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ABSTRACT: Subcutaneous allergen immunotherapy is clearly beneficial in the treatment of select patients with allergic rhinitis or asthma. However, this therapy is underused, partly because it requires administration in a medical facility. Sublingual immunotherapy (SLIT) may be a promising alternative; it appears to be associated with fewer adverse effects, which suggests that it might be administered at home. Currently, there is no FDA-approved formulation for SLIT in the United States. However, allergists are showing increased interest in this therapy, and an approved formulation may be available in the near future. A number of studies have shown the clinical efficacy of SLIT, but many questions remain unanswered, including the effective dose, optimal treatment schedules, and overall duration of treatment. (J Respir Dis. 2007;28(4):162-168)

KEY WORDS: Immunotherapy, Allergy, Allergic rhinitis

Specific allergen immunotherapy is currently the only treatment intervention that can potentially modify allergic disease. Multiple controlled studies have demonstrated its efficacy in the treatment of allergic asthma, allergic rhinitis, and Hymenoptera venom hypersensitivity. Subcutaneous immunotherapy (SCIT) is the predominant form of allergen immunotherapy in the United States. Despite its clear benefits, only a minority of allergic patients receive this treatment.

SCIT does carry a risk of systemic allergic reactions. Most of these reactions are mild, but because severe reactions can occur, it is recommended that SCIT be administered in a medical facility with at least a 30-minute wait period in the facility after the injection. The inconvenience caused by the travel time and the recommended wait period is probably why this treatment is underused and is one of the most frequent reasons for discontinuing treatment.

Sublingual immunotherapy (SLIT) is a form of allergen immunotherapy that involves administration of the allergen under the tongue. It appears to be associated with fewer serious adverse effects than SCIT, which would allow for home administration.

SLIT is currently under investigation in the United States, and an FDA-approved formulation may be available in the near future. At present, there is no Current Procedural Terminology code for SLIT. Without an FDA-approved formulation, most insurers would consider it "off-label" and would not provide reimbursement for SLIT.

In this article, I will review the evidence concerning the effectiveness of SLIT. In a subsequent article, to be published in *The Journal of Respiratory Diseases*, I will review the data on safety and discuss practical considerations concerning the use of this form of therapy.

Background

Allergen immunotherapy is one of the oldest immunomodulatory treatments, with the earliest investigations and clinical "trials" dating back more than 100 years. The earliest successful allergen immunotherapy was reported in the early 1900s by 2 English physicians, Noon and Freeman.^{1,2} In 1911, Noon¹ reported on his work with subcutaneous immunization using a distilled aqueous extract of Timothy grass pollen in patients with hay fever.

Shortly after successful treatment of grass pollen allergy with a conventional weekly immunotherapy build-up schedule, Noon and Freeman began using accelerated schedules. Freeman³ concluded that the advantages of the accelerated method were the saving of time, convenience, and patient compliance. However, he also reported what probably was the first systemic reaction to allergen immunotherapy (urticaria and a fluttering heart in a 7-year-old girl).

Investigations of alternative (noninjective) routes of immunotherapy, such as nasal, bronchial, and sublingual routes, began not long after Freeman's and Noon's first successful reports of SCIT. These investigations were driven by an interest in finding safer routes of allergen immunotherapy.

The first double-blind placebo-controlled study of SLIT was reported in 1986.⁴ Patients with allergic rhinitis (associated with dust mites) were treated with low-dose SLIT or placebo for a relatively short duration. A significant improvement was seen in morning peak nasal inspiratory flow rate in the SLIT group.

In the ensuing 20 years, the number of published SLIT studies steadily increased. MEDLINE, EMBASE, and BIOSIS had 21 SLIT citations in English in 1999 and 58 in 2004. From 1999 to 2006, there were 273. In the past 20 years, SLIT has been used with increasing frequency in Europe. In Italy and France,...