

Allergen Immunotherapy for Allergic Rhinitis

Mary Dell Railey, MD, Margaret A. Adair, MD, and A. Wesley Burks, MD

Corresponding author

A. Wesley Burks, MD
Pediatric Allergy and Immunology, Duke University
Medical Center, Durham, NC, 27710, USA.
E-mail: wesley.burks@duke.edu

Current Allergy and Asthma Reports 2008, **8**:1–3
Current Medicine Group LLC ISSN 1529-7322
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search for alternative routes of delivery. Consequently, sublingual immunotherapy (SLIT) has been suggested as an alternative, and is already used routinely in European countries [5]. SCIT has been shown to alter levels of antibodies in the blood, decrease reactions to specific allergen skin testing, and alter the immune response from T helper (Th) 2 (allergic) to Th1 (nonallergic) [6]. The immunologic effect of sublingual immunotherapy is less clear. This review examines SCIT and SLIT as treatments for allergic rhinitis when compared with placebo.

Introduction

Allergic rhinitis—the most common allergic disease—is characterized by sneezing, clear rhinorrhea, nasal itching, congestion, and itchy, watery eyes [1]. Despite advances in immunology, allergic rhinitis remains a significant health issue affecting approximately 30% of adults and 40% of children [2]. Its prevalence is increasing, especially in Western countries [3]. The morbidity of allergic rhinitis is significant, inflicting high costs on society through lost work and school time.

Allergic rhinitis “is a symptomatic disorder of the nose induced by an IgE [immunoglobulin E]-mediated inflammation after allergen exposure of the membranes lining the nose” [4]. In an atopic individual, allergen exposure causes specific IgE production, which binds to mast cell surfaces. Upon reexposure, the allergen crosslinks IgE on the mast cells, leading to degranulation and release of histamine and other inflammatory mediators [3].

Recommended treatments depend on severity of the disease [4]. Treatments include allergen avoidance, antihistamines, intranasal steroids, antileukotriene receptor antagonists, mast cell stabilizers, and decongestants. Despite treatment, many patients continue to exhibit symptoms. In addition, these treatments offer only symptomatic relief; none has been shown to abate disease activity. However, immunotherapy has been used with success and is the only treatment that may alter disease activity. Subcutaneous immunotherapy (SCIT) requires injections one to three times a week of extracts at increasing concentrations until a maintenance dose is reached. Then, the maintenance dose is given for 3 to 5 years. Reactions to SCIT, which range from mild erythema surrounding the injection site to anaphylaxis, resulted in a

Subcutaneous Immunotherapy

The clinical effectiveness of SCIT is well established. It is effective treatment for patients with IgE-mediated reactions to Hymenoptera venom [7], allergic rhinitis [8], and allergic bronchial asthma [9]. Although the clinical response to immunotherapy has been shown to be allergen-specific, evidence now shows that administration of appropriate monotherapy to monosensitized patients can reduce the chance of developing additional sensitivities from about two thirds to one fourth [10,11]. A study by Moller et al. [12] found that 3 years of pollen SCIT in children with only seasonal allergic rhinitis reduced the likelihood of their developing asthma by a factor of 2.5. Recent studies have also shown persistence of the protective effect after discontinuing immunotherapy on the development of new sensitizations, progression to asthma, and reduction of clinical symptoms [1,10,12].

Despite the known benefits of SCIT, questions arise because of real concern over safety. Many European countries have severely limited its use because of the possibility of fatal anaphylaxis. Local, systemic, and even fatal reactions are a recognized complication of SCIT. The Immunotherapy Committee of the American Academy of Allergy, Asthma, and Immunology has sent questionnaires to practicing allergists to assess the occurrence of fatalities in the United States [13,14]. In the years 1985 to 2001, 34 fatalities were reported, with 33 from immunotherapy and one from skin testing to foods. Of the patients who had a fatal reaction, 88% had poorly controlled asthma. A recent Cochrane Review by Calderon et al. [2] in 2007 evaluated the efficacy and safety of specific SCIT compared with placebo. Fifty-one randomized, double-blind,

placebo-controlled studies were identified with 2871 participants each receiving an average of 18 injections for treatment of seasonal allergic rhinitis. A meta-analysis done on 28 trials found an overall significant reduction in both symptom scores and medication use in the active immunotherapy group compared with placebo. All studies that measured specific IgG and skin reactivity found a significant increase in specific IgG levels and a decrease in skin reactivity after immunotherapy. Epinephrine was given for treatment of adverse effects in 0.13% (19 of 14,085 injections) of patients on active treatment and in 0.01% (1 of 8278 injections) of the placebo group. There were no fatalities. The authors concluded that SCIT is a safe and effective treatment option in patients with seasonal allergic rhinitis [2].

Sublingual Immunotherapy

A recent meta-analysis by Wilson et al. [5] evaluated the efficacy of SLIT, compared with placebo, for reducing symptoms and medication requirements. The review included 22 trials with 979 participants. Overall, both symptoms and medication requirements were significantly reduced following immunotherapy compared with placebo. However, in a subgroup analysis, SLIT with the perennial house dust mite allergen did not show a significant reduction in symptoms or medication use. Also, there was no significant reduction in symptoms and medication scores in those studies involving only children, but the total number of participants was low. No clear relationship could be established between results and dose or duration of therapy [5].

Safety is the major advantage offered by SLIT over SCIT. No fatal or near-fatal reactions have been reported [5,16]. In Europe, SLIT is considered so safe that it is often given by home administration. The only reported side effects include oral pruritus and swelling.

There are several unresolved questions related to SLIT including optimal dosing, frequency, and duration of treatment. Double-blind, placebo-controlled studies have been conducted with extracts of all the allergens currently standardized in the United States, and the range of effective doses in SCIT is 3 to 20 µg of major allergen [15]. The effective dose for SLIT is unknown. A review of all published studies of SLIT from 1986 to 2004 found that half of the 25 studies used a dose that was one to 50 times the customary SCIT dose. The other half used a dose that was 50 to 500 times the SCIT dose. In a review of 48 trials with SLIT, doses over a 1000-fold range were reported to produce clinical improvement. The rate of success did not increase as the dose increased [17]. The frequency and duration of treatment are also unclear from published studies.

Few studies have addressed direct comparisons between SCIT and SLIT. In one study by Khinchi et al. [18], symptom scores were reduced about twice as much by SCIT as by SLIT, and medication use was reduced

about 25% more with SCIT than with SLIT [18]. Another study by Quirino et al. [19] found that SCIT and SLIT were equally effective according to subjective clinical parameters, with a statistically significant reduction of symptoms and medication use in both groups. However, objective parameters such as total specific IgG, specific IgG4, specific IgE, and skin reactivity changed only in patients treated with SCIT [19]. The clinical effect of the objective parameters as related to SLIT is unknown.

Conclusions

SCIT is clinically effective treatment for IgE-mediated reactions to Hymenoptera venom, allergic rhinitis, and allergic bronchial asthma. Its benefits are well established, and result in altered levels of antibodies in the blood, decreased reactions to specific allergen skin testing, and altered immune response (from Th2—allergic, to Th1—nonallergic). Immunotherapy is the only treatment that can alter disease activity. Also, effective doses of SCIT are known for many common allergens.

SLIT is a promising new approach to immunotherapy that offers the benefit of increased safety. Results of meta-analyses are convincing regarding the effectiveness of SLIT in certain patient populations. Several questions remain concerning the ideal dose and treatment duration. Further research in this area is warranted due to the attractive nature of SLIT as a treatment for both children and adults with allergic rhinitis.

Disclosure

No potential conflict of interest relevant to this article was reported.

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