

Sublingual Immunotherapy for Respiratory Allergy

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Abstract

Sublingual allergen immunotherapy (SLIT) is a new alternative for the treatment of respiratory allergy. Strong evidence-based medicine data on clinical efficacy and safety about SLIT support the new standardised products register in Europe and the US. SLIT-tablets significantly reduce nasal and ocular symptoms scores, reduce the use of relief medication and improves quality of life in both adults and children with pollen respiratory allergy. New data support its efficacy and safety for house dust mites (HDM) respiratory allergy.

Keywords

Sublingual immunotherapy, allergic rhinitis, allergic asthma, respiratory allergy

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In the late 1980s, sublingual allergen immunotherapy (SLIT) was proposed as an 'alternative' to subcutaneous allergen immunotherapy (SCIT).^{1,2} The main aim was to reduce systemic reactions and the risk of anaphylaxis, which were frequently associated with SCIT and also to increase the number of patients receiving allergen immunotherapy by facilitating its regular use at home.

Over the years, through well-designed, well-powered studies, the scientific community has increased the levels of evidence of SLIT regarding its efficacy and safety. Nowadays, the use of SLIT has been included in international guidelines for the treatment of allergic rhinitis with or without conjunctivitis.³

SLIT can be administered as drops or tablets for respiratory allergies due to grass, tree and ragweed pollens, and house dust mites (HDM). Some SLIT products are commercialised and routinely used in some European countries. More recently, the US Food and Drug Administration (FDA) gave the approval for three SLIT products (two for grasses; one for ragweed).

The clinical efficacy of SLIT is well documented in different double blind, placebo-controlled, randomised clinical trials (DB PC RCTs) and meta-analyses.⁴ SLIT significantly reduces nasal and ocular symptoms scores, reduces the use of relief medication and improves quality of life in both adults and children with pollen respiratory allergy.

Large and complex clinical development programmes on SLIT have been conducted in Europe and the US. Well-powered, well-designed multinational DB PC RCTs using almost comparable clinical outcomes and well-standardised sublingual products have demonstrated sustained clinical efficacy of the SLIT tablets compared with placebo for pollen respiratory allergy. These studies have also indicated a disease modification 2 years after completion of 3 years of treatment with SLIT-tablets for grass allergy.^{5,6}

More recently, the significant clinical effect of SLIT tablets for HDM respiratory allergy have been demonstrated in adults with perennial HDM rhinitis and asthma due to HDM. Nasal and ocular symptoms and the risk of asthma exacerbations have been reduced after treatment with SLIT-tablets for HDM.

SLIT's safety profile is extremely good.⁷ Symptoms are mainly localised to the oral mucosa, such as itching/tingling of the lips or mouth, mild local swelling of lips, sublingual area or tongue. These symptoms are mild in severity and are self-limiting.⁵⁻⁷ To re-assure the patient of the safety profile and to inform about the expected local symptoms of SLIT, it is always recommended that the first dose should be taken at the doctors' office. SLIT is prescribed to be self-administrated by the patients in their homes.

Systemic reactions due to SLIT are rare. Very few 'so-called' anaphylactic cases have been reported globally. There have been no fatalities related to SLIT.

Good adherence to SLIT is critical for its success, at least three to four visits per year should be scheduled to evaluate SLIT's adherence and clinical response.

SLIT drops or tablets should be placed under the tongue, allowing the allergen to be in contact for at least 2 minutes with the oral mucosa. The proposed mechanism is that the allergens are captured by tolerogenic dendritic cells and processed as small peptides. SLIT takes advantage of this tolerogenic environment of the oral mucosa to promote tolerance to the allergen.⁸ Following the uptake of allergen during SLIT, there is differentiation of T helper cell type 1 (Th1) and the induction of interleukin (IL)-10-producing regulatory T cells. Following SLIT, allergic disease-promoting Th2 responses shift to a Th1 inflammatory response, and IL-10 and transforming growth factor (TGF)- β production by

regulatory T cells. SLIT also promotes the synthesis of allergen-specific immunoglobulin (Ig)-G and IgA antibodies that block allergen-IgE complex formation and binding to inflammatory cells, thus encouraging an anti-inflammatory environment. An early increase and a very late decrease in specific IgE levels are observed after SLIT. IgG4 levels show a relatively early increase that is dose dependent. A significant decrease in the allergen-specific IgE/IgG4 ratio occurs after several months.⁸

The potential preventive effect of asthma development in children with allergic rhinitis using SLIT grass tablet is currently being evaluated in a large DB PC RCT, the Grass Asthma Prevention trial (GAP). Children are receiving 3 consecutive years of SLIT-tablet treatment followed by 2 years observation after cessation of treatment. If the results of this study are positive, then we will have a significant change in the way children with grass allergic rhino-conjunctivitis are treated in the future.

The new SLIT products should be considered as a 'new therapeutic class' for the management of these allergic conditions. Emphasis should be put on the selection of patients. SLIT should only be prescribed to individuals with proven clinical respiratory symptoms on exposure to the culprit allergen, confirmed by positive skin test or *in vitro* testing for the allergen-specific IgE antibodies. The decision to use SLIT depends on practical considerations, experience of the prescribing physician with the respective treatment form, cost, convenience and patient's preference.

Considering all these recent advances in SLIT, which are supported by strong evidence-based medicine data on clinical efficacy, safety and with the better understanding of the immunological mechanisms involved, we are entering a new era in the treatment of respiratory allergic diseases. ■

1. Burks AW, Calderon MA, Casale T, et al., Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report, *J Allergy Clin Immunol*, 2013;131:1288–96.
2. Calderón MA, Casale TB, Togias A, et al., Allergen-specific immunotherapy for respiratory allergies: from meta-analysis to registration and beyond, *J Allergy Clin Immunol*, 2011;127:30–8.
3. Bousquet J, Schünemann HJ, Samolinski B, et al., Allergic Rhinitis and its Impact on Asthma (ARIA): achievements in 10 years and future needs, *J Allergy Clin Immunol*, 2012;130:1049–62.
4. Radulovic S, Wilson D, Calderon M, Durham S, Systematic reviews of sublingual immunotherapy (SLIT), *Allergy*, 2011;66:740–52.
5. Durham SR, Emminger W, Kapp A, et al., SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial, *J Allergy Clin Immunol*, 2012;129:717–25.
6. Didier A, Wahn U, Horak F, Cox LS, Five-grass-pollen sublingual immunotherapy tablet for the treatment of grass-pollen-induced allergic rhinoconjunctivitis: 5 years of experience, *Expert Rev Clin Immunol*, 2014;10:1309–24.
7. Calderón MA, Simons FE, Malling HJ, et al., Sublingual allergen immunotherapy: mode of action and its relationship with the safety profile, *Allergy*, 2012;67:302–11.
8. Moingeon P, Update on immune mechanisms associated with sublingual immunotherapy: practical implications for the clinician, *Allergy Clin Immunol Pract*, 2013;1:228–41.