100-fold with respect to traditional schedule) does not modify the safety profile of the treatment.⁶¹

MECHANISMS OF ACTION

Knowledge of the mechanisms of action of SCIT is rapidly evolving, and it is now well ascertained that SCIT can modulate the T_H1/T_H2 balance and increase the number of T-regulatory cells,^{62,63} thus intervening at the early stages of the immune reaction to allergens.⁶⁴ On the contrary, SLIT has been studied so far mainly from a clinical point of view to evaluate its efficacy and safety, and only a few systematic observations on the mechanisms of action have been made. Nevertheless, some of the more recent studies have begun to investigate different immunological aspects of SLIT. In vitro, SLIT has been demonstrated capable of reducing the proliferative response of allergen-specific T cells derived from atopic patients.⁶⁵ It is also well ascertained that SLIT down-regulates the expression of adhesion molecules on nasal and conjunctival epithelia and the concomitant influx of inflammatory cells.^{23,24} These observations were recently confirmed in an open study of 10 children, where SLIT reduced the expression of intercellular adhesion molecule 1 on nasal epithelium and decreased methacholine responsiveness.⁶⁶ In one of the recent double-blind, controlled trials, it was observed that SLIT produced changes in systemic immunoglobulins similar to those observed with SCIT.³⁵ In the study by Ippoliti et al,³⁸ no change in CD40⁺ peripheral lymphocytes was detectable, but a decrease of serum ECP and interleukin 13 levels was clearly shown in the active treatment group. In particular, the decrease of interleukin 13 accounts for a reduced T_H2 activity. This latter fact is in agreement with the hypothesis of an effect on the T_H1/T_H2 balance. A recent study by Marcucci et al,⁶⁷ conducted in a double-blind fashion on 24 children with mite allergy, showed that SLIT prevents the increase of nasal tryptase after specific allergen challenge, although no change in nasal ECP levels could be detected.

It seems that contact of the vaccine with the oral mucosa is critical to the effectiveness of SLIT. This is suggested by the fact that when the allergen is immediately swallowed (oral route) the clinical effects are negligible, whereas the sublingual route works. In addition, the pharmacokinetics studies performed in vivo in humans with the radiolabeled ¹²³I-Par j

1 allergen have shown that the allergen does not cross the oral mucosa, but it persists adsorbed for hours after its administration.^{68,69} With the same technique, it was shown that when the allergen is spat out, approximately 70% of the dose is retained in the mouth anyway.⁷⁰

Overall, the clinical effects of SLIT are identical to SCIT, and the data currently available suggest that the mechanisms of action should not differ between the 2 routes. Nevertheless, a more detailed definition of the mechanisms of action of SLIT is mandatory, and it will probably represent a major research field for the future years.

CONTROVERSIAL POINTS

Dose

Based on the data of literature, the effective dose of allergen to be administered ranges from 3 to 375 times the doses of SCIT (Table 4), but this is the only available information. Nevertheless, some considerations can be made. First, the dose interval of efficacy is wide, and there is no proof that one particular dosage performs better than another. This point is controversial, since in some cases both positive and borderline results have been obtained either with very high doses (>100 times the corresponding SCIT) or lower doses (3 to 5 times the corresponding SCIT). Second, it is difficult to compare the various trials, since in some of them the amount of major allergen(s) administered is not reported. Third, there is no clear evidence that the efficacy is proportional to the dose administered, within the mentioned range. Nevertheless, the recent study by Andr  et al has suggested that the clinical efficacy improves as the dose of allergen given increases. On the other hand, it is ascertained that increasing the dose of allergen increases the occurrence of gastrointestinal adverse effects.

Preventive Effect

It has been formally proven that SCIT is able to prevent the onset of asthma in rhinitis patients, thereby modifying the natural history of the allergic disease.⁷¹ Such a demonstration is still lacking for SLIT. This is obviously due to the fact that SLIT has only been used during the last 15 years, and studies on prevention require long follow-up times. We have recently studied a large population of patients with asthma and/or rhinoconjunctivitis receiving SLIT in a real-life setting.⁷² The study was randomized and open-controlled and involved 319 active treatments plus 192 controls who received only drug therapy. In addition to the clinical evaluation and the methacholine challenge, the effect of the treatment on the onset of new sensitizations was also evaluated. A significant reduction (approximately 50%) of the clinical scores and the positivity to methacholine challenge was seen during 3 years of therapy. After the third year, new skin sensitization appeared in 5.8% of the SLIT patients and 38% of the controls ($P < .001$). This was the first demonstration that SLIT exerts a preventive effect on new sensitizations. This is in agreement with the observation previously reported for subcutaneous immunotherapy.^{73,74}

Table 4. Dose Equivalence (Cumulative) of SLIT vs the Corresponding SCIT Dose as Reported in the Published Clinical Trials

Source, y	Allergen	Approximate SLIT dose vs SCIT dose	Effective
Tari et al, ¹⁴ 1990	Mites	5	Yes
Sabbah et al, ¹⁵ 1994	Grasses	50	Yes
Feliziani et al, ¹⁶ 1995	Grasses	6	Yes
Troise et al, ¹⁷ 1995	<i>Parietaria</i>	20	Yes
Hirsch et al, ¹⁸ 1997	Mites	5	No
Passalacqua et al, ²³ 1998	Mites	20	Yes
Vourdas et al, ²¹ 1998	Olive	300	Yes
Clavel et al, ¹⁹ 1998	Grasses	100	Yes
Horak et al, ²⁰ 1998	Birch	NS	Yes
Hordijk et al, ²² 1998	Grasses	NS	Yes
Bousquet et al, ²⁵ 1999	Mites	200	Yes
Passalacqua et al, ²⁴ 1999	<i>Parietaria</i>	7	Yes
Pradali� et al, ²⁷ 1999	Grasses	150	Yes
La Rosa et al, ²⁸ 1999	<i>Parietaria</i>	375	Yes
Purello-D'Ambrosia et al, ²⁶ 1999	<i>Parietaria</i>	3	Yes
Pajno et al, ³⁰ 2000	Mites	4	Yes
Guez et al, ²⁹ 2000	Mites	2	No
Caffarelli et al, ³¹ 2000	Grasses	5	Yes
Ariano et al, ³² 2001	Cypress	5	Yes
Bahceciler et al, ³³ 2001	Mites	NS	Yes
Voltoolini et al, ³⁴ 2001	Trees	5	Yes
Lima et al, ³⁵ 2002	Grasses	50	No
Mortemousque et al, ³⁶ 2003	Mites	NS	Yes
Andr� et al, ³⁷ 2003	Ragweed	NS	Yes
Ippoliti et al, ³⁸ 2003	Mites	5	Yes

Abbreviations: NS, not stated; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

Adherence

Adherence is defined as "the degree to which a patient's behavior coincides with the physician's recommendations for treatment." Similar to drug therapy, adherence to immunotherapy is also critical for the successful outcome of the treatment. In the case of SLIT, adherence has always been regarded as a weak point, because the treatment is self-administered. In the case of SCIT, adherence is believed to be optimal, since a physician or nurse gives injections. Indeed, looking at the few studies available for SCIT, the rate of spontaneous discontinuation is high, ranging from 10% to 34%, mainly due to inconvenience.⁷⁵⁻⁷⁷ These figures would not support the expected optimal adherence to SCIT. We attempted to systematically evaluate adherence to SLIT in a

Table 5. Costs of Immunotherapy (1 Year of Continuous Treatment Hypothesized)*

	Sublingual immunotherapy			Subcutaneous immunotherapy	
	Cost, \$	Comment		Cost, \$	Comment
Cost of the extract	360	3 vials		150	1.5 vials
Visits	100	1 or 2 interim visits		...	Patient seen at each injection
Injections	...	No injection		144	\$12 per injection 12 times
Time lost	...	Self-administered		240	\$10 per hour, 2 hours per injection 12 times
Total	460			534	

* Partly modified from Canonica and Passalacqua.⁷⁹

real-life setting.⁷⁸ Consecutive patients receiving SLIT in tablets for mites or pollens underwent random telephone interviews and were asked to count the remaining tablets at that moment. By means of a computerized program, it was possible to establish exactly the number of tablets taken vs the expected number at a given time. After 1 year of observation, the data from 86 patients (mean age, 35 years) were available. The adherence was 95% for pollen immunotherapy and 97% for mite immunotherapy.

Costs

Concerning costs, the dose of allergen given via the sublingual route is greater than the usual dose of SCIT, and therefore the costs of the vaccine are in general 20% to 30% higher with respect to SCIT. This higher cost is balanced by the reduced need for medical and nursing time and by the absence of the cost of injections. Overall, taking into account all these aspects, the global cost of SLIT is even less than that of SCIT,⁷⁹ as summarized in Table 5. Nevertheless, a formal cost-benefit analysis is still lacking.

CONCLUSIONS

The treatment of respiratory allergy is based on allergen avoidance, pharmacologic treatment, and immunotherapy. Immunotherapy is a unique allergen-oriented immunomodulator that affects the immune response to allergens and whose action develops over long times (months). SLIT represents a

significant advance in immunotherapy, mainly because of its safety, as testified by numerous controlled trials and several postmarketing surveillance studies. Of note, in the few months preceding the publication of the present article, 4 new controlled trials of SLIT came out.^{80–83} The good safety profile makes SLIT, in principle, an optimal choice for pediatric patients.⁸⁴ The more recent data from the literature have shown that SLIT is similar to traditional SCIT, since it exerts a long-lasting effect and can prevent the onset of new sensitizations. It is therefore conceivable that the mechanisms of action of SLIT do not greatly differ from those of SCIT. Furthermore, since a clinical effect on both asthma and rhinitis has been demonstrated, the existence of a systemic immunological effect should be postulated.

It is true that several points need further development⁸⁵: the definition of an optimal maintenance dose, the formal demonstration of a preventive effect on asthma, and a cost-effectiveness analysis. SLIT is self-administered and therefore requires careful instruction and strict follow-up of the patients. On the other hand, SCIT is prescribed by specialists after a detailed diagnosis has been established and the expected benefit-cost ratio has been carefully evaluated. Based on the preliminary data available, adherence to treatment seems not to represent a real problem. Currently, the indications for SLIT are the same as for SCIT (Fig 1); in addition, SLIT can be used for those patients who refuse injections or had severe adverse events with SCIT. After several years of skepticism, there has recently been a gradual change in the general opinion of SLIT. SLIT has become, at least in Europe, a well-accepted modality of immunotherapy.^{86–88}

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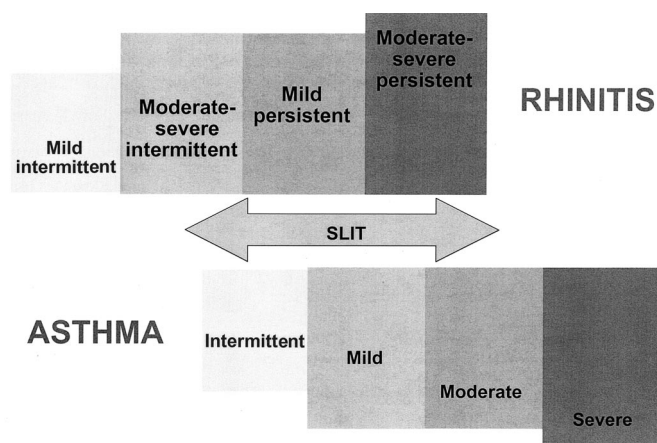


Figure 1. Indications for sublingual immunotherapy (SLIT).

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- Requests for reprints should be addressed to:
Giovanni Passalacqua, MD
Allergy and Respiratory Diseases
Department of Internal Medicine
Padiglione Maragliano
L.go R. Benzi 10
16132 Genoa, Italy
E-mail: passalacqua@unige.it
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CME Examination

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Self-Assessment Examination Questions

- Which of the following aspects of sublingual immunotherapy (SLIT) have been established through clinical trials?
 - optimal maintenance dose
 - efficacy in the treatment of allergic rhinitis
 - efficacy in food hypersensitivity
 - optimal duration of therapy
- What is the reported occurrence of life-threatening adverse events with SLIT?
 - approximately 10%
 - less than 5%
 - 1% to 2%
 - no life-threatening event has been reported
- SLIT is usually administered as:
 - drops or tablets
 - chewable tablets
 - flavored syrup
 - capsules
- The efficacy of SLIT has been demonstrated in:
 - seasonal rhinitis only
 - seasonal rhinitis and asthma in adults only
 - asthma and rhinitis in adults and children
 - perennial rhinitis and asthma in children
- The sublingual route involves:
 - the administration of a steady dose of vaccine
 - a build-up phase followed by a maintenance phase
 - a build-up phase with injections followed by sublingual maintenance
 - a build-up phase followed by a monthly maintenance dosing

Answers found on page 103.