

Sublingual swallow immunotherapy in the new world

For years, sublingual drops for immunotherapy endured a poor reputation in the United States and Canada. Some allergy specialists performed it empirically in the absence of evidence from an organized collection of data, and most others regarded it as an ineffective route for immunotherapy. From Europe, a different view emerges based on controlled studies from many clinics. Locally applied immunotherapy, whether oral (swallowed), sublingual (with or without swallowing), nasal, or bronchial, was extensively reviewed in 2003 by Canonica and Passalacqua,¹ who performed many investigations of local, principally sublingual, immunotherapy (often referred to as SLIT). According to their review, the nasal and bronchial routes have generally been abandoned because of local adverse effects. Straight swallow (ie, no retention in the mouth) is less favored than SLIT because the dose required is larger and more likely to induce gastrointestinal adverse effects. Canonica and Passalacqua¹ reviewed 22 double-blind, placebo-controlled trials of SLIT conducted using adequate methods and analyses that were published in peer-reviewed journals. All but 3 studies confirmed the clinical efficacy of SLIT in rhinitis induced by common allergens such as grass, mites, birch, and *Parietaria*. There were also single positive studies with olive, cypress, and mixed-tree extracts. The magnitude of the clinical efficacy ranged from an approximately 20% to a 50% reduction in symptom or medication scores, which was superior to the placebo effect and close to the effect of subcutaneous immunotherapy.

Now, in this issue of the *Annals*, comes a study by Bowen et al² of SLIT with the quintessential North American allergen, ragweed. Conducted simultaneously in 9 centers in Canada, it shows a modest but significant improvement in symptom scores from a brief preseasonal course of SLIT. To be evaluated, patients had to reach a daily dose of at least 116 μ g of Amb a 1 major antigen, and many reached a daily dose of 314 μ g of Amb a 1. These doses are in excess of the 5 to 20 mg of Amb a 1 recommended as a maintenance dose for subcutaneous immunotherapy. The dose was sufficient to increase ragweed IgG4 levels significantly. As is common during the initiation of immunotherapy, ragweed IgE levels were increased also.

No anaphylactic adverse reactions that required treatment occurred. Reactions were confined to the gastrointestinal tract and consisted of mouth itch, tongue swelling, and nausea.

Nine patients discontinued home use of the oral extract because of these reactions. On the other hand, 9 patients who received placebo discontinued use because of lack of efficacy. This raises a question about the effectiveness of the blind that is not readily answered.

The European studies and now the North American study used substantially larger doses of extract than are given in subcutaneously administered immunotherapy. Effective doses have ranged from approximately 3 to 5 times to 375 times the doses used in subcutaneous immunotherapy. The rate of success in these studies may well depend on a dose large enough to induce the immunologic effects, such as increases in allergen specific IgG4 antibody levels, that are common with subcutaneous immunotherapy. Not all of the European studies looked at this issue, however. Increases in specific IgG4 levels and decreases in IgE levels have been found at times, but not regularly. One study³ also found decreased in vitro proliferative responses to allergen but no change in cytokine production by allergen-specific T-cell clones with grass pollen extract after a modest cumulative 1-year dose (80 μ g of major allergen).

Anaphylaxis from SLIT has yet to be reported, and local reactions are relatively minor. Several commercial allergen extracts prepared specifically for local use, particularly sublingual, are available in Europe. The study by Bowen et al² used one such preparation made by the French-based company, Stallergenes SA. No such preparations are approved for use in the United States or Canada.

Although the study by Bowen et al moves ragweed into the list of allergens potentially useful for SLIT, several questions remain to be answered regarding dosage, timing, and immunologic responses. Is preseasonal dosing the best way to give SLIT? Would a longer period of dosing be more effective and still safe? How long do the effects last after discontinuance? Would several years of treatment produce long-lasting effects? Could SLIT be used for allergic asthma? How would multiple allergies be treated? Little of the investigation of the mechanism of action of subcutaneous immunotherapy has been performed with SLIT.⁴ It is at least possible that mucosal application of extracts excites a different response to allergens than injection. Controlled studies encourage a reorientation of traditional views on the efficacy of SLIT. The change depends on studies that have used doses considerably larger than traditionally used.

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