WAO POSITION PAPER
SUB-LINGUAL IMMUNOTHERAPY
WORLD ALLERGY ORGANIZATION POSITION PAPER 2009

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• **Historical Perspective**
  • Before the 1980s there was no allergen standardization; this resulted in marked variations in allergenic strength among allergen vaccine batches produced in different phases.

In the 1990s, when sublingual immunotherapy first appeared on the market, the available vaccines for SLIT were only single allergen preparations, as required by the first guideline in this field.
• According to Guideline 2001/83/EC, allergens are immunologic medicinal products and therefore, in general, require a marketing authorization. However, in several countries national regulations are implemented that still allow marketing of allergen products as “named patient preparations” (NPPs) without a marketing authorization.
• Increased availability of authorized allergen products with proven quality, safety and efficacy will lead to an improved benefit for allergic patients and may also improve the general acceptance of SIT as an established treatment by regulatory agencies.

• Sublingual vaccines seem to have heralded a new era in specific allergen desensitization; because of their efficacy and safety, they have been considered eligible for submission for registration by many regulatory authorities.
INTRODUCTION AND HISTORICAL BACKGROUND TO SUBLINGUAL IMMUNOTHERAPY
• Subcutaneous immunotherapy (SCIT) currently represents the standard immunotherapy modality, with well ascertained clinical efficacy.
• The first SLIT randomized DBPC-RCT was published in 1986. The rationale proposed for SLIT was to improve the safety and to make the treatment more convenient.
• The first DBPC-RCT trial with tablets was published in 1986.
SLIT was firstly accepted as a viable alternative to SCIT in the World Health Organization (WHO) position paper, published in 1998, and then included in the ARIA guidelines.

Since 1986, 60 DBPC-RCT trials have been published.
• The available meta-analyses are in favor of SLIT (rhinitis in adults, asthma, and rhinitis in children), although the conclusions are limited by the great heterogeneity of the studies.

• Adequately powered, well-designed DBPC-RCTs involving hundreds of patients, published in the last 3 years have clearly confirmed the efficacy and the dose-dependent effect of SLIT for grass allergens in both adults and children.
• In 1986, the British Committee for the Safety of Medicines reported several deaths caused by SCIT, and raised serious concerns about the safety and the risk/benefit ratio of SIT, also because cheaper and effective drugs (eg, oral H1-antihistamines and topical corticosteroids) had become available for the treatment of respiratory allergy.

• In this scenario, the interest in noninjection routes of immunotherapy (IT) increased again,14 and in 1986 the first randomized controlled trial with the sublingual route (SLIT) was published.15
• In the subsequent years, the number of DBPC-RCTs of SLIT rapidly increased, and SLIT began to be mentioned in official documents.

• In 1993 the European Academy of Allergy and Clinical Immunology (EAACI) stated in its position paper that SLIT could be regarded as a “promising route” for desensitization.

• Five years later, the WHO, based on the results of 8 DBPC-RCTs, stated that SLIT “may be considered as a viable alternative to the injection route in adults.

• In the same year, EAACI produced a position paper on noninjection routes, stating that the use of SLIT in clinical practice is justified because of the ascertained efficacy and the favorable safety profile.
• In 2001, the ARIA position paper accepted the use of SLIT in adults and children, as a valid alternative to SCIT22 and this was confirmed by the ARIA update in 2008.
• Nowadays, more than 50 DBPC-RCTs are available in the literature.
• Concerning safety, all clinical trials and postmarketing surveys have consistently agreed that SLIT is safe, and the majority of side effects are local and mild.

• In more than 20 years of clinical trials and everyday use, only 6 cases of anaphylaxis with SLIT have been reported, some of which were with mixtures of multiple unrelated allergens using nonstandardized extracts, but 2 patients had a severe reaction after the first dose of a grass tablet.
• the safety profile of SLIT does not differ in children below the age of 5 years (a relative contraindication to SCIT).
• SLIT is currently commercialized and used in most European and South American countries, and in Australia and Asian countries, but not in the United States.
- Clinical trials for FDA registration in the US are currently ongoing.
- There are several aspects of SLIT still needing investigation and confirmation, including the optimal dose, the long-lasting effect, the preventive action and the exact mechanisms of action.
- This relative lack of information is not surprising if we consider that the history of SLIT is only 20 years in duration, and that the majority of studies were aimed at demonstrating the efficacy and safety of the treatment.
• The most important concern that still remains is to determine the optimal dose of allergen for SLIT, because the treatment has been shown effective over a very large range of doses (from 5–300 times the dose used for SCIT).

• However, it is clear that the effective doses of allergens for SLIT must be higher than for SCIT (in fact, we commonly speak of high-dose SLIT).
SLIDE 1. History of sublingual immunotherapy.
ALLERGEN SPECIFIC IMMUNOTHERAPY
• Many double-blind, placebo-controlled studies confirm the efficacy of subcutaneous injection allergen specific immunotherapy (SCIT) for treatment of both allergic rhinitis and allergic asthma.

• These studies showed efficacy with extracts of various pollens, animal danders, HDMs, and fungi. For most classes of allergens, results support efficacy.

• However, although a few small size studies report positive results treating patients with *Cladosporium* and *Alternaria*, studies supporting immunotherapy with many of the other available fungal allergen extracts are lacking.
• Despite its clinical and disease-modifying efficacy, SCIT has some disadvantages: it is not ‘patient friendly’ because of the regular injections, which may arouse fear among children and some adults, and it has some indirect costs such as travel to the doctor’s office and lost work/school hours.
• Attempts to improve the former have lead to trials with accelerated treatment schedules, while the latter has been addressed by modifying the allergen extracts or administering them by routes other than injection.

• Alternatives to the weekly build-up include administering clusters of 2 or 3 injections, usually 30 minutes apart, during a single clinic visit with visits spread over several weeks.

• This cluster schedule is not associated with an increased incidence of adverse reactions.
• However, a more rapid build-up, in which maintenance is achieved in just one or a few days, is associated with an increased incidence of reactions even when treatment subjects are premedicated.

• Extract modification includes adsorption of the extract to aluminum to achieve a depot effect and modifying the extracts with formaldehyde or glutaraldehyde to reduce reactivity with specific IgE.
MECHANISMS OF SUBLINGUAL IMMUNOTHERAPY
• Allergen immunotherapy provides an opportunity to study antigen-specific tolerance in man.
• Subcutaneous immunotherapy suppresses allergic ‘TH2-mediated’ inflammation and increases antigen-specific IgG probably by induction of T regs, immune deviation (TH2 TH1) and/or apoptosis of T cells.
• Oral mucosa is a natural site of immune tolerance (Langerhans cells, FcER1, IL-10, IDO [indoleamine 2,3-dioxygenase]).
• Sublingual immunotherapy in optimal doses is effective and may induce remission after discontinuation and prevent new sensitizations, features consistent with induction of tolerance.
MECHANISMS OF SUBLINGUAL IMMUNOTHERAPY

• Retention of allergen in sublingual mucosa for several hours.
• Modest increases in antigen-specific IgG4 and IgE-blocking activity.
• Inhibition of eosinophils, reduction of adhesion molecules in target organ.
• Some evidence of increase in peripheral T cell IL-10.
• SLIT induces modest systemic changes consistent with SCIT, but additional local mechanisms in oral mucosa and/or regional lymph nodes are likely important.
CLINICAL EFFICACY OF SUBLINGUAL IMMUNOTHERAPY
• Up to June 2009, there were 60 DBPC-RCTs of SLIT, of which 41 conducted with grass or HDM extracts. The majority of these studies is heterogeneous for allergen dose, duration and patients’ selection.
• Forty-eight trials provided overall positive results and 12 were totally or almost totally negative.
• The literature suggests that overall, SLIT is effective, although differences exist among allergens.
• The available meta-analyses are in favor of SLIT (rhinitis in adults, asthma, and rhinitis in children), although the conclusions are limited by the great heterogeneity of the studies.
• The clinical efficacy and dose dependency have been demonstrated, in adequately powered, well-designed DBPC-RCTs, for rhinoconjunctivitis because of grass pollen.
• Dose-finding trials and large studies with properly defined outcomes and sample size are needed for the other relevant individual allergens.
SAFETY OF SUBLINGUAL IMMUNOTHERAPY
• SLIT appears to be better tolerated than SCIT.
• SLIT should only be prescribed by allergy-trained physicians.
• Specific instructions should be provided to patients regarding the management of adverse reactions.
• The majority of SLIT adverse events appears to occur during the beginning of treatment.
• A few cases of SLIT-related anaphylaxis have been reported but no fatalities.
• Risk factors for the occurrence of SLIT severe adverse events have not yet been established.
DEFINITION OF SUBLINGUAL IMMUNOTHERAPY PATIENT SELECTION
• To be eligible for SLIT, patients should have:
  - A clinical history of allergy.
  - Documented ALLERGENSPECIFIC IgE positive test. - The allergen used for immunotherapy must be clinically relevant to their clinical history.

• Age does not seem to be a limitation.
• Presently use of SLIT in Latex Allergy, Atopic Dermatitis, Food Allergy and Hymenoptera Venom Allergy is under investigation: more demonstrations are needed to support clinical use.
• There is no indication whatsoever for treating non-IgE-mediated hypersensitivity (for instance nickel sensitivity) with SLIT.
• SLIT may be considered as initial treatment. Failure of pharmacological treatment is not an essential prerequisite for the use of SLIT.
• SLIT may be proposed as an early treatment in respiratory allergy therapeutic strategy.
• Special SLIT indications exist in the following patients.
  - Patients uncontrolled with optimal pharmacotherapy (SCUAD).
  - Patients in whom pharmacotherapy induces undesirable side effects.
  - Patients refusing injections.
  - Patients who do not want to be on constant or long-term pharmacotherapy.

F M Aarestrup, MD, PhD
• A meta-analysis showed that SLIT is effective in children 3–18 years of age with allergic rhinitis

• A meta-analysis of DBPC-RCTs evaluated SLIT efficacy in the treatment of allergic asthma in children. Nine studies reported 441 subjects who had concluded treatment and had received a final clinical assessment. SLIT with standardized extracts (mainly mites) reduced both symptom scores and rescue medication use in children with allergic asthma compared with placebo
• SLIT with a standardized mite extract showed efficacy in children with mild-moderate allergic atopic dermatitis, whereas the benefit was variable in the severe form.

• Allergen immunotherapy is an effective treatment for allergic rhinitis and can potentially modify the disease. Clinical benefits may be sustained years after discontinuation of treatment, may prevent the development of new allergen sensitization and reduce the risk for the future development of asthma in some patients.
GUIDELINES AND RECOMMENDATIONS ON SUBLINGUAL IMMUNOTHERAPY
• Several adequately powered, well-designed, randomized clinical trials have been published on sublingual immunotherapy.

• High-dose sublingual specific immunotherapy is effective in carefully selected patients with rhinitis, conjunctivitis and/or asthma caused by pollen and/or HDM allergy.

• Randomized clinical trials have confirmed that sub-lingual immunotherapy is safe. However, many patients report local side effects.

• SRs have only been reported rarely.
• SLIT is effective in allergic rhinitis in children 5 years of age.
• SLIT may be safe in allergic rhinitis in children 3 years of age.
• SLIT can be used for allergic rhinitis in children with asthma.
• SLIT should not be suggested as monotherapy for treating asthma.
• There are many unmet needs with SLIT in children.
• More studies are needed with SLIT in children in large randomized trials.
• Allergen specific immunotherapy may alter the natural history of respiratory allergy by preventing the onset of new skin sensitizations and/or reducing the risk of asthma onset.
  • There are two randomized open controlled studies suggesting that SLIT reduces the risk of asthma onset in children with rhinitis.
  • Two open randomized studies show that SLIT reduces the onset of new allergen sensitizations.
  • One DBPC-RCT and one nonrandomized prospective study suggest the persistence of the clinical effects for 3–5 years after discontinuation.
• There have been 4 case reports of SLIT-associated anaphylaxis:
• One occurred on the 3rd day of build-up with a multiallergen SLIT extract in a 31-year-old woman with allergic rhinitis and asthma.4
• One occurred in a 11-year-old girl with allergic rhinitis and asthma shortly after administration of mixed pollen