

Recommendations for appropriate sublingual immunotherapy clinical trials

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Sublingual immunotherapy is gaining widespread attention as a viable alternative to subcutaneous immunotherapy for the treatment of allergic rhinoconjunctivitis. In addition, sublingual immunotherapy has been studied in other allergic disorders including asthma. However, a review of published studies indicates that there are deficiencies and considerable heterogeneity in both design and data interpretation of sublingual immunotherapy studies. These deficiencies have made it somewhat difficult to assess the appropriate place of sublingual immunotherapy in guidelines for the therapy of allergic diseases. Moreover, several unpublished oral and sublingual immunotherapy studies in the United States failed to meet primary endpoints. This article reviews data from sublingual immunotherapy trials and makes recommendations about appropriate designs of future sublingual immunotherapy studies. It is hoped that these recommendations will result in more adequately designed sublingual immunotherapy trials to facilitate the appropriate placement of this therapy to treat patients with allergic rhinoconjunctivitis and other allergic diseases. (*J Allergy Clin Immunol* 2009;■■■:■■■-■■■.)

Key words: Immunotherapy, sublingual immunotherapy, subcutaneous immunotherapy, allergic rhinitis, allergic conjunctivitis, allergic asthma

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Abbreviations used

AE: Adverse event
PCT: Placebo-controlled superiority trial
QOL: Quality of life
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy

Sublingual immunotherapy (SLIT) is becoming increasingly prescribed by allergists around the world. In several European countries, SLIT provides the standard of care for patients receiving immunotherapy. SLIT is a relatively new therapy that has been recognized by guidelines for the therapy of allergic respiratory diseases and the World Health Organization (Fig 1). This recognition has come from increased numbers of studies demonstrating efficacy in patients with rhinoconjunctivitis.

There are a large number of published SLIT clinical trials, but only 58 have been randomized, double-blind, placebo-controlled trials. Of those, almost 80% show positive results. In addition, recent meta-analyses and reviews also suggest that SLIT is an effective therapy.¹⁻⁴

Despite the evidence suggesting that SLIT is an effective therapy for allergic disorders, there is a great deal of heterogeneity in the designs of such studies, making it difficult to assess the true value of SLIT accurately. A review of the double-blind, placebo-controlled trials of SLIT indicates that many of the studies have a duration of less than 12 months (38/58) and involve small numbers of subjects (lt;100 in 40/58). In addition, although not always published, a number of SLIT trials are reported to have failed to meet their primary endpoint, especially in the United States.

Our goals were to identify key elements accounting for positive and negative results and to summarize the critical issues in designing future SLIT clinical trials that best capture the clinical utility of this treatment. This article focuses primarily on SLIT trials for pollen rhinoconjunctivitis, but the principles recommended for future SLIT clinical trials are broadly applicable to other allergens and allergic diseases.

NECESSITY FOR RANDOMIZED CONTROLLED TRIALS

Neither clinician nor patient can sometimes distinguish between an effective and an ineffective treatment for allergic diseases because of the variability in individual clinical responses, the unpredictability and variability of allergen exposure,

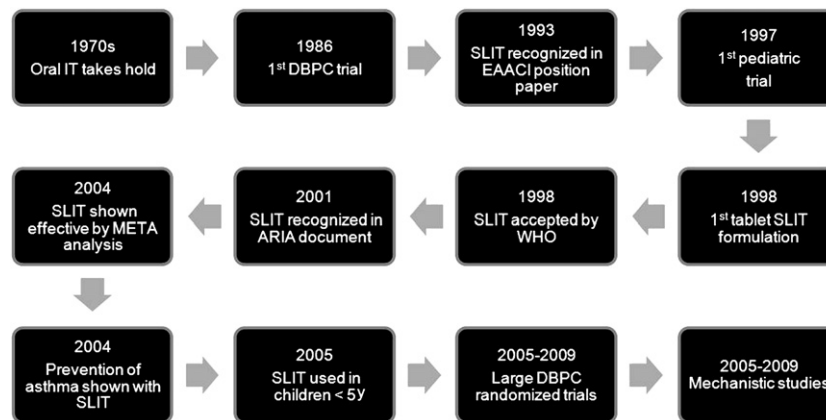


FIG 1. Historical review of milestones in SLIT development. *ARIA*, Allergic Rhinitis and its Impact on Asthma; *DBPC*, Double-blind placebo-controlled; *EAACI*, European Academy of Allergy and Clinical Immunology; *IT*, immunotherapy; *WHO*, World Health Organization.

and the subjective nature of symptoms assessment.⁵ Therefore, only double-blind, placebo-controlled trials should be used to study treatments, such as SLIT, for allergic disorders. Primary design options include the active control superiority trial, the active control noninferiority trial, and the placebo-controlled superiority trial (PCT). A properly conducted PCT gives an estimate of the absolute effect of the therapy. However, if the trial is positive, clinicians and patients do not necessarily know the clinical relevance of the effect (ie, is the effect clinically important?). PCT may provide insufficient information about safety because of the lower number of enrolled patients. In addition, the measurement of the effect is subject to greater statistical error than in the larger, active control trials.

Confirmatory trials on SLIT should be performed by using a randomized, placebo-controlled, double-blind design,⁶ and all studies should be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement.⁷ A prospective baseline period is preferred and should be included whenever possible because patients should experience an appropriate minimum number of symptoms before they are randomized.⁶ However, the unpredictability and variability of allergen exposure, especially to pollen allergens, may limit the value of information obtained from a baseline period. Furthermore, for SLIT trials involving pollens, unless one uses data from the previous year, a baseline period is unlikely to be helpful because treatment typically begins >8 weeks before the pollen season, and patients do not qualify on the basis of their symptoms before the onset of treatment. Retrospective scoring of the previous year's symptoms by patients with a sufficient symptom level can be used, but this method suffers from memory bias and therefore is not ideal.

Sublingual immunotherapy is usually recommended for patients not under control despite optimal pharmacologic treatment.⁸ However, there are limited data to demonstrate the effect of SLIT or subcutaneous immunotherapy (SCIT) under these circumstances. Therefore, investigators are obligated to define their exclusion criteria in the methods section of the study, and to discuss the generalizability of their findings to the broader population.

PATIENT SELECTION

Eligible patients should have a history of allergy to the allergen being administered and a positive IgE test: skin test positivity or

antigen-specific IgE blood test. A predefined *post hoc* analysis to correlate treatment effect with baseline levels of antigen-specific IgE may be useful.

The effects of SLIT have been documented in both adults and children.¹⁻⁴ Considering the data on the safety of SLIT in young children,^{9,10} age does not appear to be a limitation, although the lower age limit to start SLIT is not yet defined.

The study of SLIT in patients with very mild symptoms might create difficulties in detecting significant differences with the control patients, and thus, patients with at least moderate symptom severity should be used.

Monosensitized patients or patients polysensitized to noncross-reacting allergens with nonoverlapping pollen seasons are ideal for a single allergen study. However, the majority of subjects in real life are polysensitized with cross-reacting allergens having overlapping pollen seasons. In most European SLIT trials, a single allergen treatment has been successfully used in monosensitized patients. Recently, a single allergen SLIT study showed good efficacy in polysensitized patients.¹¹ Nonetheless, polysensitization could be a confounding factor in evaluating the clinical efficacy of single-allergen SLIT. Different pollen seasons can overlap, and exposure to multiple perennial allergens increase variances in the global efficacy evaluation.

Other recommendations are to restrict site selections for studies to those that have consistent and well defined pollen seasons and to select fewer sites with a greater number of subjects. If the number of recruiting sites is large, and the start and end of the pollen season vary across sites, normalization of the data for the peak 2 weeks of pollen season is recommended. This adjustment may correct seasonal and geographical variabilities in pollen counts.

PLACEBO EFFECT

The use of a placebo is essential in any study and especially with SLIT, because a high percentage of patients may experience local adverse effects. Ideally, the placebo should have the same characteristics as the active allergen in appearance, smell, taste, and consistency, and should cause local symptoms consistent with a standardized allergen extract. In practice, the placebos used in SLIT trials do not have the same characteristics as the active extract and do not produce local side effects. This could influence

TABLE I. Summary of percentage of patients with local symptoms from SLIT allergen versus placebo

	Grass	Mite	Tree	<i>Parietaria</i>	Ragweed	Others
Allergen	0-65	0-52	0-65	0-5	~70	>5
Placebo	0-29	0 to <5	0-25	0-5	13-40	0 to <5

the active treatment group to lower symptom scores and hence bias the results. Histamine under the tongue does not elicit itching, nor are there any other substances that produce symptoms similar to an allergen extract in a person with allergy. In addition, the local adverse events (AEs) from SLIT typically remit within a week or 2. Because it is very difficult to devise an active placebo, any analysis of efficacy should take into account the incidence of side effects. However, in a dose-ranging study, it has been found that the efficacy was not related to the incidence of side effects.¹¹

The issue of an adequate placebo for SLIT is illustrated by the range of local and other AEs reported in clinical trials (Table I and II). The lack of local side effects in many of the double-blind, controlled studies is curious. In many studies, local and other AEs are not adequately described, and in some, neither are the contents and characteristics of the placebo. As a result, important issues include the following:

- Why is there such a disparity about local side effects in SLIT studies?
- Could local side effects associated with SLIT influence outcomes?
- Most studies, even those with a high percentage of local side effects with allergen versus placebo, do not factor this into their conclusions.
- If there is a high prevalence of local side effects in a study, will this lead to a greater reporting bias?

In summary, ideally, the placebo should be described in detail and should match the active treatment in color and taste as closely as possible. Local AEs should be well described in all studies and analyzed separately from systemic signs or symptoms. The reported analysis should include the incidence of AEs associated with different doses, and AEs in the active versus the placebo group should be appropriately assessed in the analysis of SLIT efficacy.

DOSING REGIMENS

The amount of allergen administered is crucial for both the efficacy and safety of specific immunotherapy. Concerning SCIT, there are few dose-finding trials,^{12,13} but the longstanding clinical experience and the large number of trials allow the optimal maintenance doses for the most relevant allergens to be defined. However, SLIT doses used in clinical trials were mostly chosen on an empirical basis, and the amount in micrograms of major allergens used is explicitly stated only in some studies. Another problem is that the dose ratio SLIT/SCIT usually refers to the preparations of different manufacturers, so an absolute comparison is not feasible. Third, it is not known whether the dose-dependency of the effect, if any, is the same for all allergens. In the 58 randomized, double-blind, placebo-controlled trials, the doses of allergen used vary largely, ranging between 3 and 375 times the doses of the corresponding monthly SCIT dose. Positive and negative results have been reported within the whole range of doses for all

TABLE II. Types of AEs reported during an 8-week SLIT trial¹⁹

Category	No. (%)
Nose	12,515 (50.5)
Mouth/throat	4,478 (18.1)
Eye	4,099 (16.5)
Lung	2,066 (8.3)
Ear	1,052 (4.2)
Gut	420 (1.7)
Skin	142 (0.6)
Headache	4 (0.02)

A total of 24,756 adverse events were reported by 88 participants.

the allergens studied, although a dose dependency of the efficacy has been reported in several trials. One point is that the amount of allergen must be greater than with SCIT, and this is the reason why the treatment is also called *high-dose SLIT*. Two dose-ranging grass tablet trials demonstrated that the efficacy of SLIT is dose-dependent, and the optimal maintenance dose is 15 to 25 µg major allergen per day, which is roughly 30 times the monthly dose of SCIT. It is clear that similar trials are urgently needed for all the relevant allergens. However, a minimal average daily allergen dose should be based on carefully controlled dose-ranging studies, but consensus opinion of the authors suggests a dose of approximately 5 µg per day.

Among the published trials, the administration regimen can be from once daily to weekly. In about 50% of the published studies, once-daily administration was adopted, but there are no trials comparing the efficacy of the different schedules. The traditional up-dosing phase seems to be unnecessary, and starting with the maintenance dose does not appear to increase the risk for AEs.¹⁴⁻¹⁶

For pollen allergens, the administration regimen can be preseasonal, seasonal, continuous, or pre-co-seasonal, although no study directly compared these alternatives. Nonetheless, the large majority of trials used the pre-co-seasonal regimen, and therefore this should be considered optimal. Moreover, recent trials have shown that the clinical efficacy is dependent in part on the duration of the preseasonal phase, with 8 weeks the minimum required to achieve a good efficacy.¹⁷ Studies directly comparing the different SLIT dosing regimens are needed to prove the optimal course of administration including duration.

Another issue is the use of single versus multiple allergen SLIT. To date, there are few published results from double-blind, randomized, placebo-controlled clinical trials with multiple allergens. Until such data are forthcoming and show definitive positive results, this regimen should be considered experimental. These recommendations are summarized in Table III.

SELECTION OF APPROPRIATE ENDPOINTS AND POWER CALCULATIONS

It is generally agreed that the appropriate primary endpoints for assessing the response of allergic rhinoconjunctivitis to immunotherapy are the symptom and rescue medication scores, which may be reported separately or in a single combined score. The symptoms most commonly assessed are nasal (obstruction, itching, rhinorrhea, and sneezing), ocular (gritty feeling/itching and tearing), and, if present, pulmonary (wheezing, chest tightness/shortness of breath, and cough). Individual symptoms are typically graded on a scale of 0 to 3 (none, mild, moderate, severe).

TABLE III. Points to consider for randomized controlled trials in SLIT

Allergen vaccine	
Composition	Single allergen or mixtures
If mixture	Compatible allergens in liquid form with proven stability
Standardization	Defined based on major allergen content
Updosing regimen	Not required
Dose	~5 µg major allergen/d recommended
Patient selection	
Assess all sensitizations (monosensitization or polysensitization)	Panel of allergens using skin prick tests
Prove concordance of sensitization and symptoms because not all sensitizations are clinically relevant	Skin prick tests and serum-specific IgE Optional: allergen challenge
Assess severity of symptoms before SLIT	● Historical: moderate to severe symptoms with exposure in previous year ● Run-in (difficult to do for seasonal allergens) with low pretreatment symptoms
Report comorbidities	May be used in the analysis
Exclude patients who received SIT within 5 y	
Study design	
● Randomized ● Double-blind ● Placebo-controlled: appropriate predefined minimal symptom increase during pollen season ● Superiority trial	
Study duration	● Treatment of allergic symptoms: short-term trial ● Sustained clinical effect: trial of 2-3 y ● Disease modifying effect: 3-y trial and efficacy after stopping
Rescue medication	● Standardized list ● Weighted medication score
Primary outcome	● Total symptom score ● Combined symptom-medication score (preferred) ● For asthma: coprimary, FEV₁ or peak expiratory flow
Secondary outcomes	● Rescue medications ● Individual symptoms ● Visual analog scale ● QOL ● Asthma control ● Symptom-free days ● Physician and patient rated clinical global improvement
Exploratory analyses	● Evaluation of nasal or conjunctival challenges ● Evaluation of skin tests to allergens ● Allergen-specific immunoglobulins ● Other immunologic parameters ● Nonspecific bronchial hyperresponsiveness (asthma) ● Inflammatory biomarkers: induced sputum, FeNO (asthma)
Assess exposure to allergen	● Pollen counts ● Allergen content in individual homes
Record safety assessments	● Use MedDRA ● Local AE ● Anaphylactic events

TABLE III. (Continued)

Statistical analysis	Depends on study objectives and endpoints, but must include power analysis
Publication of results	CONSORT statement

CONSORT, Consolidated Standards of Reporting Trials.

Symptoms are usually recorded either once daily (in the evening) or twice daily and reflect the period since the last recording. Usually the symptoms are averaged daily, weekly, or for the season.

An alternative method of symptom scoring is to use a visual analog scale. Here the patient is presented with a line from 0 (worst possible) to 100 (best possible) and asked to mark on the line where the symptoms fall.

It is generally felt to be unacceptable to ask patients in season-long or perennial studies not to use rescue medication. There is typically a hierarchy of treatments, with each step-up reserved for those failing to obtain relief with medication of the lower step. Different values are assigned to the different classes of medication by different investigators, but in general, antihistamines and topical antiallergic medications are given the lowest score, topical steroids an intermediate score, and oral corticosteroids the highest score.

Secondary outcomes may be divided into (1) individual symptoms, (2) global assessments of response, (3) quality of life (QOL), and (4) objective assessments such as nasal peak inspiratory flow, rhinometry, and blood parameters.

Quality-of-life questionnaires may be either disease-specific or nonspecific. They appear to reflect an impact of the disease not detected by symptom and medication scores. Separate rhinoconjunctivitis-specific QOL questionnaires have been developed and validated for adults, adolescents, and children. QOL questionnaires cannot be used as a primary outcome, because they cannot adjust for use of rescue medications.

Combining symptom and medication scores

Because both symptom and medication scores are reduced by effective treatment of allergic rhinoconjunctivitis, it would be advantageous to be able to combine these 2 responses into a single symptom/medication score. When this is attempted, the mean symptom scores and mean medication scores are usually adjusted to have equal maximal values, and a mean of the 2 is calculated.¹⁸ To combine the 2 scores, there should be some method of assigning a relative value to the rescue medication that reflects its efficacy. One method is to use data from studies in which the rescue medications were compared for their relative efficacy in allergic rhinitis. Application of this approach to many trials yielded the following values for each day of use: oral loratadine, 0.5 points; oral cetirizine and olopatadine eye drops, 1.0 point; nasal corticosteroids, 2 points; and oral corticosteroids (24 mg/d), 2 points. These point scores are probably not additive except for olopatadine. The results from this analysis are similar to those in a World Allergy Organization document⁶: nasal, ocular, oral antihistamine, and bronchodilator, 1 point; nasal and inhaled corticosteroids, 2 points; and oral prednisone, 3 points.

Power calculations

Many of the studies of SLIT include small numbers, and often a meta-analysis of multiple trials is necessary to prove efficacy.

However, the use of small studies in meta-analyses, especially those that are heterogeneous, could lead to an overestimation of the size effect of intervention, or could miss small positive effects. It is far better to include studies with sufficient numbers of subjects so that a reliable determination of outcome can be made on the basis of individual studies alone. To ensure this, the number of subjects required to give the study a reasonable chance of success should be determined before initiating the study by performing a power calculation composed of 4 elements. First is a primary outcome for which the population variability (SD) is known for the population to be studied. Next is the minimal/least difference that is desired to be shown between the treatment of interest and either placebo or comparator or, alternatively, the likelihood of showing a difference. The third element is the acceptable level of α error; this is usually $P < .05$. From these 3 factors, it is possible to determine the number of subjects needed to complete the study. An estimate of the dropout rate will give the number needed to be enrolled.

AE PROFILE

Safety of sublingual immunotherapy

The heterogeneity in classifying and reporting SLIT AEs in the published clinical trials makes comparisons and analysis of safety difficult. The Food and Drug Administration's definition of AE, which is "any untoward medical occurrence that may present itself during treatment or administration with a pharmaceutical product and that may or may not have a causal relationship with the treatment," was used in a US phase 1 safety and dosing SLIT trial that reported a total of 24,756 AEs in 88 subjects during the 8-week period¹⁹ (Table II). The difficulty in evaluating these results is that AEs included the patients' daily symptoms related to their rhinitis and/or asthma, and the treatment-related AEs were not described in detail.

Recognizing the need for a more uniform classification of immunotherapy adverse reactions, a Joint Task Force representing members of the American College of Allergy, Asthma & Immunology, the American Academy of Allergy, Asthma & Immunology, the European Academy of Allergy and Clinical Immunology, and the World Allergy Organization immunotherapy committees is designing a uniform classification of immunotherapy systemic reactions.

Frequency of severe SLIT-induced adverse reactions

A review of articles on SLIT indicates that severe adverse reactions including anaphylaxis are very rare, and no fatalities are reported.²⁰⁻²⁴

Two anaphylactic events occurred on the first dose of a grass tablet in patients who had previously had systemic reactions with SCIT. A previous systemic reaction has been identified as a risk factor for SCIT. Two occurred in patients who received multi-allergen SLIT.

No significant difference in terms of AEs between single-allergen and multiple-allergen SLIT regimens have been reported.^{25,26}

Risk factors for SLIT AEs

Risk factors for SLIT AEs have not been clearly established. There does not appear to be a consistent association between the

AE rate or severity and the administered SLIT dose or the induction schedule. Further studies are needed to identify and characterize SLIT risk factors and appropriate patients for this home-based treatment.

CONCLUSION

The lack of adherence to specific issues important in best defining optimal patient selection, dosing regimens, and trial design could account for varying efficacy in SLIT trials. As with any treatment, appropriate clinical trial design is absolutely necessary truly to define the therapeutic potential of SLIT (Table III). Issues such as an inadequate placebo for SLIT trials need to be addressed in either study design or discussion and interpretation of study results. Restricting studies to appropriate patients and clinical trials sites is absolutely essential. The use of homeopathic or low-dose SLIT is not supported by the literature.

It is hoped that the recommendations and discussion put forth in this article will ultimately result in better designed SLIT trials that will serve to facilitate the appropriate placement of SLIT in therapeutic guidelines for allergic rhinoconjunctivitis and other allergic disorders, including asthma.

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