Clinical Applications of Sublingual Immunotherapy

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KEYWORDS

• Sublingual immunotherapy • Allergic rhinitis • Allergic asthma • Asthma
• Atopic dermatitis • Food allergy • Allergy • Immunotherapy

KEY POINTS

- Sublingual immunotherapy (SLIT) reduces symptoms and medication use in allergic rhinitis. Literature suggests that SLIT efficacy may persist for up to 8 years following a 4-year course of treatment.
- SLIT reduces the risk of moderate/severe allergic asthma exacerbations and is indicated in patients who remain symptomatic. Uncontrolled asthma is a contraindication for SLIT.
- Although additional studies are needed, SLIT is effective for some food allergies.
- In appropriately selected patients, SLIT safety profile is excellent. Anaphylaxis does occur, but at an estimated rate of 1 case per 100 million doses, the risk is exceedingly small.

INTRODUCTION

Approximately 25% of the population of the United States has an allergic disease, encompassing rhinitis, conjunctivitis, asthma, atopic dermatitis, urticaria, and food allergy.[1] Allergic rhinitis (AR) is the most common chronic childhood disease and the fifth most common overall; it is responsible for $3.4 billion in direct medical costs annually.[2,3] Asthma is also very common, with 7.8% of the US population and 300 million people worldwide affected.[4]

Allergy prevalence is increasing. The rates of AR, peanut allergy, and asthma have nearly doubled between 1980 and 2000.[1] The World Health Organization expects 100 million new asthma diagnoses in the next 10 years.[4] The hygiene hypothesis, recently retitled the microflora, biodiversity, or microbiome hypothesis, refers to microbiome disruption in childhood by antibiotic use as well as lifestyle, diet, and birth practice

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changes, leading to an increased risk of allergic disease.[5–7] This hypothesis, coupled with worldwide development, are commonly implicated for rising allergy prevalence.[8]

More than one-third of patients with allergic syndromes remain undiagnosed or do not receive appropriate therapy.[1] Both physician-related and patient-related causes are implicated. Physicians often overlook allergy screening or overestimate the degree of control achieved with current therapy. Therefore, therapies are not escalated when treatment fails.[1] Often, patients do not seek medical care for AR. More than 50% of patients with uncontrolled AR symptoms had not seen a physician in the past year for treatment. Those who do seek care wait until symptoms are "intolerable."[9] Further, almost half of patients receiving specialist care report nonadherence.[1] Some patients avoid treatment due to medication cost or side effects, as well as unfounded concerns about the habit-forming nature of medications. The least common reason is lack of efficacy.[9]

In general, patients desire therapies that treat the root cause of their disease and provide lasting relief. Immunotherapy is the only disease-modifying and durable therapy for allergic disease. However, only 5% of eligible patients are offered allergy immunotherapy (AIT).[1]

AIT induces allergen tolerance by initially producing a population of $CD4^+CD25^+$ T lymphocytes (regulatory T cells) that secrete inhibitory cytokines (interleukin-10 and/or transforming growth factor-β). These cytokines decrease antigen-specific production of immunoglobulin (Ig)E by B cells; reduce proinflammatory cytokine release from mast cells, eosinophils, and T cells; and lead to tolerance of T cells by inhibiting the CD28 costimulatory pathway. Long-term AIT leads to a shift from a T_H2 to a T_H1 cytokine response.[10]

AIT was first described in 1900 for hay fever and used an oral ragweed extract.[11] Subcutaneous immunotherapy (SCIT) has traditionally been the favored route of AIT administration in the United States. However, following 26 SCIT-related anaphylaxis deaths in the United Kingdom, there was increased interest in alternative IT routes with improved safety profiles.[12] Aqueous allergen extracts are not currently approved by the US Food and Drug Administration (FDA) for sublingual immunotherapy (SLIT), but they are often used off-label by US practitioners. This review summarizes SLIT efficacy and safety for the treatment of several allergic diseases and provides tips for the practical implementation of SLIT.

SUBLINGUAL IMMUNOTHERAPY FOR ALLERGIC RHINITIS

AR is a IgE-mediated type I hypersensitivity reaction causing inflammation of the nasal mucosa with exposure to an inciting trigger. Characteristic symptoms include nasal congestion, rhinorrhea, and sneezing.[2] An estimated 500 million people worldwide have AR.[8,13] AR treatments include antihistamines, corticosteroids, leukotriene receptor antagonists, and AIT (SCIT and SLIT), among others. Only AIT alters the natural course of the disease.[2]

Indications and Contraindications

The American Academy of Otolaryngology–Head and Neck Surgery recommends "…immunotherapy (sublingual or subcutaneous) for patients with AR who have inadequate relief of symptoms with pharmacologic therapy…."[2] Many patients undergo empiric pharmacotherapy with intranasal corticosteroids, second-generation oral H_1-antihistamines, and/or intranasal H_1-antihistamines initially.[2]

Skin or in vitro allergy testing is often next undertaken in patients with AR. If results of allergy testing are positive, indicating type I IgE-mediated reactivity, an association