

21 Administration of Sublingual Vaccines

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INTRODUCTION

Historical Perspective

Since inception (1), specific immunotherapy has generally been administered via subcutaneous injections [also known as subcutaneous immunotherapy (SCIT)], but other modalities of administration were proposed and investigated during the 20th century. In some approaches, the rationale was to specifically desensitize the target organs (nose or bronchi) by giving the allergen as a nasal spray (local nasal immunotherapy) or inhaled aerosol (bronchial immunotherapy). Alternatively, a systemic desensitization was targeted by administering the allergen orally or sublingually. Among these "local" or "noninjection" routes of administration, intranasal immunotherapy was extensively investigated with favorable clinical results (2). In contrast, the oral (allergen immediately swallowed) and the local bronchial routes were abandoned in the 1970s because of lack of efficacy or unacceptable side effects (3). In 1986, the British Committee for the Safety of Medicines (4) reported several deaths associated with SCIT and raised serious concerns about the safety and the risk/benefit ratio of immunotherapy. Although some cases of life-threatening events were due to avoidable human errors (wrong dose, improper prescription, incorrect administration) (5), most cases of anaphylaxis are unexplained and unpredictable (6).

The sublingual administration of allergens, which was clinically ineffective, has been used in the USA for many years (7). However, low-dose sublingual immunotherapy (SLIT) for respiratory allergy was firstly described in a controlled trial in 1986 (8) and it appeared as a promising therapeutic option, especially for the favourable safety profile. The original rationale of SLIT was that of achieving a prompt and rapid absorption of the vaccine through the oral mucosa. It was then demonstrated that no relevant, direct absorption occurs through the sublingual mucosa, but SLIT proved effective in a number of trials (9,10) and became the most used noninjection route for immunotherapy in Europe. After a review of the literature existing in 1998, a panel of experts of the World Health Organization concluded that SLIT is a viable alternative to SCIT (11). This statement was confirmed in a position paper of the European Academy of Allergology and Clinical Immunology (12) and in the ARIA (allergic rhinitis and its impact on asthma) document (13) that extended the indications of SLIT to children. A summary of the history of SLIT is depicted in Figure 1.

General Aspects of Sublingual Vaccines

The history of SLIT is chronologically short and encompasses a period of only 20 years. The sublingual approach was initially proposed empirically, without knowledge of the bio-distribution of allergens and of the possible mechanism of action. As a consequence, the practical aspects of SLIT (i.e., allergen dose, frequency of administration, build-up modality) were selected by investigators on the basis of personal experience, often translating into SLIT, the protocols used for SCIT. The result is significant variability in administration schedules, dosages, and duration of SLIT courses (Fig. 2). Nonetheless, the clinical trials in the latter 20th and early 21st century began to address this variability, and there is a trend toward more uniform SLIT protocols, similar to the previous development for SCIT. Because of regulatory issues, SLIT is not used worldwide but is employed in clinical practice in Europe and other select countries and regions, including South Africa and Latin America.

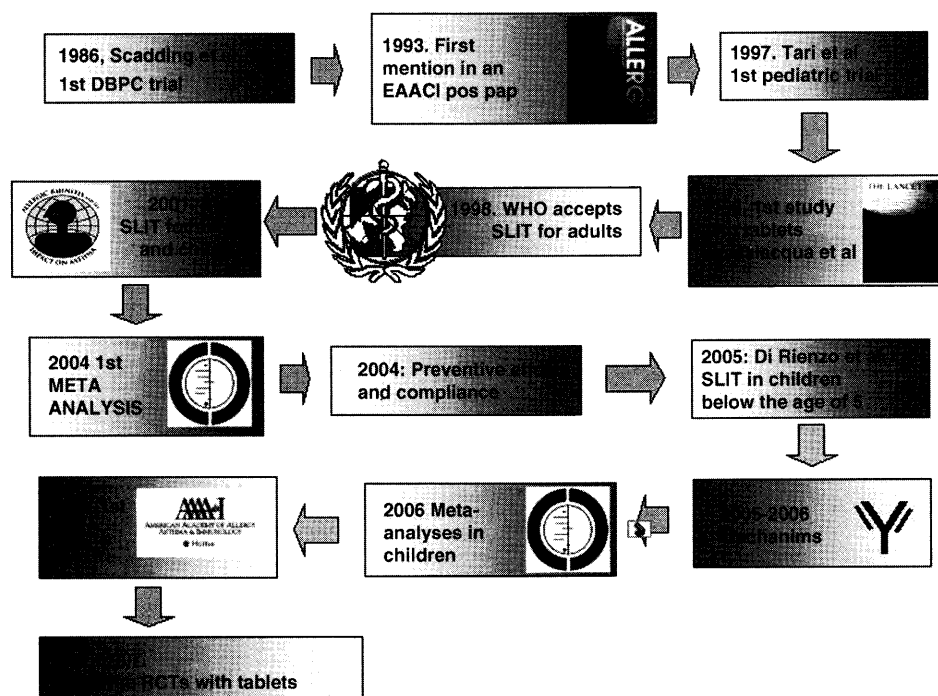


Figure 1 The main steps in the development of SLIT.

Practical aspects of SLIT

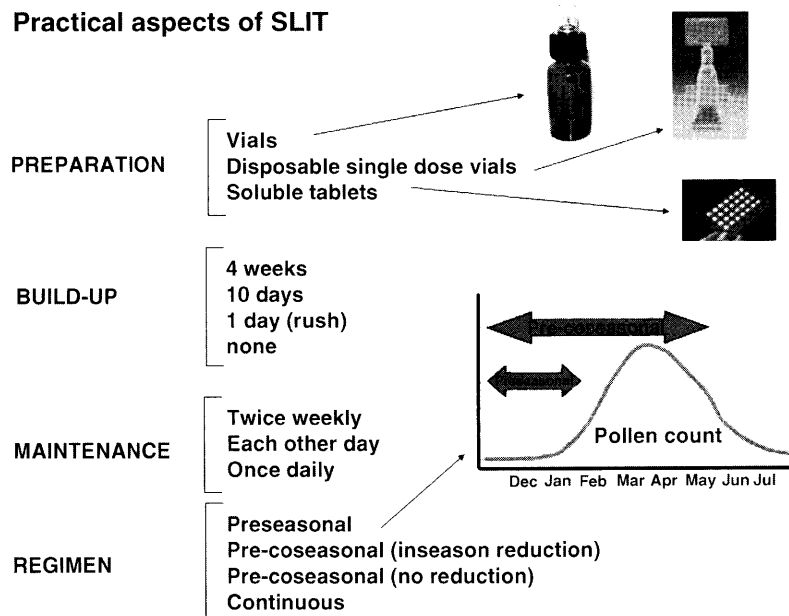


Figure 2 The variable practical aspects of SLIT.

PRACTICAL ADMINISTRATION OF SLIT

Vaccines

SLIT is currently marketed by several European manufacturers, and the administration schedules and amount of allergen(s) largely vary, depending on the producer. Almost all the SLIT vaccines commercialized in Europe are standardized, either biologically or immunologically (14). As is true for SCIT, the standardization methods are largely based on in-house

references; thus, the extracts are labeled in units that differ from one manufacturer to another. Some of the more common labeling units are allergen units (AU), index of reactivity (IR), biological units (BU), standard units (STU). The content in micrograms of the major allergens is available for many extracts, and this has allowed a quantitative approach to determine the optimal SLIT dose. In general, the maintenance dose of allergen is 5 to 300 times higher (according to the manufacturer) with SLIT compared to SCIT. The term "high-dose SLIT" is sometimes used to indicate this dose difference.

The vaccines for SLIT are available in two principle pharmaceutical forms.

1. Buffered solution to be delivered by drop-counters, predosed actuators (minipumps) or disposable single-dose vials.
2. Tablets with appropriate composition facilitating slow (1–2 minutes) dissolution in the mouth upon contact with saliva.

For the build-up or up dosing phase, vials or blisters of tablets at increasing concentrations are provided by the manufacturers.

SLIT is not approved in the United States, as there are no FDA-licensed products. The American Medical Association's manual *Current Procedural Terminology 2005* defines immunotherapy as "parenteral administration of allergenic extracts as antigens at periodic intervals" (15). Currently, U.S. physicians who give SLIT might incur increased medical liability, particularly since two cases of anaphylaxis with heterogeneous mixtures of allergens have been described with SLIT (16,17).

Technique of Administration

The vaccine, in tablets or solution, is usually administered in the morning with the patient in the fasting state. The drops or tablets are kept under the tongue for one to two minutes and then swallowed (*sublingual-swallow* mode). Alternatively, in some trials, the allergen is kept under the tongue and then spat out (*sublingual-spit* mode) (18–20). In biodistribution studies (21), at least 30% of the allergen is retained on the oral mucosa even after spitting. However, because of practical considerations and clinical results, the sublingual-swallow route is the modality currently used in trials and clinical practice. The acronym SLIT, unless stated differently, indicates the sublingual-swallow modality.

Immunotherapy in Europe is prescribed for one or, at most, a few allergens. Mixtures are not used as commonly as in the United States. There is no contraindication to administering multiple allergens with SLIT, except for the possibility of one allergen extract enzymatically digesting another extract with loss of potency/stability. A study of SLIT treatment with a mixture of two unrelated allergens (grass and birch) showed more efficacy than the use of the single allergen alone (22). The administration of numerous extracts mixed together may increase the risk of adverse events. In support of this point, two of three cases of anaphylaxis described with SLIT used heterogeneous mixtures of more than three different allergens (16,17).

Buildup and Maintenance

SLIT traditionally involves a build-up phase (with gradually increasing doses) and a maintenance phase with the maximum dose. This approach is similar to SCIT but more accelerated. The build-up phase is usually four to six weeks. The vaccine is prepared in separate vials (or in separate blisters of tablets) at increasing concentrations. The treated subject starts with the lowest concentration and gradually increases, using the different dosage preparations, until the maintenance dose is reached. An example of build-up regimens is reported in Tables 1 and 2. European manufacturers provide for each extract a suggested maintenance dose on the basis of clinical trials. Of note, the relative safety of SLIT does not strictly limit the maximum dose, and this contributes to the variability of the maintenance dosages used in clinical trials. This is evident in a dose-ranging, safety study of SLIT completed in 2006 (23). In this study, one of the groups received 1,000,000 standardized quality units per day, corresponding to 200 µg of Phl p 5 allergen and 40-fold greater than the lowest dose (23). Dose-dependent side effects occurred, but even with the greatest amount of allergen, the untoward effects were mostly local (oral itching/swelling) and mild or moderate in severity.

Table 1 Example of a Traditional SLIT Schedule with Tablets^a

	1st BLISTER tab 25 AU	2nd BLISTER tab 100 AU	3rd BLISTER tab 300 AU	4th BLISTER tab 1.000 AU
Wk 1	1 tab e.o.d.			
Wk 2	1 tab e.o.d.			
Wk 3		1 tab e.o.d.		
Wk 4		1 tab e.o.d.		
Wk 5			1 tab e.o.d.	
Wk 6			2 tab e.o.d.	
Maintenance				1 tab twice weekly

^ae.o.d., every other day.**Table 2** Example of a Traditional SLIT Schedule with Drops

	1st VIAL 0.1 IR/mL	2nd VIAL 1 IR/mL	3rd VIAL 10 IR/mL	4th 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			
Day 8–14		The same as Vial 1		
Day 15–21			The same as Vial 2	
Day 22–28				The same as Vial 3, up to 20 drops
Maintenance				20 drops thrice weekly

The treatment at the various doses up to 1,000,000 standardized quality units did not result in any serious, systemic, or significant (leading to withdrawal) adverse events. Similar results were obtained in another study, investigating the safety of SLIT in patients with grass-induced asthma (24). A consequence of these observations is that with SLIT the concept of "maximum tolerated dose" is less applicable than with SCIT.

The suggested maintenance dose interval varies among manufacturers and investigators. The most used regimen is once daily (25), but alternate day (26) and once weekly administration have been utilized (27).

SLIT can be administered either preseasonally (start prior to the season and stop at the beginning of the season), pre-coseasonally (start prior to the season and stop at the end of the season) or continuously. Preseasonal and pre-coseasonal schedules are commonly used for pollen allergy. In this case, the treatment is commenced about two months before the expected pollen season. In the pre-coseasonal regimen, no dose reduction during the pollen season is usually applied. On the other hand, for nearly perennial or perennial allergens, a continuous treatment (all year round) is preferred.

Duration of SLIT

There is no controlled study on the optimal duration of a SLIT treatment, thus the recommendations are derived from the SCIT experience. A typical SLIT course is usually three to five years and discontinued if there is no benefit after two years of treatment (11,13). A 15-year follow-up of subjects treated with SLIT for three, four, or five years suggests that a four-year course represents the best compromise between clinical efficacy and long-term effect (28).

PRESCRIPTION OF SLIT

SLIT appears efficacious for IgE-mediated respiratory allergy. SLIT is specific for the allergen and not the disease. The major issue to be determined before initiating SLIT, or any allergen immunotherapy, is the causal importance of a specific allergen or allergens.

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The allergy diagnosis is made by clinical history, physical examination, skin testing, and/or serum specific IgE assays. Since the European preference is the administration of one extract, or at most a few extracts, in a vaccine, the selection of allergens responsible for allergic symptoms may be facilitated with conjunctival or nasal provocation tests in some cases (29,30). SLIT is generally an individually prepared product in Europe that is sent directly to the patient or to the doctor by the manufacturer. The preparation follows recommendations of the treating physician. This is similar to prescribing a pharmaceutical therapy. The introduction of standardized tablets, which have been mutually recognized by European pharmaceutical agencies, will make SLIT even more similar to usual pharmaceuticals. SLIT is self-managed by the patient at home, thus detailed instructions, schedule of administration, and possible side-effect discussions are mandatory. The manufacturers usually provide written instructions with SLIT, but it is common practice for most allergists to see the patient before he/she starts the treatment, to provide additional information and verify understanding. A contact physician for telephone reporting of adverse events should be provided.

As per guidelines, SLIT is indicated in patients with rhinitis or asthma or both, especially those who refuse injections or previously experienced severe adverse reactions to SCIT. Although there is no formal evidence of increased risk, SLIT is usually not recommended for patients with severe/uncontrolled asthma. The clinical efficacy of SLIT in mild, intermittent rhinitis is less defined. Ideally, SLIT should be used in an integrated treatment plan, including avoidance measures and appropriate pharmaceutical therapy.

Finally, although SLIT is safe and easy to use, SLIT should be prescribed by a specialist after a detailed diagnostic workup. In support of this point, a controlled study in which patients were selected for SLIT by general practitioners showed only a marginal benefit (31).

ADHERENCE AND COSTS

Adherence

SLIT is self-administered and usually managed at home; thus, concerns about compliance (32), monitoring, or adherence are potential problems. Adherence with SCIT is documented, since it is given in the presence of a physician. Some studies have attempted to quantify the adherence to SLIT therapy by means of unscheduled telephone interviews. This could be done as the treatments were prepared as tablets or single-dose vials, allowing a count of the remaining doses and a calculation of adherence. In one study, involving 126 adult patients receiving SLIT in tablets, the compliance was reported as greater than 90% over a one-year period (33). In another observational study of 442 patients, the compliance measured at three and six months was greater than 75% in 86% of the patients (34). Similar results were documented in a population of 71 children (35). Compliance data were available for all children at three months, and for 56 children at six months. At three months, 85% of subjects had a compliance rate greater than 75% (69% greater than 90%) and at six months, 84% had a compliance rate greater than 75% (66% greater than 90%). Finally, in a large, randomized controlled trial with grass vaccine in tablets (25), adherence was 94% to 98%. In conclusion, published trial data show adherence to SLIT is very high.

Costs

The cumulative dose of allergen given via sublingual route is greater than SCIT, and therefore, the cost of the vaccine is greater. The cost of the vaccine is offset by the reduced need for medical and nursing time, so the global cost of SLIT may be less than SCIT. A cost-benefit analysis, using a validated pharmacoeconomic model (36) shows that SLIT for pollinosis in patients with rhinitis and/or asthma leads to significant savings in terms of both direct and indirect costs. Similar analyses, based on mathematical models, were conducted with SLIT in tablets for grass allergy in two multinational studies in northern (37) and southern Europe (38). In both cases, the treatment with tablet SLIT was economically superior to symptomatic treatment alone, after adjusting for the comparable cost differences among national health care services. SLIT resulted in a significant gain of quality-adjusted life years (QALY) and in a significant cost saving.

NEW DIRECTIONS FOR SLIT ADMINISTRATION

The favorable safety profile of SLIT is reported in adults (9,39) and in children younger than five years (40,41). The safety of SLIT has led some investigators to try ultra-rush (reaching maintenance within 2 hours of initiating SLIT) or no-updosing (initiation of SLIT with maintenance vaccine concentration). Both of these approaches may be feasible (24,25,42-46). Such protocols are simpler and more convenient to manage. Two large, randomized trials (24,25) were performed with the no-updosing regimen, and safety was as favorable as studies performed with the traditional updosing approach. A third randomized trial compared the safety of the traditional updosing regimen with no-updosing (46) in 135 patients and showed no difference in the rate and type of adverse events between the two groups of patients.

SLIT can be administered in different forms (drops, single-dose vials, predosed dispensers, tablets). Soluble tablets were first introduced in Italy during the 1980s (47) and proved to be a convenient and easy way to manage modality for treatment. Large trials have used soluble tablets in the later 20th and early 21st centuries. Tablets have the advantage of simplicity, thus minimizing possible dosing errors. The rate of dissolution in the oral cavity can be adjusted by modifying the formulation. Some allergen tablets can be stored at room temperature, improving the convenience of the treatment. On the other hand, soluble tablets cannot be divided, and therefore adjusting or reducing the dose may be a problem. Nonetheless, most likely soluble tablets will be the preferred method of SLIT administration in the future.

POTENTIAL CHALLENGES

The efficacy of SLIT has been demonstrated by clinical trials and meta-analyses (10,48-51). Nevertheless, answers to several questions are needed. These include the following:

1. The optimal dose of allergen is probably the most important variable to be defined. Clinical trials were conducted with variable doses of allergens, usually labeled in arbitrary units and often not reported with the content of allergens in micrograms. Positive and negative clinical results occur with doses ranging from 5 to 300 times greater than the doses used in an analogous SCIT course. Thus, it is currently not possible to specify the optimal SLIT dose. A 2006 study with grass allergen SLIT in tablets compared the effects of three different doses labeled as 2500, 25,000, and 75,000 SQ-T (25). These doses correspond to 0.5, 5, and 15 μg of Phl p 5, respectively. The results show dose-dependent efficacy of SLIT, with the greatest dose (15 μg of Phl p 5) being the most efficacious. This is the first rigorous dose-ranging trial performed with SLIT. Such studies are complex, expensive, and time-consuming but necessary before SLIT can be confidently used in clinical care.
2. Long term benefits from SLIT, such as persistent symptom relief after discontinuations or prevention of disease progression, are not fully established. The optimal SLIT duration for maximum, if any, long-term benefit is not known. Persistent symptom improvement has been suggested by the results of a single, open, nonrandomized trial (52). Additional data with more rigorous designs are needed. There is only one randomized, nonblinded trial, suggesting a reduced occurrence of asthma after completion of a course of SLIT (53).
3. The mechanisms of action of SLIT are not yet fully understood. Some data would suggest that SLIT may act via the Treg cells (54), but other studies suggest that the mechanisms of action differ from SCIT (55,56). A more detailed knowledge of the molecular events underlying clinical efficacy are required to improve the treatment (57).
4. Combination therapy with multiple allergens has not been sufficiently evaluated from both an efficacy and safety perspective. Adverse reactions to SLIT, including anaphylaxis, may occur, particularly with multiple allergen mixtures or non-standardized products. Since SLIT is generally administered at home without professional supervision, the risk of serious reactions needs optimal clarification to properly inform the treated patient and protect the treating physician.

CONCLUSIONS

Specific immunotherapy is a cornerstone in the management of respiratory allergy since it is allergen specific, immunomodulating, and affects disease progression. SLIT, introduced about 20 years ago, is potentially a significant advance, offering an excellent safety and acceptance profile. The efficacy trials and experience with SLIT have led to confusion concerning the wide range of doses and variable frequency and regimens of administration. SLIT is commercialized in Europe as an individualized prepared product offered by several manufacturers, each with their own standardization procedure and suggested maintenance dose, similar to variability associated with SCIT. There is a trend to more consistent dosing and administration of SLIT. Moreover, in the more recent trials, the definition of an optimal dose is better identified, and there is a general trend toward more standardization of the administration. The potential of using little or no up dosing with the convenience of once-daily maintenance is very promising, and such products have been approved by the European drug agency. SLIT is self-administered and managed by the patient at home, thus detailed instructions and careful follow-up of treated patients are required. The prescription of SLIT should be made by a specialist with detailed knowledge of the strengths, limitations, and adverse effects of SLIT compared with alternative therapies, including SCIT. Effective application of SLIT requires an accurate diagnosis of allergic disease and an evaluation of the expected benefit/cost ratio compared with other alternatives.

SALIENT POINTS

- Low-dose SLIT was first introduced in 1986, and it is now accepted as a viable alternative to the injection route (SCIT) and is routinely used in many European countries.
- The clinical efficacy of SLIT has been demonstrated in many clinical trials and meta-analyses.
- SLIT can be administered as either drops or tablets, preseasonally or continuously.
- Regimens and maintenance doses are highly variable among manufacturers.
- The usual SLIT course involves a build-up phase followed by a maintenance phase. The excellent safety profile has resulted in regimens without an induction or up dosing phase. This approach is desirable for simplicity.
- The SLIT prescription requires a fund of knowledge similar to SCIT. Thus, the decision to initiate SLIT should be made by a trained specialist after thorough evaluation, proper diagnosis, and consideration of other therapeutic options.
- The enduring and potential disease modifying effects of SLIT need to be confirmed.
- The mechanisms of action of SLIT, although partially similar to SCIT, need to be clarified, and additional studies will be necessary.

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