

Allergen immunotherapy: definition, indications, and reactions

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ABSTRACT

Specific allergen immunotherapy is the administration of increasing amounts of specific allergens to which the patient has type I immediate hypersensitivity. It is a disease-modifying therapy, indicated for the treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma, and Hymenoptera hypersensitivity. Specific immunoglobulin E (IgE) antibodies for appropriate allergens for immunotherapy must be documented. Indications for allergen immunotherapy include (1) inadequate symptom control despite pharmacotherapy and avoidance measures; (2) a desire to reduce the morbidity from allergic rhinitis and/or asthma, or reduce the risk of anaphylaxis from a future insect sting; (3) when the patient experiences undesirable adverse effects from pharmacotherapy; and (4) when avoidance is not possible. Several studies reported that immunotherapy in allergic rhinitis seems to prevent the development of new allergic sensitizations and/or new onset asthma. Humoral-, cellular-, and tissue-level changes occur with allergen immunotherapy, including induction of allergen-specific regulatory T and B cells, interleukin 10, and transforming growth factor β production; suppression of T-helper type 2 cell proliferation; large increases in anti-allergen IgG4 antibodies; and reduction in basophil, mast cell, and eosinophil mediator release. Allergen immunotherapy can be administered either subcutaneously in the physician's office or sublingually by the patient at home. The use of immunotherapy in food allergy is still under investigation.

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Specific allergen immunotherapy, colloquially called “allergy shots,” refers to the administration of increasing amounts of specific allergens to which a patient has type I immediate hypersensitivity.¹ Allergen immunotherapy provides the patient with protection against the inflammatory reactions and allergy symptoms associated with exposure to the allergen. Although the precise mechanism that explains the efficacy of immunotherapy is unknown, many of the immunologic changes that occur with immunotherapy have been identified (Table 1).

INDICATION AND DURATION

Immunotherapy is indicated for patients who have clinically significant immunoglobulin E (IgE) mediated allergic rhinitis, allergic conjunctivitis, allergic asthma, and Hymenoptera sensitivity. The use of immunotherapy in the treatment of atopic dermatitis remains controversial and requires further research to determine its effectiveness.² Specific IgE for appropriate allergens must be documented, and symptoms should correlate

with exposure to the specific allergens selected for immunotherapy.^{1,3} Other indications for allergen immunotherapy include inadequate symptom control despite pharmacotherapy and avoidance measures, undesirable adverse effects from pharmacotherapy, and when avoidance is not possible.¹ In addition, immunotherapy may prevent the development of new sensitizations and/or new onset asthma.^{1–4} The relative contraindications to allergen immunotherapy include severe or uncontrolled asthma, significant cardiovascular disease, or any medical condition that decreases a patient's ability to survive a systemic allergic reaction.³ Although not a contraindication, β -blocker use increases the risk of severe and treatment-refractory anaphylaxis and should be a consideration before immunotherapy initiation.³ Immunotherapy is not recommended for chronic urticaria and/or angioedema, and is under investigation for use in food allergy.³

Multiple controlled studies demonstrated the effectiveness of immunotherapy in the treatment of allergic rhinitis due to pollens (grass, ragweed, and trees) and dust mites, and in asthma due to pollens, dust mites, cat, and fungi (*Cladosporium*, *Alternaria*).⁵ Patients with mild asthma are more likely to benefit from immunotherapy than patients with moderate or severe asthma who may be at an increased risk for adverse reactions to immunotherapy. To appropriately choose allergens for cutaneous testing and immunotherapy, it is important to be familiar with the significant aeroallergens in a patient's geographic location.

Immunotherapy has traditionally been administered subcutaneously; however, sublingual immunotherapy

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Table 1 Immunologic changes with immunotherapy*

Antibody changes
Increase in allergen-specific IgG blocking antibody (predominantly IgG4)
Initial increase in baseline allergen-specific IgE, then gradual decline
Blunting of expected seasonal rise of specific IgE
Cellular changes
Increase in allergen-specific regulatory B cells
Increased secretion of IL-10 and TGF- β
Increase in allergen-specific regulatory T cells
Suppression of Th2 cell proliferation
Decreased mediator release from mast cells, basophils, and eosinophils
Reduction of tissue mast cells and eosinophils
Decrease in histamine-releasing factors

IgG = Immunoglobulin G; IL = interleukin; TGF = transforming growth factor; Th2 = T-helper type 2.

**Source: Adapted from Refs 1, 2, and 5.*

(SLIT) has been shown to be a safe and effective alternative. Subcutaneous immunotherapy (SCIT) with inhalant allergens is initiated with once or twice weekly subcutaneous injections of aqueous allergen vaccines at very low doses that are very unlikely to cause anaphylaxis. Doses are then increased over several months until an efficacious dose, also known as maintenance dose, is reached. The injection interval is increased to twice a month and then monthly intervals. Approximately 90% of appropriately selected patients who receive optimal dose maintenance immunotherapy for a year will notice a 50–75% improvement in symptoms.⁶ In a controlled study in which immunotherapy for grass pollen allergy was discontinued after 3 to 4 years of successful treatment, seasonal symptom scores and the use of rescue medication remained low for 3 years after the discontinuation of immunotherapy.⁷ Approximately 90% of patients who complete 4 to 5 years of successful immunotherapy will maintain their symptomatic improvement.⁶

SLIT is administered under the tongue as either a rapidly dissolving tablet that contains allergen extracts or a liquid with a dropper. Currently, the only U.S. Food and Drug Administration approved SLIT preparations are the 5-grass (Oralair, Stallergenes Greer, London), Timothy grass (Grastek, ALK-Abelló, Hørsholm, Denmark), ragweed (Ragwitek, ALK-Abelló, Hørsholm, Denmark), and house-dust mite (Odactra, ALK-Abelló, Hørsholm, Denmark) tablets.⁸ SLIT is administered at doses of 50- to 100-fold of the doses used in SCIT, while still maintaining a high safety profile with a low incidence of significant adverse effects.⁹ Dosage schedules for

SLIT vary, depending on formulation, but tablets are generally taken once a day beginning 3–4 months before the pollen season.¹ The first dose of SLIT should be administered with the patient under medical supervision for 30 minutes of observation, and then subsequent doses can be taken in the patient's home.⁸

SLIT has been shown to reduce symptoms and rescue medication use by 30–40% in seasonal allergic rhinitis.⁹ The optimal duration of treatment is under investigation, but therapy for at least 3 years is recommended.¹⁰ Indeed, additional years of SLIT may contribute to the durability of treatment response, which, in grass pollen studies, extended at least 2 years after cessation of therapy.⁹ Meta-analyses that compared SCIT and SLIT indicate that SLIT is safer, whereas SCIT is more efficacious.^{1,10}

REACTIONS TO IMMUNOTHERAPY

The most common adverse effects of SLIT are localized symptoms, such as oromucosal itching or swelling; although rare, systemic allergic reactions can occur.⁸ Most reported systemic reactions and epinephrine administrations have been with the first dose of SLIT.⁸ Nonetheless, an epinephrine autoinjector should be prescribed to all patients who are receiving SLIT.⁸

SCIT postinjection reactions of erythema and induration of <20 mm and that last <2 days are known as local reactions.¹ Local reactions are common with SCIT and can be treated with antihistamines and ice. Currently, there are no indisputable data to suggest that large local reactions predict subsequent systemic reactions.⁵ However, it may be advisable to repeat the dose for the next injection because patients may express concern about experiencing repeated large local reactions.

Anaphylaxis manifested by urticaria, angioedema, injected conjunctiva, laryngeal edema, vomiting, bronchospasm, hypotension, shock, and even death may occur after administration of an allergen extract. Most systemic reactions occur within 30 minutes after a SCIT injection, and, therefore, after an injection, patients should remain in the physician's office for at least 30 minutes for monitoring.³ Administering an incorrect dose can result in severe or fatal systemic reactions; the patient, vial, dilution, and immunotherapy schedule must be carefully identified before administration of an injection of inhalant allergen. The condition and stability of asthma should also be evaluated before administering each dose of immunotherapy.

IMMUNOTHERAPY IN PREGNANCY

Allergen immunotherapy is effective in the pregnant patient. Initiation of SCIT is not recommended during

pregnancy due to the potential for systemic reactions and their adverse effects on the mother, fetus, or both.^{3,11} If pregnancy occurs during the build-up phase, when a patient is not receiving a therapeutic dose, discontinuation of immunotherapy should be considered.³ Allergen immunotherapy can be continued during pregnancy for those on maintenance therapy if doses are well tolerated.³ There are insufficient data about the safety of SLIT in pregnancy and breastfeeding.⁸

IMMUNOTHERAPY FOR FOOD ALLERGY

Food immunotherapy involves the administration and gradual increase in doses of allergens to achieve desensitization and, ultimately, tolerance to a selected food.¹² Several approaches to food immunotherapy, including oral immunotherapy, epicutaneous immunotherapy, and SLIT are currently under investigation.^{12,13}

NOVEL THERAPIES

Ongoing research is being conducted to improve immunotherapy efficacy while decreasing adverse effects, including the development of hypoallergens that induce IgG4 and T-cell tolerance without causing IgE cross-linking on mast cell surfaces, which allows for greater efficacy and fewer systemic reactions.^{1,2} Other approaches include the use of adjuvants to modulate the T-helper type 2 response, T-cell peptides to induce tolerance, and B-cell peptides to induce IgG4 without activation of allergen-specific T cells.^{1,2}

CLINICAL PEARLS

- Specific allergen immunotherapy is indicated for the treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma, Hymenoptera hypersensitivity, and carefully selected cases of atopic dermatitis. Allergen immunotherapy is currently not indicated for the treatment of chronic urticaria and/or angioedema but is under investigation for use in food allergy.
- Systemic reactions to immunotherapy usually occur within 30 minutes of injection, with those that develop more quickly being the most severe.

- Immunotherapy is contraindicated in severe or uncontrolled asthma.
- SLIT has been shown to be safer than SCIT, although SCIT is more efficacious.

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