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 Moreover, several unpublished oral and sublingual immunotherapy studies in the United States failed to meet primary endpoints.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;124:665-70.)

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

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,

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Disclosure of potential conflict of interest: T. B. Casale has received research support from Stallergenes. J. Bousquet is an advisor and board member for Stallergenes and has received honoraria from ALK-Abelló. L. Cox is a consultant for Stallergenes and Hollister-Steir, is on the speakers' bureau for Genentech/Novartis and Sanofi-Aventis, has received research support from Hollister-Steir, and is a member of the Food and Drug Administration Allergic Products Advisory Committee. G. W. Canonica has received research support from ALK-Abelló, Stallergenes, Lofarma, and Anallergo. H. S. Nelson is a consultant for Genentech/Novartis, Abbott Laboratories, MediciNova, AstraZeneca, Amgen, GlaxoSmithKline, Schering-Plough, Dyson, Sepracor, and NyCoMed; has received research support from Schering-Plough, Novartis, Genentech, Ception, and AstraZeneca; and is on the speakers' bureau for GlaxoSmithKline. G. Passalacqua and R. F. Lockey have declared that they have no conflict of interest.

Received for publication April 3, 2009; revised July 20, 2009; accepted for publication July 31, 2009.

Available online September 22, 2009.

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0091-6749/$36.00

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doi:10.1016/j.jaci.2009.07.054

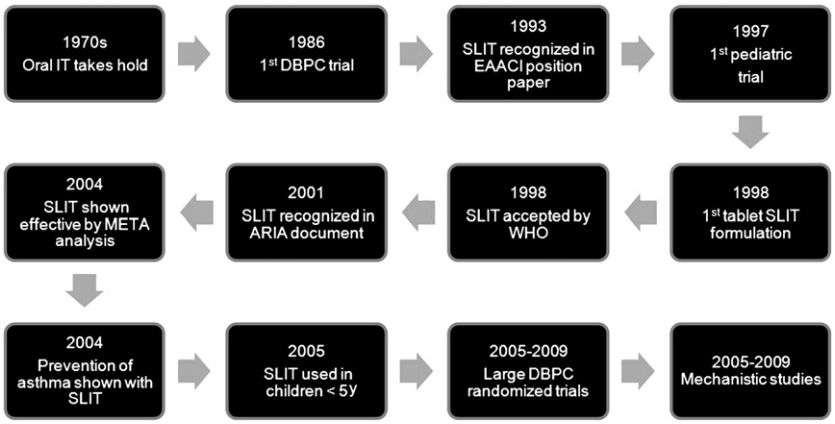

FIG 1. Historical review of milestones in SLIT development. *ARIA,* Allergic Rhinitis and its Impact on Asthma; *DBPC,* Double-blind placebo-controlled; *EAACI,* European Academy of Allergy and Clinical Immunology; *IT,* immunotherapy; *WHO,* World Health Organization.

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

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