Sublingual Immunotherapy: Other Indications

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KEYWORDS

• Sublingual immunotherapy • Atopic dermatitis • Food allergy • Latex allergy • Hymenoptera venom

Subcutaneous immunotherapy (SCIT) has been the only available and accepted route of administration for several decades. It still represents the standard immunotherapy route for the treatment of respiratory allergy and hymenoptera venom hypersensitivity. SCIT is effective and safe when properly prescribed and administered, although there is a potential risk of severe side effects, such as life-threatening anaphylaxis. The SCIT risk/benefit ratio has prompted the search for safer administration routes such as nasal, bronchial, oral, and sublingual.[1] Among those noninjection routes, sublingual immunotherapy (SLIT) is the most recent, but it was immediately recognized as a promising approach. In less than 20 years, an impressive amount of clinical data has conferred credibility to SLIT, such that it was introduced in the literature as a viable alternative to the standard SCIT.[2,3] To date, SLIT is commercialized and routinely used in almost all European countries and in many other parts of the world. However, in the United States, no SLIT product has been approved by the Food and Drug Administration for clinical use to date, although several large studies are ongoing.

THE RATIONALE FOR EXPANDING THE INDICATIONS

During the last 20 years, more than 60 randomized clinical trials of SLIT in respiratory allergy have been published.[4] Despite considerable design heterogeneity, the clinical results in these studies were generally favorable, confirming the efficacy of SLIT. This efficacy is further supported by several meta-analyses performed in rhinitis only,[5–7] asthma only,[8] and asthma and rhinitis in children.[9,10] The other relevant aspect of SLIT is the favorable safety profile, which seems to be superior to that of SCIT.[4,11] Mild local side effects (oral itching/swelling, altered taste perception, itching of the

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tongue, nausea) account for most of the adverse events associated with SLIT. In most cases, these side effects are usually self-limiting and require no medical intervention In the published literature, there have been no reported fatalities associated with SLIT in more than 20 years, although 6 cases of SLIT-associated anaphylactic reactions have been described.[4] The tolerability of SLIT is good even in children less than the 5 years of age.[12–14] SLIT also exerts a systemic immunologic effect that seems to be similar to that of SCIT; a reduction in symptoms or reactivity on organ-provocation challenge has been shown in multiple organ systems, such as the nose, eye, and bronchi.[15,16] Recent studies suggest that the mechanisms of action of SLIT are similar to those of SCIT, involving the Th1/Th2 balance and the activation of T regulatory cells.[17–22]

Safety, systemic effects, and immunologic mechanisms represent the main rationale for exploring the use of SLIT in allergic disease other than respiratory allergy. The clinical effect of specific immunotherapy in allergic diseases is expected to correlate with the immunoglobulin E (IgE)–mediated component of the disease (as in food allergy or hymenoptera venom allergy; **Fig. 1**).

SLIT IN FOOD ALLERGY

IgE-mediated food allergy reactions (eg, nut anaphylaxis), for which dietary avoidance is the standard treatment, represents an target for specific allergen immunotherapy. In the past, attempts to vaccinate peanut-allergic patients subcutaneously have been made. In a preliminary study investigating the efficacy of SCIT with an aqueous extract of peanut, there was a reduction of symptoms during oral challenge, which ranged from 60% to 100%.[23] In a subsequent study of 12 peanut-allergic subjects, the clinical benefits of peanut SCIT were found to be incomplete, and the treatment induced an unacceptably high rate of systemic reactions.[24] For this reasons, the SCIT approach was virtually abandoned.

Enrique and colleagues[25] performed a randomized, double-blind, placebo-controlled trial with SLIT in 23 hazelnut-allergic subjects, evaluating the oral threshold dose before and after treatment, which was administered in a 4-day rush buildup. A significant increase of the oral threshold dose was seen only in the active group, paralleled by an increase in hazelnut-specific immunoglobulin G4 (IgG4). The rate of systemic reactions was 0.2% of administered doses. A similar study was conducted in 49 peach-allergic subjects, with a purified extract standardized for Pru p 3 content.[26] In this study, a significant increase in the oral challenge threshold dose was seen, along with a reduction of the skin test response to the Pru p 3 extract. There were 16 systemic reactions in more than 1500 adverse events, all mild and spontaneously resolving. Other studies have been performed with a peanut extract. In these

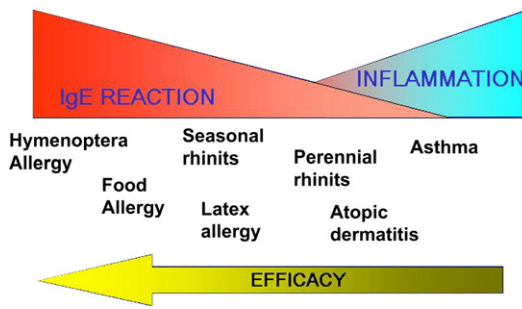

Fig. 1. Where immunotherapy works in allergic diseases.