

Allergen Immunotherapy

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Allergen immunotherapy involves exposing a patient to a gradually escalating dose of a specific allergen with the intention of decreasing allergic and inflammatory responses, ultimately leading to a sustained decrease in allergic symptoms. A build-up phase (once weekly injections) is followed by a maintenance phase (once monthly injections) that generally continues for 3 to 5 years. Allergen immunotherapy is indicated for select patients with allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. The safety and efficacy of allergen immunotherapy have been confirmed by numerous well-designed studies. Recent research has helped uncover the mechanisms by which allergen immunotherapy exerts its therapeutic effect, paving the way for the development of safer, more effective therapy for a wider range of allergic diseases.

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AIT = allergen immunotherapy; ARC = allergic rhinoconjunctivitis; CI = confidence interval; EPR-3 = Expert Panel Report-3 Asthma Full Report; GINA = Global Initiative for Asthma; IgE = immunoglobulin E; JCAAI = Joint Council of Allergy, Asthma, and Immunology; OR = odds ratio; SLIT = sublingual immunotherapy; VIT = venom immunotherapy

Allergic rhinoconjunctivitis (ARC), allergic asthma, and stinging insect hypersensitivity are commonly encountered medical conditions that cause substantial morbidity and mortality worldwide. Affecting between 5% and 22% of the population and decreasing quality of life, ARC was estimated in one study to have the 5th highest direct and indirect economic burden, with only hypertension, heart disease, mental illness, and arthritis ranked higher.¹⁻³ Asthma, too, is a chronic disease leading to substantial morbidity and mortality, causing thousands of deaths and nearly 500,000 hospitalizations annually.⁴ Although the prevalence of asthma may have plateaued in some areas, it remains a concerning and costly epidemic that is largely unexplained.⁵ Hypersensitivity reactions to honeybee, wasp, yellow jacket, hornet, or fire ant stings lead to potentially life-threatening reactions in 0.4% to 0.8% of children and 3.0% of adults, causing an estimated 40 deaths per year.^{6,7}

Avoidance of the suspected allergen(s) is the first-line treatment for these conditions. However, in many cases, exposure to a particular allergen cannot be completely avoided. Medical therapies directed at reversing allergic inflammation (corticosteroids) and controlling the effects of released mediators (antihistamines and leukotriene modifiers) are not always fully effective or well tolerated.

Allergen immunotherapy (AIT) offers a unique approach, one that reduces allergic symptoms on a long-term basis by altering the immune response. First reported in 1911 with grass pollen extracts, AIT administration has remained an important treatment option for ARC, allergic

asthma, and venom hypersensitivity.^{8,9} Research has clarified the immunological mechanisms underlying AIT¹⁰; the immune system is steered from a type 2 (allergic) to a type 1 (nonallergic) T helper cell response through a variety of immunological pathways. Allergen immunotherapy leads to increased production of specific IgG4 antibodies that block immunoglobulin E (IgE)-mediated histamine release from basophils and disrupts IgE-mediated antigen presentation to T cells.¹⁰ Interleukin 10, elevated levels of which are observed after AIT, has been shown to suppress mast cells, eosinophils, and T cells.¹⁰ Our understanding of the immunological mechanisms of AIT has improved, and controlled prospective studies have provided insight into AIT administration. However, the allergist must artfully apply the currently available evidence to patients because each requires an individual assessment of benefit and risk.

IMMUNOTHERAPY FOR ALLERGIC RHINOCONJUNCTIVITIS

Poorly controlled ARC causes poor performance at work and school and a diminished quality of life. Medications and avoidance provide suboptimal control in up to 40% of some patient populations.¹¹ A meta-analysis of AIT for ARC showed that patients receiving AIT had significant improvements in symptom and medication scores (odds ratio [OR], 1.81; 95% confidence interval [CI], 1.48-2.23).¹² A double-blind, randomized, placebo-controlled study¹³ showed that patients with grass allergy that was inadequately controlled with standard drug therapy experienced significant reductions in their symptom and medication scores (a reduction of 29% and 32%, respectively) after just one season of grass AIT, suggesting that AIT may be of some benefit to patients whose allergy is inadequately controlled by conventional medical therapies. Clinical and immunological evidence supports the long-term efficacy of AIT, an attractive aspect for patients wishing to reduce or avoid allergy medications in the future.¹⁴

Additionally, AIT may play an important preventive role in the pediatric population. Preliminary data from Italy and France suggest that AIT, when initiated early, may decrease the development of new allergic sensitivi-

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ties.¹⁵⁻¹⁷ It may prevent the onset of asthma; 5- and 10-year follow-up of the preventive allergy treatment study showed that 3 years of AIT with grass or birch pollen decreased the likelihood of asthma development in the long term.^{18,19}

IMMUNOTHERAPY FOR ASTHMA

A meta-analysis reviewed placebo-controlled trials for AIT and asthma; compared to placebo, patients treated with AIT were more likely to have statistically significant improvement in asthma symptoms (OR, 2.76; 95% CI, 2.22-3.42) and pulmonary function (OR, 2.87; 95% CI, 1.82-4.52), increases in protection against bronchial challenge (OR, 1.81; 95% CI, 1.32-2.49), and decreases in medication requirements (OR, 2.00; 95% CI, 1.46-2.72).²⁰ A Cochrane review of AIT and asthma found that the number needed to treat to avoid a deterioration of asthma symptoms is 4, and the number needed to treat to avoid an increase in asthma medication is 5.²¹ The review found that AIT significantly reduced bronchial hyperreactivity but had no consistent effect on pulmonary function.²¹ An interesting study that compared inhaled budesonide and AIT for 1 year found them to be equal at 12 months for symptom scores and forced expiratory volume in the first second of expiration, but also noted that the budesonide group improved more rapidly.²² However, the AIT group maintained efficacy after treatment was stopped, whereas the budesonide group did not.²² Patients with allergic asthma benefit from AIT, but safety concerns arise when AIT is used for patients with severe uncontrolled asthma. Caution is advised for patients with asthma who have a forced expiratory volume in the first second of expiration that is less than 70% of predicted.

IMMUNOTHERAPY FOR STINGING INSECT HYPERSENSITIVITY

Venom immunotherapy (VIT) is an effective treatment option to reduce the risk of an anaphylactic reaction in an allergic patient after a sting. A comprehensive management program for stinging insect hypersensitivity also includes instruction in sting avoidance and prescription of epinephrine and directions for its appropriate use.²³ Only patients with systemic symptoms after the sting should be tested for allergy; those with large local reactions have not been shown to benefit from VIT (although research is ongoing in this area). Falsely negative venom skin tests are possible, especially immediately after the anaphylactic reaction.²⁴ Patients with negative venom skin tests should undergo further assessment with venom-specific IgE antibody tests.²⁴ Patients with negative skin or in vitro tests are not good candidates for VIT. Controlled trials have found the

efficacy of VIT to be 95% to 98%.^{25,26} In fact, only 5% of children treated with VIT experience a subsequent systemic reaction if stung again within 10 to 20 years after VIT, compared to 32% of untreated children.²⁷ Local reactions are common in VIT, but they should not substantially alter the planned treatment course. Rush VIT programs have been used successfully and safely.⁷ Duration of therapy is typically 3 to 5 years but may be longer for those with a history of a near-fatal reaction, a systemic reaction while receiving VIT, or honeybee allergy.²⁸

PATIENT SELECTION

Carefully identifying appropriate candidates is the first step in designing an effective and safe AIT program (Table 1). Strong candidates for AIT are the following: those who have positive immediate hypersensitivity skin test results (or serum-specific IgE test results) that correlate with clinical symptoms and are not controlled by avoidance measures and medications; those who wish to avoid the adverse effects of medications; those who wish to reduce the long-term costs of allergy medication; or, in the case of venom hypersensitivity, those who have had a systemic reaction after an insect sting. It is important to identify any patient characteristics (such as uncontrolled asthma) that may increase the risk of a serious reaction.²⁹ In a study that reviewed fatal anaphylaxis, late epinephrine administration was associated with an increased risk for fatal anaphylaxis after AIT administration.²⁹ Patients taking β -blocker medications and those with serious heart disease may respond poorly to resuscitative efforts should anaphylaxis occur. Caution should be exercised in administering AIT to children younger than 5 years because they may not be able to report symptoms of impending anaphylaxis. Allergen immunotherapy can be continued in pregnant patients as a maintenance prescription, but a new build-up prescription should be delayed until after delivery.

IMMUNOTHERAPY SAFETY

After careful selection of the AIT candidate, the allergist must discuss the risks and benefits of AIT with the patient so that he or she can make an informed decision. On the basis of data from a large survey, the risk of a fatal anaphylactic reaction from AIT has been calculated to be 1 in 2.5 million injections (about 3 deaths per year in the United States); near-fatal reactions occur once in every 200,000 injections.^{29,30} The dosing schedule also plays a role in the reaction rate. It involves a build-up phase, during which the allergen dose is gradually increased, and a maintenance phase, during which the target dose of allergen that is immunologically necessary to decrease allergic symptoms

is administered. A rush immunotherapy schedule, in which the maintenance dose is very rapidly achieved, can result in a higher reaction rate. Recent data suggest that cluster immunotherapy, which involves 2 to 4 injections per week, is as safe as a standard schedule of 1 injection per week.^{31,32} Because many patients find the frequent visits to a medical office and the requisite 30-minute monitoring period after injection to be inconvenient, patient nonadherence can compromise the safety of an AIT program.

IMMUNOTHERAPY ADMINISTRATION

To ensure proper administration, an AIT program should be monitored by an allergist at 6- to 12-month intervals. However, patients may prefer to receive their injections in the office of their primary care physician. Thus, primary care physicians must understand how to administer immunotherapy and how to identify and treat adverse reactions. Recently published guidelines emphasize the need to standardize injection administration and prescription forms, mixing protocols (using color-coded bottles), and, when possible, extracts (Table 2).³³

After receiving a subcutaneous injection in the upper arm, the patient must be monitored for an adverse reaction for at least 30 minutes. Local reactions can be treated with cool compresses, topical corticosteroids, or antihistamines, whereas systemic reactions must be treated with administration of epinephrine (preferably intramuscular), placement of a tourniquet above the injection site, and other supportive measures (oxygen, intravenous fluids, and inhaled β -agonists).³⁴ Delayed adverse reactions should be reported to the allergist. It is important to decrease the dose by approximately 50% after receiving a new lot of allergen, as even standardized vials differ from bottle to bottle in their actual concentrations.

THE FUTURE OF AIT

Clinical evidence strongly supports the efficacy and safety of AIT for pollens, dust mites, cat allergy, and venom; however, fewer studies have examined the use of AIT for mold and dog allergy. Small, well-controlled trials suggest that 3 to 5 years of successful AIT may result in long-lasting benefit, but confirmatory studies are needed. Further studies in the pediatric population are needed to confirm any preventive effects of AIT.

Perhaps the best studied investigational approach is high-dose sublingual immunotherapy (SLIT). A meta-analysis of available SLIT data from randomized controlled trials found a significant reduction in symptoms and medication use in the SLIT group.³⁵ More studies are needed to clarify the efficacy of SLIT vs standard subcutaneous immunotherapy.

TABLE 1. Allergen Immunotherapy Indications

Allergic rhinoconjunctivitis
Positive allergy test results correlate with symptoms
Symptom control is inadequate despite avoidance measures and medications
Patient wishes to avoid cost or adverse effects of medications
Allergic asthma
Positive allergy test results correlate with symptoms
Asthma control is inadequate while patient is taking daily preventive medications
Symptoms occur nearly year round
Allergic rhinitis coexists with allergic asthma
Stinging insect hypersensitivity
Skin or in vitro testing reveals evidence of venom-specific IgE
There is evidence of systemic (not local) reaction
There is evidence of urticarial reaction (in those older than 16 years)
Patient has a high risk of exposure

Currently, SLIT is not licensed in the United States and is much more commonly prescribed in Europe.

In a second investigational approach, anti-IgE therapy is administered before and during AIT. Reductions in the rates of anaphylactic reactions to immunotherapy (up to a 5-fold decrease) and in symptom scores have been observed in prospective studies.³⁶⁻³⁸ The Federal Drug Administration, which recently added a black box warning for omalizumab that describes the risk of anaphylaxis, recommends that patients be observed for at least 2 hours after administration and that they be educated in the recognition and treatment of anaphylaxis.³⁹

Third, novel vaccine delivery systems have been developed to improve the efficacy and safety of AIT. Recombinant vaccines, smaller peptides, or costimulatory adjuvants have been used to improve immune recognition. Creticos et al⁴⁰ showed that long-term clinical efficacy could be achieved with a ragweed pollen antigen that had been conjugated to an immunostimulatory DNA sequence capable of binding dendritic cell toll-like receptors.

Finally, promising studies using immunotherapy for food allergies and atopic dermatitis have been published.^{41,42} Future research in these areas may expand the therapeutic repertoire for these challenging diseases.

GUIDELINES FOR AIT

The 2003 guidelines for AIT will soon be updated by the Joint Task Force on Practice Parameters representing the American Academy of Allergy, Asthma, and Immunology;

TABLE 2. Standardized Allergy Extracts

Cat hair and pelt
Dust mites (<i>Dermatophagoides pteronyssinus</i> and <i>D farinae</i>)
Short ragweed
Grasses (Bermuda, perennial rye, orchard, Timothy, sweet vernal, Kentucky bluegrass, meadow fescue, red top)
Hymenoptera venoms (yellow jacket, honeybee, wasp, yellow hornet, and white-faced hornet)

the American College of Allergy, Asthma, and Immunology; and the Joint Council of Allergy, Asthma, and Immunology (JCAAI). Other guidelines related to immunotherapy include the Expert Panel Report-3 Asthma Full Report (EPR-3) (in preparation), the Global Initiative for Asthma (GINA),⁴³ the JCAAI practice parameters for stinging insect hypersensitivity,⁷ and the JCAAI practice parameters for the diagnosis and management of anaphylaxis.³⁴

Both the GINA and draft EPR-3 guidelines recognize the importance of allergic triggers in asthma. The draft EPR-3 guidelines recommend careful history taking combined with testing for specific IgE sensitivities. Persistent asthma should be treated with daily preventive medications, such as inhaled corticosteroids or leukotriene modifiers. According to the draft EPR-3 guidelines, AIT for asthma may be considered if there is clear evidence of symptoms and exposure (with a confirmed IgE sensitivity), if symptoms occur nearly year round, and if the asthma is not controlled by medications.

CONCLUSIONS

Allergen immunotherapy is a safe and effective therapy for ARC, allergic asthma, and stinging insect hypersensitivity. It should be considered for all patients with ARC as well as for those with persistent asthma, confirmed allergic sensitivities, and poor asthma control despite treatment with inhaled corticosteroids or leukotriene modifiers. Allergen immunotherapy should be strongly considered for patients with poor symptom control or adverse reactions to medications and for those with systemic reactions to insect stings and confirmatory skin or in vitro testing. Exciting new research in AIT may very well expand the allergic patient population that could benefit from this therapy.

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Questions About AIT

1. A 24-year-old man who was diagnosed as having asthma 2 years ago presents with a 15-year history of rhinorrhea, nasal congestion, and sneezing. His symptoms are not well controlled on a current medical regimen of a second-generation antihistamine, an intranasal corticosteroid, and a leukotriene modifier. He notices increased wheezing and breathlessness during late summer. Which one of the following is the next step in management?
 - a. Prescribe systemic corticosteroid
 - b. Prescribe monoclonal anti-IgE therapy
 - c. Obtain skin tests or serum specific IgE tests for airborne allergens
 - d. Try an alternative antihistamine
 - e. Try an alternative intranasal corticosteroid
2. A 14-year-old girl has been receiving AIT in her primary care physician's office for 8 weeks based on a prescription written by an allergist whose office is 100 miles away. On this occasion, she develops widespread urticaria, wheezing, and a hoarse voice 5 minutes after receiving her injection. Which one of the following is the next step in management?
 - a. Phone the prescribing allergist for advice
 - b. Call the local emergency response team
 - c. Administer intramuscular epinephrine immediately
 - d. Administer intramuscular diphenhydramine immediately
 - e. Observe and treat only if she develops hypotension
3. A 43-year-old woman comes to your office for an emergency department follow-up visit 2 weeks after a systemic reaction to a bee sting. She was given a self-injectable source of epinephrine to use in case of another reaction. Which one of the following is the next step in this patient's management?
 - a. Make no further recommendations at this time
 - b. Refer her to an allergist for consideration of VIT
 - c. Prescribe a daily antihistamine
 - d. Question her further about the bee to identify the hymenoptera species
 - e. Perform serum-specific IgE tests for stinging insects; if negative, tell her that she is not allergic to bee stings
4. A 26-year-old man with a history of asthma and allergic rhinitis presents in winter. During the past summer and fall, he had difficulties controlling his asthma despite high doses of inhaled corticosteroid, long-acting β -agonist, and leukotriene modifier. He required 3 separate systemic corticosteroid courses. He has had positive skin test results to grasses and weeds in the past. Which one of the following is the next step in optimizing his asthma control?
 - a. Plan to start systemic corticosteroids 2 weeks before summer allergy season
 - b. Prescribe an additional inhaled corticosteroid
 - c. Refer him to an allergist for consideration of AIT and/or monoclonal anti-IgE therapy
 - d. Recommend scheduled use of short-acting β -agonist during allergy season
 - e. Make no further recommendations because he is already receiving maximal medical therapy
5. A 6-year-old boy presents in spring with swollen, itchy, red, and watery eyes along with rhinorrhea and frequent sneezing for the past 3 weeks. He had similar trouble last spring and was advised to begin taking an intranasal corticosteroid 2 weeks before the spring season and to use systemic and ocular antihistamines to control his symptoms. You prescribe systemic corticosteroids. Which one of the following is the next step in managing this patient's symptoms?
 - a. Consider AIT if testing is positive for spring allergens
 - b. Prescribe a low dose of systemic corticosteroid for the next spring season
 - c. Prescribe antibiotic eye drops
 - d. Tell the parents that he should improve soon, because his current illness is likely related to a viral infection
 - e. Discontinue the intranasal corticosteroid because it is providing ineffective symptom control

Correct answers: 1. c, 2. c, 3. b, 4. c, 5. a