Sublingual grass and ragweed immunotherapy: Clinical considerations—a PRACTALL consensus report

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Sublingual allergen immunotherapy provides a new option for patients with allergic rhinitis in the United States. The efficacy of these sublingual immunotherapy tablets in the treatment of allergic rhinitis has been firmly established in large multicenter clinical trials. In addition, the clinical benefits of sublingual immunotherapy might persist after treatment is discontinued. Local reactions, such as gastrointestinal or oropharyngeal symptoms, are common. However, severe anaphylaxis is rare, and therefore the immunotherapy tablets can be administered at home. Sublingual immunotherapy for allergic rhinitis has been used successfully for years in Europe, and these products might be appropriate for patients who do not do well with standard drug therapy or for those who prefer a disease-modifying approach. (J Allergy Clin Immunol 2016;137:369-76.)

Key words: *Sublingual, immunotherapy, ragweed, sublingual immunotherapy*

Abbreviations used
AIT: Allergen immunotherapy
FDA: US Food and Drug Administration
PI: Package insert
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual allergen immunotherapy

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For the first time in more than 100 years, a new form of allergen immunotherapy (AIT) has been introduced in the United States. In early 2014, the US Food and Drug Administration (FDA) approved 3 sublingual AIT products (Table I[1-3]) based on their demonstrated safety and efficacy in multicenter, multicountry clinical trials with large patient

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TABLE I. Characteristics of SLIT tablets available in the United States[1-3]

Brand name	Components	Clinical indications	Doses	Regimens	Updose	Observe first dose	Children	Sustained benefit
Grastek	Timothy grass	Allergic rhinitis/rhinoconjunctivitis with/without controlled asthma in patients with specific IgE antibodies to relevant allergens	Daily tablet	Precoseasonal (start ≥12 wk before season) or year-round	No	Yes	5-17 y	For sustained effectiveness for 1 season after treatment cessation, take daily for 3 y
Oralair	Sweet vernal, orchard, perennial rye, timothy, Kentucky bluegrass	Allergic rhinitis/rhinoconjunctivitis with/without controlled asthma in patients with specific IgE antibodies to relevant allergens	Daily tablet	Precoseasonal (start 4 mo before onset of season)	Yes, for first 3 d	Yes	10-17 y	No indication
Ragwitek	Short ragweed	Allergic rhinitis/rhinoconjunctivitis with/without controlled asthma in patients with specific IgE antibodies to relevant allergens	Daily tablet	Precoseasonal (start 12 wk before onset of season)	No	Yes	No	No indication

populations and supported by years of real-life use in Europe. The safety of sublingual allergen immunotherapy (SLIT) allows for home administration, and this might be attractive for patients with allergic rhinitis that is not well controlled with standard pharmacotherapy and who prefer a disease-modifying approach but cannot commit the time required for subcutaneous immunotherapy (SCIT) to be administered in a medically supervised setting.

The purpose of this document is to offer practical guidance informed by long-term experience in Europe for the use of SLIT in the United States. Responses to the following key clinical questions provide a basis for rational decision making for the use of these new options in the management of allergic diseases.

WHAT ARE THE CLINICAL INDICATIONS FOR SLIT?

The 3 sublingual allergen tablets approved in the United States, 5-grass (Oralair; Stallergenes, Antony, France), short ragweed (Ragwitek; Merck & Co, Whitehouse Station, NJ), and timothy grass (Grastek; Merck & Co), are indicated for "the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies"[2] for the allergens contained in the specific product (see Boxes 1 and 2). In Europe the indication is for "allergic rhinitis with/without asthma." The decision to use SLIT depends on practical considerations, experience of the prescribing allergists/immunologists with the respective treatment form, cost, convenience, and patient preference.

The majority of studies for SLIT were conducted in patients with allergic rhinitis/rhinoconjunctivitis. Because pivotal studies were not designed to study asthma, none of the FDA-approved tablets list asthma as an indication. However, the pivotal SLIT tablet trials included patients with controlled asthma, and beneficial effects on asthma symptoms were demonstrated in those studies.[4] A systematic review of AIT for allergic rhinoconjunctivitis and asthma yielded 63 studies with 5131 participants who met the inclusion criteria.[4] Thirteen studies evaluated SLIT (aqueous solution) for the control of asthma symptoms. Those studies demonstrated statistically significant improvement in asthma symptoms in the SLIT group relative to the placebo group, with a "strong" association in 69% of the studies. There is also evidence suggesting a reduction in asthma symptoms in children treated with SLIT (also see the section entitled "Is SLIT effective and safe for children?").[5]

Nevertheless, neither the US- nor European Medicines Agency–licensed package inserts (PIs) include asthma alone as a clinical indication, and all PIs state that the tablets have not been studied in "subjects with moderate or severe asthma."

Similar to SCIT, the US SLIT tablet PI warning states that it might not be "suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction" or for patients "who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta blockers."[2,3]

With respect to pregnancy, there are very limited data on the safety of any form of AIT. The PIs for the 3 SLIT tablets state the following, as for SCIT: "Because systemic and local adverse reactions with immunotherapy may be poorly tolerated during pregnancy, [the product] should be used during pregnancy only if clearly needed."

HOW DOES SLIT'S EFFECTIVENESS COMPARE WITH THAT OF SCIT?

In the United States SCIT is administered through the subcutaneous route, and extracts are often mixed in a physician's office, whereas SLIT is administered through the sublingual route, with tablets produced by manufacturers. Other countries might have different SCIT and SLIT products available. There is insufficient evidence to do a meaningful comparison of efficacy between SCIT and SLIT; however, existing evidence suggests both routes are effective in reducing symptom scores and medication use in patients with allergic rhinitis and asthma compared with placebo. Several systematic reviews and meta-analyses of randomized controlled trials of SCIT, SLIT, or both versus placebo (indirect and indirect comparison) suggest that SCIT might provide greater clinical and immunologic efficacy (Table II).[6-11]

The main outcomes used to evaluate efficacy in those studies were reduction of symptoms, need for rescue medication, combined symptom and medication scores, and improvement in quality of life.

A comparison of Cochrane meta-analyses suggests that the clinical effect size for SCIT might be greater than for SLIT, but the findings are not definitive.[12-14] Comparisons of effect size are hampered by substantial methodological and clinical