

Update on Allergen Immunotherapy for Treatment of Allergic Diseases

Kenny Y. Kwong, MD^{a,*}, Sydney Leibel, MD^b

^aDivision of Allergy-Immunology, Department of Pediatrics, Harbor-UCLA Medical Center, 1000 West Carson Street, N-25, Torrance, CA 90509, USA; ^bAllergy-Immunology, Kindercare Pediatrics, 301-491 Eglinton Avenue, Toronto, Ontario M5N 1A8, Canada

Keywords

• Immunotherapy • Allergy • Allergic rhinitis • Asthma • Allergic march

Key points

- Allergen immunotherapy is effective in treatment of allergic rhinitis, allergic conjunctivitis, and asthma.
- Allergen immunotherapy significantly reduces risk of developing asthma in allergic children.
- Allergen immunotherapy significantly reduces risk of sensitization to additional allergens in children already sensitized.
- Effective allergen immunotherapy requires identification of clinically relevant allergens and in the administration of correct doses.

INTRODUCTION

Allergen immunotherapy (or simply immunotherapy) was the first and only effective therapy used to treat allergic diseases more than a century ago before the development of modern allergic medications [1]. Through the twentieth century, the advent of each new class of antiallergy agent brought forth predictions of the demise of immunotherapy. The end for immunotherapy, whether because of H1 antagonists, topical steroids, monoclonal antiimmunoglobulin (Ig) E antibodies, or biologics, never materialized. These potent and selective agents have reduced morbidity and mortality in a large number of patients with allergies and asthma. However, significant numbers of patients have

Funding Sources: KY Kwong, Thermo-Fisher Scientific; S Leibel, none.

Conflict of Interest: KY Kwong, consultant and Speaker's Bureau for Thermo-Fisher Scientific; S Leibel, none.

*Corresponding author. E-mail address: kkwong@labiomed.org

suboptimal or no response to these therapies. Many other patients are responsive but suffer unacceptable side effects from these agents. Others may prefer immunotherapy as an effective alternative to pharmacologic agents. Immunotherapy also remains the only antiallergy therapy that induces immune tolerance to allergens resulting in a cure in up to 50% of patients who are compliant with treatment over time [2]. In young patients with allergic rhinitis who are predisposed to development of asthma, immune modulation from immunotherapy often results in prevention of asthma development [3]. Moreover, immunotherapy is protective against development of sensitization to multiple allergens (polysensitization) in patients who have already developed allergic sensitization to a single allergen (monosensitized) [4,5]. Taken together, immunotherapy remains a potent therapeutic agent in the treatment of allergic diseases. This article discusses the current understanding of the mechanisms involved in immunotherapy, which diseases are effectively treated with immunotherapy, and future directions of this important form of treatment.

ALLERGIC DISEASES EFFECTIVELY TREATED WITH IMMUNOTHERAPY

Case study

A 13-year-old boy presents to his pediatrician's office for continued evaluation and treatment of seasonal and perennial allergic rhinitis. The patient's symptoms began at approximately 5 to 6 years of age and consist of watery nasal discharge, pruritus, sneezing and congestion. Over the last 2 years these have worsened in severity and frequency, with progression to almost daily and nightly symptoms. Intranasal steroids were initiated on a routine basis 1 year ago with moderate improvement of some symptoms. Despite addition of as-needed nonsedating oral antihistamines, decongestants, and leukotriene receptor antagonist, the patient still experienced persistent symptoms. In vitro IgE testing performed and corroborated by history showed that he was allergic to dust mite, cat, grasses, and trees endemic to his area. Environmental controls were instituted with covering of bedding in dust mite-proof covers, removal of the carpet from the patient's bedroom, and use of a high-efficiency particulate air (HEPA) filter during the evening. These controls resulted in some further improvements in symptoms. Because of partial improvement of symptoms despite use of multiple pharmacologic agents and allergen avoidance the patient was started on subcutaneous immunotherapy to dust mites, grasses, and trees once a week. The patient did not own a cat. After 8 months the patient achieved the maintenance dose of immunotherapy and was switched to once-a-month injections. Over the next few months his symptoms improved gradually and he was able to discontinue most of his allergic medications 4 months after first reaching his maintenance immunotherapy dose.

Given the effectiveness of immunotherapy to treat allergic rhinitis it was tempting for early allergy providers to use this treatment modality to target other allergic diseases such as atopic dermatitis and food allergies. However, studies have shown that immunotherapy is most effective for allergic rhinitis,

allergic conjunctivitis, allergic asthma, and stinging insect hypersensitivity. As such, the American College of Asthma Allergy and Immunology (ACAAI) and the American Academy of Asthma Allergy and Immunology (AAAAI) recommend immunotherapy only for the treatment of these conditions [6].

Allergic rhinitis

Rigorous double-blind placebo-controlled studies have repeatedly shown high efficacy of immunotherapy in the treatment of seasonal and perennial allergic rhinitis [7–10]. A large meta-analysis involving 759 patients in 16 studies compared immunotherapy with placebo. Fifteen studies (94%) showed that immunotherapy was effective, as shown by reduction in symptoms, medication use, and allergen-specific IgE. Allergens used in these studies included dust mites, ragweed, grass and tree pollen, and mold [11]. Immunotherapy had a 1.81 odds risk of clinical improvement.

Allergic conjunctivitis and rhinoconjunctivitis

Some patients have allergic conjunctivitis alone but many have allergic rhinoconjunctivitis. Ocular symptoms often mirror nasal symptoms, particularly with forms of conjunctivitis such as vernal keratoconjunctivitis [12]. Although there are fewer rigorous studies showing the efficacy of immunotherapy in allergic conjunctivitis alone because of coexistence with nasal disease, there is ample clinical evidence and experience that shows immunotherapy to be effective in ocular allergic disease [13,14].

Allergic asthma

Immunotherapy is a well-accepted treatment modality for bronchial asthma in the United States. However, there are well-controlled studies that raise questions regarding immunotherapy's efficacy in these patients, particularly when there is sensitization to multiple allergens. In carefully selected asthmatic patients who are sensitized to grass pollen, cats, and dust mites, immunotherapy clearly shows clinical effectiveness. In 75 randomized control trials, 3188 subjects were analyzed in a meta-analysis. Allergens studied included dust mites, animal dander, pollen, and mold. Multiple allergens were included in 6 studies. Although results were not as dramatic as those for allergic rhinitis, they clearly favored immunotherapy rather than placebo in asthmatic patients. Symptom scores and bronchial hyper-reactivity improved, whereas medication requirements diminished with immunotherapy compared with placebo [15]. However, a few large-scale, double-blind, placebo-controlled studies recently failed to show significant advantage of immunotherapy both in adults and children with persistent asthma compared with specialist-driven standard of care treatment [16,17]. In the pediatric study, patients had moderate persistent asthma and were multiallergen sensitive [16]. Although immunotherapy is likely an effective treatment of bronchial asthma, careful selection of patient phenotypes and allergen sensitization may be required for optimal efficacy.

Stinging insect hypersensitivity

Immunotherapy is a mainstay in prevention of anaphylaxis and reduction of risk of progression to anaphylaxis in patients in response to various stinging insects. These insects include Hymenoptera (bees, wasps, hornets, and yellow jackets), fire ants, and bed bugs [18,19]. Well-controlled studies have shown that patients who achieve maintenance immunotherapy with insect venom have greatly diminished risk of anaphylaxis on re-sting or bite [20,21]. In general, immunotherapy is indicated when patients have experienced anaphylaxis to stinging insects, and in patients more than 16 years of age who experienced systemic cutaneous nonanaphylactic reactions to insect stings. Children younger than 16 years who have systemic cutaneous anaphylactic reactions and children and adults with large local reactions to insect stings have low risk of disease progression and do not need to receive venom immunotherapy. This article does not include stinging insect immunotherapy but there are multiple reviews on this subject [18,22,23].

Case study

A 5-year-old boy presents for consultation for risk of development of asthma. At 3 years of age he developed allergic rhinitis with symptoms of frequent rhinorrhea, clear nasal discharge, and nasal pruritus. These symptoms are currently fairly well controlled with a routine intranasal corticosteroid and as-needed nonsedating antihistamine. His parents both have persistent asthma. Furthermore, the patient's 2 older siblings have severe persistent asthma requiring high-dose corticosteroids for control and have frequent urgent-care visits. The parents wonder whether anything can be done to prevent, or at least attenuate, development of asthma in their youngest son. The patient was skin tested and found to be sensitized to dust mites and grass pollen. He was given environmental controls and started on dust mite and grass pollen immunotherapy once weekly. Within a few months of reaching maintenance injections the patient's nasal symptoms improved and intranasal corticosteroids could be discontinued. He received monthly maintenance immunotherapy for the next 5 years and never developed asthma symptoms.

Prevention of development of asthma and further allergen sensitization

Apart from observations by a century of immunotherapy administering providers, large-scale prospective studies have also shown the protective effects of immunotherapy against development of asthma and further allergen sensitization in allergic patients. In the Preventive Allergy Treatment (PAT) study, children with rhinoconjunctivitis associated with birch and/or grass pollen allergy were randomized to receive immunotherapy to these allergens or placebo for 3 years. Children who received active immunotherapy had a 2.5-fold reduced risk ($P < .001$) of development of asthma compared with the placebo group [3]. Longer term studies include a 14-year follow-up of children given immunotherapy versus placebo. At the date of the children's 16th birthday, 22% of patients given placebo, compared with 72% who received immunotherapy, were asthma free [24]. In an open but large-scale study, 7182 patients

with single-allergen sensitization were given immunotherapy. At the end of 3 years, 27% of these patients developed additional allergen sensitization compared with 68% of open controls consisting of 1214 patients [25]. In a similar study, 45% of monosensitized children receiving immunotherapy developed additional allergen sensitivity compared with 100% of similar patients who were given placebo [26].

Compared with conventional modalities of treatment of allergies and asthma, immunotherapy to date remains the only therapy that can significantly reduce risk of disease progression.

Atopic dermatitis and urticaria/angioedema

Recent evidence supports the role of aeroallergens in the pathogenesis of atopic dermatitis [27–31]. Aeroallergen immunotherapy logically should be effective in the treatment of atopic dermatitis. A small number of studies have shown that immunotherapy, especially with dust mite, improves atopic dermatitis scores [32,33]. Patients with more severe disease seem to have less improvement with immunotherapy [34]. Thus, immunotherapy may have a potential role in the treatment of patients with atopic dermatitis who are sensitized to inhalant allergens, particularly for those with concomitant respiratory allergy. In contrast with atopic dermatitis, there is no evidence that immunotherapy has any effect on either acute or chronic urticaria/angioedema.

MECHANISMS OF IMMUNOTHERAPY: TARGETING MULTIPLE POINTS OF THE ALLERGIC CASCADE

Immunologic changes resulting from immunotherapy are complex and the precise pathways involved are being continuously elucidated. At present, a rigorous body of evidence supports that multiple areas of the allergic cascade are involved (Fig. 1), including modulation of T-lymphocyte response, induction of regulatory T lymphocytes, and IgE and IgG responses [35].

Patients genetically and environmentally predisposed to atopy exhibit a preferential TH2 lymphocyte response to various allergenic antigens. On exposure to previously sensitized allergens, TH2 lymphocyte responses elaborate cytokines such as interleukin (IL)-4 and IL-13, which facilitate development of IgE (IgE switching) against the associated antigen [36]. Furthermore, TH2 lymphocytes may also secrete cytokines such as IL-5 that recruit and activate inflammatory cells such as eosinophils and basophils, which express inflammatory peptides into the local milieu. Persistence of these signals from chronic allergen exposure results in chronic inflammation in most patients with allergic rhinitis and asthma [37,38]. Data have shown that successful immunotherapy with previously sensitized allergens results in a change from a TH2 to TH1 lymphocyte response, which results in reduction of IgE switching in preference for more IgG responses [39].

Immunotherapy with allergens such as grass pollen, house dust mite, and insect venom has been shown to generate T-regulatory cells that elaborate regulatory cytokines, namely IL-10 and TGF- β [40]. T-regulatory cells may in part

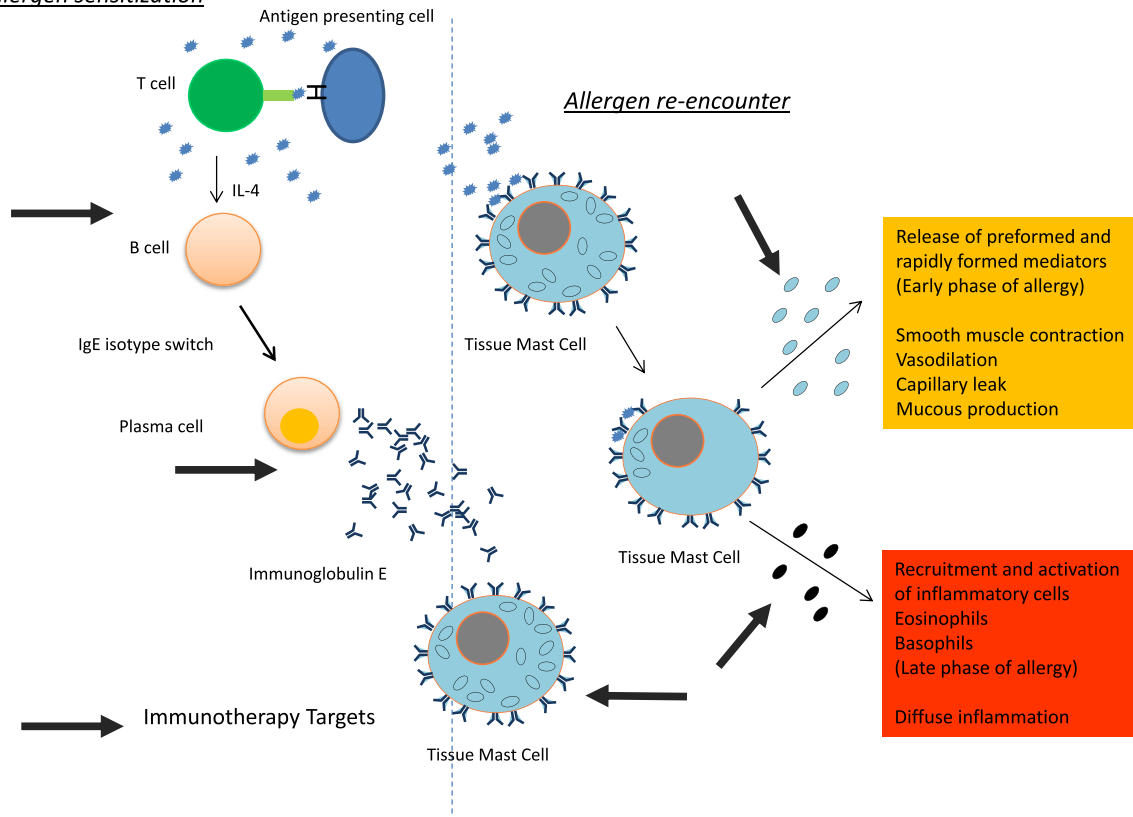
Allergen sensitization

Fig. 1. Targets of immunotherapy along the allergic cascade.

serve as dampeners of lymphocyte activation, reducing the skewed TH2 lymphocyte responses in allergic patients [41]. B-cell-specific IgE production has been shown to be inhibited, whereas IgG4 expression is conversely stimulated by IL-10 from T-regulatory cells [42]. Proinflammatory cytokine release from mast cells and eosinophils can be inhibited by IL-10. In addition, elective inhibition of the CD28 costimulatory pathway by IL-10 elicits T-cell tolerance during immunotherapy [43,44].

CAVEATS ON CLINICAL RESPONSE TO IMMUNOTHERAPY

Case study

A 14-year old girl with perennial and seasonal allergic rhinitis tested positive for dust mite, grass, and tree pollen. She was started on immunotherapy, initially twice weekly for 4 months until she achieved maintenance dose, and thereafter she received once-monthly injections. Three months later she began experiencing fewer symptoms, and by 14 months did not require intranasal steroids or antihistamines. She continued immunotherapy until she was 19 years of age, when she was no longer covered by her parents' health insurance. Her allergic rhinitis symptoms seem to have resolved.

In general, several levels of clinical response can be observed with immunotherapy treatment. These levels include early, progressive, persistent, and preventative effects.

Within a year of attaining maintenance doses of immunotherapy, most patients experience improvement in allergy symptoms and reduction in rescue medication use. This early effect has been documented in multiple large-scale randomized studies. For instance, symptom scores for rhinoconjunctivitis improved and medication requirements were reduced in hundreds of recruited subjects after immunotherapy with grass pollen antigen in several well-controlled studies [45–47]. These results have been duplicated for other allergens [8,10].

Continued treatment with immunotherapy beyond the first year results in further reduction in symptoms and medication needs. Robust studies have shown this effect with grass pollen, dust mite, dog, and cat antigens, although smaller and similar studies have shown efficacy with many other allergens such as tree and weed pollens [48,49]. In addition, studies have shown that immunotherapy during the second year may produce decreased symptoms and medication requirements of a larger magnitude compared with the first year of treatment [50]. During this progressive effect, many studies show improvement in objective measures in addition to subjective symptom improvement. For instance, asthmatic patients allergic to dust mite and grass pollen and receiving immunotherapy had reduced airway hyper-reactivity in response to methacholine by the 18th and 24th month of allergen injections respectively [51,52]. In addition, studies have shown that, in asthmatic children and adults, immunotherapy significantly attenuates allergen-induced late-phase airway responses [53]. It is also likely that changes in the immune response to allergen exposure (as described previously) occur during this phase of immunotherapy. Increased

expression of interferon-gamma representing a TH1 lymphocyte pattern was found in peripheral blood of patients receiving grass pollen immunotherapy after 12 months of treatment, but not after 3 months [54]. Pollen-specific IgG levels similarly increased minimally after 1 year of grass pollen immunotherapy, but significantly during the second year of treatment in another study [55].

One of the most convincing arguments for immunotherapy as a mainstay for treatment of allergic diseases despite relative inconvenience is the persistence effect even after cessation of treatment. Although this occurs only in approximately half of patients, this is the only treatment that can afford a cure for allergic disorders. In a large randomized trial, patients with allergic rhinitis who previously received grass pollen immunotherapy were given either placebo or continued grass pollen antigen. Patients who were discontinued from active immunotherapy (placebo group) had sustained symptom improvement and medication scores that were not significantly different from those in the active (continued treatment) group. This effect was persistent for 3 years after discontinuation of therapy [2]. In the aforementioned PAT study, children who received immunotherapy had sustained eye and nasal symptom improvements for up to 10 years after discontinuation of therapy compared with similar children who never received treatment [3].

As previously discussed, immunotherapy significantly reduces the progression of allergic disease and sensitization to new allergens in atopic patients (interruption of the atopic march).

CLINICAL EFFECTIVENESS OF IMMUNOTHERAPY VERSUS PHARMACOLOGIC TREATMENT OF ALLERGIC DISEASES AND HOW IMMUNOTHERAPY FITS IN WITH REGULAR THERAPY

The AAAAI/ACAAI joint task force's third practice parameter on allergen immunotherapy recommends specific indications for immunotherapy (Box 1) [6]. However, these indications are broad, and considerable discretion is left to both the provider and patient with regard to initiating immunotherapy. Scenarios range from one extreme, wherein immunotherapy is begun because of patient demand without any trials of medications and environmental controls, to the opposite extreme, in which immunotherapy is withheld by providers and insurance payers until every modality of treatment is exhausted. It is likely that, in many instances, which patient receives immunotherapy is dictated by insurance coverage, provider's knowledge or passion to start treatment, and the insistence of patients themselves. However, given the broad indications for immunotherapy, knowledge of efficacy of immunotherapy compared with regular treatment helps providers and patients decide whether to begin immunotherapy in a rational manner.

The most straightforward decision to initiate immunotherapy is when patients do not respond optimally to standard medical therapy, which is especially evident with allergic rhinitis. At present, first-line treatments of allergic rhinitis with frequent symptoms are intranasal corticosteroids with nonsedating antihistamines and oral decongestants added on an as-needed basis [56]. Despite

Box 1: General indications for allergen immunotherapy

For allergic rhinitis, allergic conjunctivitis, and asthma: in patients in whom there is (1) evidence of specific IgE antibodies to allergens, and (2) clinical history and symptoms that are consistent with exposure to these allergens, immunotherapy may be indicated based on (but not limited to) the following factors:

- Patient's preference/acceptability
- Poor adherence
- Multiple and or high-dose medication requirements
- Incomplete response to allergen avoidance
- Medication side/adverse effects
- Therapy for coexisting allergic rhinitis and asthma
- Potential prevention of allergic march and development of asthma in patients with allergic rhinitis

Potential indication: atopic dermatitis, in which inhalant allergen is associated with disease.

Indications for allergen immunotherapy in patients with Hymenoptera stings:

- Anaphylactic reaction to Hymenoptera sting in both children and adults with demonstrable clinical significant specific IgE to Hymenoptera venom
- Cutaneous nonanaphylactic systemic reaction to hymenoptera sting in adults and children older than 16 years with demonstrable IgE antibodies to hymenoptera venom
- Children and adults with systemic reactions to fire ants with demonstrable IgE antibodies

Potential indication: patients with large local reactions to Hymenoptera stings that are deliberating and frequent.

Adapted from Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol 2011;127(1):S1–S5; with permission.

commercial advertisements suggesting that these agents are effective for a most patients with rhinitis, large bodies of evidence show that a significant number of patients achieve incomplete relief of symptoms. The National Allergy Survey Assessing Limitations showed that, despite current treatments, significant numbers of patients with allergic rhinitis had difficulty with sleep, decreased quality of life, and reduced work productivity. Twenty-eight percent of patients were dissatisfied with intranasal steroids because of bothersome side effects [57]. In one study using budesonide irrigation, only 60% of patients achieved significant symptom resolution [58].

Response to inhaled corticosteroids in patients with asthma follows a bell-shaped response curve. In a study with the primary outcome set as number of symptom-free days, a large number of patients placed on either fluticasone or montelukast experienced increased number of symptom-free days; however, up to 16% of patients had no change in asthma-free days [59]. A similar study

with change in forced expiratory volume in 1 second (FEV_1) as primary outcome showed that 20% to 30% of patients with asthma given inhaled beclomethasone or oral montelukast experienced no improvement in FEV_1 [60]. In a large study involving pediatric patients with asthma, there was a differential response to combination therapy involving either corticosteroids plus long-acting bronchodilator or montelukast. Neither combination strategies were able to produce complete asthma control in 100% of the patients [61]. In the Gaining Control of Asthma (GOAL) study, up to 70% of patients never achieved asthma control despite being given high-dose inhaled corticosteroid/long-acting bronchodilator agents [62]. A similar percentage of pediatric patients in a real-world inner-city disease management program also failed to achieve asthma control despite guideline-based care [63]. Although there are less rigorous studies examining differential response to medications in patients with allergic rhinitis, international consensus groups have found that a significant number of patients experience chronic unacceptable symptoms despite guideline-based treatment [64].

Despite the availability of multiple preparations of intranasal corticosteroids, a significant number of patients experience bothersome side effects such as nasal irritation and postnasal drip. For instance, in the NASL (National Survey Assessing Limitations) survey up to 66% of patients surveyed indicated that they experienced discomfort at least some of the time from these agents, and 28% of patients in the survey who requested changing intranasal corticosteroids cited side effects of the current preparation as the reason for switching [57]. Studies have shown that inhaled corticosteroids also produce troublesome side effects in a significant number of asthmatics. In one survey, up to 40%, 30%, and 14% of patients experienced cough during inhalation, thirsty feeling, or dysphonia respectively while taking either inhaled budesonide or beclomethasone [65]. Furthermore, side effects were more frequent and severe with increased daily doses of medication.

Although most agents used in the treatment of asthma and allergies have excellent safety profiles, there are some side effects associated with their use. In particular, inhaled corticosteroids used at high doses result in small but tangible adverse side effects. Less severe and reversible effects include dysphonia, oral irritation, and oral thrush [66]. More lasting effects include growth velocity reduction in children [67,68]. This growth rate reduction is thought to be transient and ultimate adult height was found to be unaffected because of catch-up growth in earlier studies. However, recent evidence suggests that this catch up does not occur. The reduction in ultimate height in these children compared with their predicted midparental height is small, in the magnitude of 0.3 to 0.5 cm [69].

In addition, despite favorable outcomes associated with multiple pharmacologic agents, compliance plays a major role in achieving disease control in many patients with asthma and allergies. Multiple studies have shown that noncompliance with medication plays a role in most patients who do not achieve control of their symptoms [70,71].

Taken together, these data show that immunotherapy may be beneficial in a spectrum of clinical scenarios. These scenarios include when medications do not adequately control symptoms, when medications control symptoms but have bothersome side effects, when medications control symptoms but result in adverse side effects, when compliance with medications are poor, and when patients prefer receiving once-weekly to once-monthly allergy injections compared with daily inhaled, intranasal, and oral medications. The provider should work in concert with patients in deciding whether immunotherapy is a good clinical choice in each scenario.

SAFETY AND ADVERSE EVENTS ASSOCIATED WITH ALLERGEN IMMUNOTHERAPY

Injection of allergens into previously sensitized patients incurs the risk of allergic reactions that range from local urticaria to anaphylactic shock and death. Emergency equipment should be available during immunotherapy administration for potential systemic reactions (Box 2). However, the risk of serious anaphylactic reactions is rare when immunotherapy is administered appropriately. In an AAAAI longitudinal survey of physician AAAAI members from 1990 to 2001, the incidence of reported near-fatal reactions (NFR) was 23 per year, culminating in 5.4 events per 1 million injections. The total number of fatal reactions during this survey period was 41, culminating in 1 fatal reaction per 2.5 million injections [72]. However, large local reactions associated with immunotherapy are common, ranging from 26% to 86%. Most studies have shown that large local reactions, although a discomfort to the patient, are benign. Patients who experience large local reactions are usually not at any higher risk of systemic reactions with the next injection [73,74]. Only 1 study found that patients with large local reactions of 25 mm or larger have a higher

Box 2: Examples of emergency equipment recommended for treatment of immunotherapy systemic reactions

Aqueous adrenaline 1:1000

Oxygen delivery equipment

Airway patency equipment

Intravenous fluid equipment

H1 antagonist

H2 antagonist

Corticosteroids

Glucagon (for patients receiving β -blockers)

Equipment for intravenous access, intramuscular medication delivery, blood pressure monitoring

Adapted from Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol 2011;127(1):S1–55; with permission.

likelihood of subsequent systemic reactions [75]. In addition, almost all patients receiving immunotherapy have transient local pain and discomfort at the injection site.

Risks of severe allergic reactions are associated with several factors and these can be minimized when immunotherapy is administered in an appropriate fashion. Because morbidity is associated with asthma, immunotherapy should not be given to patients with unstable or poor asthma control [6]. Up to 70% of systemic reactions occur within 30 minutes of injection [76]. In the AAAAI fatal and NFR survey, 96% of patients experiencing NFR and 77% who died after immunotherapy had onset of symptoms within 30 minutes of the initial injection [77]. Therefore, patients should receive immunotherapy in a medical setting that is equipped to handle anaphylactic emergencies and wait at least 30 minutes before leaving. A longer observation period is necessary for more sensitive patients who may also be given self-injectable adrenaline for late reactions, although these are rare [6].

High-risk patients

Although immunotherapy is generally safe for patients with various underlying diseases such as immune deficiency, caution must be taken with patients who are at higher risk of morbidity and mortality from anaphylaxis. Death from anaphylaxis is often caused by respiratory failure and therefore patients with uncontrolled asthma are poor candidates for immunotherapy until their disease is controlled [77–79]. Likewise, patients previously well but experiencing asthma exacerbations should not receive their injections until clinically improved [6]. Relative contraindications to immunotherapy include certain medications that may antagonize agents used for the treatment of anaphylaxis and may themselves increase the risk of anaphylaxis. These agents include β -blockers and angiotensin-converting enzyme inhibitors [80–82]. These patients should be switched to other agents whenever possible if immunotherapy is to be initiated. Immunotherapy is generally safe for pregnant patients but risk to the fetus occurs if there are systemic reactions resulting in placental-utero insufficiency. In general, patients who become pregnant while on immunotherapy can continue but not have any dose escalation to reduce risk of systemic reactions [83,84]. Patients with unstable cardiovascular disease similarly have reduced survivability during systemic reactions and the benefits of immunotherapy must be carefully weighed against the risks. For instance, a patient with anaphylaxis to bee stings and who has unavoidable exposure to bees may elect to receive venom immunotherapy despite having unstable angina [6,85].

PRACTICAL ASPECTS OF IMMUNOTHERAPY

Case study

The mother of a 14-year-old boy with seasonal and perennial allergic rhinitis hears that allergy shots may better control her son's allergy symptoms. She brings him to a provider who performs an allergy blood test, which is positive for everything, including dust mites, dog, cat, several species of mold, multiple

species of grass, trees, and weeds. A history of environmental associations with allergy symptoms is not taken. The provider starts the patient on immunotherapy consisting of 4 shots twice a week. Each shot is drawn from a vial consisting of mixtures of several different antigens. After 18 months of shots the patient's allergy symptoms have not significantly improved.

Careful selection of antigens administered in correct doses is necessary for effective immunologic and clinical changes to occur in response to subcutaneous injection therapy. Improper selection and mixing of allergens, subtherapeutic doses, and use of allergens with no clinical association to symptoms often results in minimal clinical response.

Allergen selection

Skin testing is often the preferred method for identification of antigens for immunotherapy, although modern specific IgE serum tests are acceptable alternatives. Patients may have positive skin or serum IgE tests to certain allergens but have no clinical consequence when exposed to them (sensitized but with no clinical reactivity). Therefore, it is imperative that the provider takes a detailed history to determine which allergens correlate with clinical symptoms before using the particular allergen for immunotherapy. For instance, a patient may have a positive skin test to dogs but show no symptoms when exposed to dogs. Use of canine antigen for immunotherapy therefore would not result in any therapeutic benefit. Inclusion of clinically irrelevant allergens may also result in dilution of other relevant allergens, reducing overall effectiveness.

There is diverse flora in the United States, with local geographic areas having a predominance of certain species. Given the large numbers of pollen species in the United States, it is impossible to test for every single one. Moreover, there is extensive cross reactivity between grass allergens, thus only a few species are required even if patients are clinically reactive to more. Cross reactivity between trees and between weeds is much less. Thus the immunotherapy provider must have knowledge of the local aerobiology to choose a practical but relevant series of allergens for testing. Omitting clinically relevant allergens results in decreased effectiveness of immunotherapy.

Pollens such as grass and ragweed have been shown in multiple studies to be effective and safe in immunotherapy [86–88]. However, there are many other clinically relevant pollens that have not undergone similar study. Extrapolation of known data to these is reasonable and likely effective. At present there are no commercially available allergens to some clinically relevant molds such as ascospores and others may be antigenically suboptimal, including *Aspergillus* and *Cladosporium* [89–91]. Certain molds are found predominantly indoors, whereas others are found outdoors. Thus the provider must ascertain the clinical relevance of each. For patients clinically reactive to dander from animals such as dogs and cats, the first line of treatment should be avoidance. However, avoidance is not possible in some patients, such as veterinarian staff, or because of personal choice. In such cases, cat and dog antigen immunotherapy is effective. Multiple studies have shown that dust mite immunotherapy is effective

and useful in conjunction with dust mite avoidance strategies. In addition, patients clinically reactive to cockroach benefit from cockroach immunotherapy, particularly together with aggressive pest elimination strategies [92].

Antigen standardization

The minimum amount of antigen needed to achieve clinical improvement is called the maintenance dose. At present, this dose has been determined for a range of allergens (Table 1). In the past, allergists prepared their own extracts by compounding various allergens from local fauna using weight-per-volume formulas, which often resulted in wide ranges of allergen concentrations being given to patients. Current commercial extracts have more consistent antigen content and many allergens are standardized in terms of equivalent biologic units. In the United States, these are calculated based on the amount of antigen required to elicit a certain erythema size in subjects highly sensitized to that particular allergen. Standardized antigens are available for dust mite, cat, and grasses. Other antigens, such as dog and trees, are still prepared by the weight-to-volume method. Providers should use standardized antigens for immunotherapy when possible to ensure that maintenance doses are achieved.

Most studies showing effectiveness of immunotherapy have used only single allergens. In reality, patients are usually allergic to multiple antigens (polysensitized) and may need multiple allergens administered for immunotherapy. Most patients are able to tolerate up to 4 subcutaneous injections per session.

Table 1

Examples of effective dosing ranges for standardized and nonstandardized licensed antigens in the United States

Allergen extract	Labeled potency/ concentration	Probable effective dose range
Dust mites: <i>Dermatophagoides farinae</i> / <i>Dermatophagoides pteronyssinus</i>	3000, 5000, 10,000, and 30,000 AU/mL	500–2000 AU
Cat hair/pelt	5000 and 10,000 BAU/mL	1000–4000 BAU
Bermuda grass	10,000 BAU/mL	300–1500 BAU
Standardizes miscellaneous grass	100,000 BAU/mL	1000–4000 BAU
Short ragweed	1:10, 1:20 wt/vol, 100,000 AU/mL	6–12 µg or 1000–4000 AU
Nonstandardized AP dog	1:100 wt/vol	15 µg
Nonstandardized pollen extracts	1:10 to 1:40 wt/vol, 10,000–40,000 PNU/mL	0.5 mL of 1:100 or 1:200 wt/vol
Nonstandardized mold/fungi	1:10 to 1:40 wt/vol, 10,000–40,000 PNU/mL	Highest dose tolerated

Abbreviations: AP, acetone precipitated; AU, Allergy units; BAU, Bioequivalent allergy units; PNU, Protein nitrogen unit, wt/vol, weight/volume.

Adapted from Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol 2011;127(1):S1–55; with permission.

Thus several antigens are often combined in a single injection stock vial. Subcutaneous injection of more than 0.4 to 0.5 mL is usually difficult to tolerate long term. Although there are a limited number of studies that have examined efficacy of multiantigen immunotherapy, it is likely that this mode of immunotherapy is effective. Care must be taken not to combine too many antigens in a single stock vial and dilute the effective maintenance concentrations of each antigen. Thus the provider must be skilled in including clinically relevant antigens and excluding those that are irrelevant [6].

Immunotherapy schedule

There are 2 phases involved in immunotherapy: buildup and maintenance. The former involves gradually increasing concentrations of antigen over weeks and the latter is when therapeutic doses are achieved and maintained over time. If the starting allergen doses are too dilute, then the time needed to achieve maintenance is prolonged and unnecessarily large numbers of injections are given. In contrast, if the starting doses contain too much antigen, then the risk of reactions is increased. Current guidelines recommend starting at 1:10,000 to 1:1000 dilution of the maintenance concentration. Doses are usually increased 1 to 3 times a week depending on patients' convenience, and their ability to tolerate the number of injections. Table 2 shows a typical schedule. Maintenance is usually achieved in 3 to 6 months. Very sensitive patients may have to begin at more dilute concentrations and dose escalation frequency needs to be slowed when there are systemic reactions. Large local reactions without systemic symptoms usually do not necessitate dose escalation reduction [6]. Once maintenance dosing is achieved, dosing intervals may be spaced to once monthly [93].

Cluster and rush immunotherapy

Because conventional immunotherapy requires months of injections before maintenance is achieved, efforts have been made to adjust dosing and reduce time to the maintenance phase. Cluster immunotherapy involves giving 2 or more injections of allergens per session, which results in achieving maintenance doses in as early as 4 weeks compared with 3 to 6 months. Rush immunotherapy involves giving multiple injections over the course of hours, resulting in maintenance doses in as little as 6 days. Risk of reactions associated with both cluster and rush immunotherapy are increased, although most are not severe. Premedication also reduced the risk of these reactions. Patients usually require to be hospitalized for rush schedules.

Duration of immunotherapy

Patients usually experience improvement of symptoms within 1 year of achieving maintenance doses. Vigorous studies in venom immunotherapy show that 5 years of therapy is sufficient for most subjects to be protected against future stings. Although there are fewer similar studies involving inhalant allergens, it is accepted that 3 to 5 years of inhalant immunotherapy provides the best chance of a cure for patients with allergic rhinitis. Approximately half of patients who have no to minimal symptoms after 3 to 5 years of immunotherapy

Table 2
Sample immunotherapy injection record

Patient Name

Medical Record Number

Date of Birth

Vial A Extract Name: _____

Dilution	1:10,000 (w/v)	1:1000 (w/v)	1:100 (w/v)	1:10 (w/v)	1:1 (w/v)
Color	Silver	Green	Blue	Yellow	Red
Vial Number	5	4	3	2	1
Expiration Date	/ /	/ /	/ /	/ /	/ /

				Vial A				
Date	Time	Peak flow	Health screen	Vial Dilution	Vial Number			
				Arm	Volume injected	Local reaction (mm)	Injector sign.	
1	/ /		Normal/Abnorm	R L				
2	/ /		Normal/Abnorm	R L				
3	/ /		Normal/Abnorm	R L				
4	/ /		Normal/Abnorm	R L				
5	/ /		Normal/Abnorm	R L				
6	/ /		Normal/Abnorm	R L				
7	/ /		Normal/Abnorm	R L				
8	/ /		Normal/Abnorm	R L				
9	/ /		Normal/Abnorm	R L				
10	/ /		Normal/Abnorm	R L				
11	/ /		Normal/Abnorm	R L				
12	/ /		Normal/Abnorm	R L				
13	/ /		Normal/Abnorm	R L				
14	/ /		Normal/Abnorm	R L				
15	/ /		Normal/Abnorm	R L				
16	/ /		Normal/Abnorm	R L				
17	/ /		Normal/Abnorm	R L				
18	/ /		Normal/Abnorm	R L				
19	/ /		Normal/Abnorm	R L				
20	/ /		Normal/Abnorm	R L				
21	/ /		Normal/Abnorm	R L				
22	/ /		Normal/Abnorm	R L				
23	/ /		Normal/Abnorm	R L				
24	/ /		Normal/Abnorm	R L				
25	/ /		Normal/Abnorm	R L				
26	/ /		Normal/Abnorm	R L				
27	/ /		Normal/Abnorm	R L				
28	/ /		Normal/Abnorm	R L				

relapse. Therefore, some patients elect to continue treatment for longer periods of time [2].

Taken together, it is highly recommended that immunotherapy be prescribed and administered by trained providers such as allergist-immunologists and performed in appropriate medical settings.

FUTURE DEVELOPMENTS

Sublingual allergen immunotherapy

The inconvenience, pain, and risk of rare but severe systemic reactions associated with injection immunotherapy have caused clinicians to develop other modalities of allergen delivery. Bronchial, intranasal, and oral routes have proved to be ineffective [94–96]. Direct oral absorption of antigen was first introduced in the United States in the 1940s but did not gain acceptance. Dust mite antigen delivered via this route was first described in 1986 and intense interest and studies reemerged in sublingual immunotherapy (SLIT), particularly in Europe [97,98]. The World Health Organization (WHO) and the European Academy of Allergy and Immunology currently support the use of SLIT in allergen desensitization of pediatric and adult patients with allergic diseases. In the United States, clinicians offering this modality of treatment do so in an off-label fashion because there are no US Food and Drug Administration (FDA)–approved formulations of SLIT allergens.

Studies have shown similar efficacy between SLIT and subcutaneous immunotherapy (SCIT), although studies involving the latter are more extensive and comprehensive. SLIT has been shown to be effective in treatment of allergic rhinitis and asthma in pediatric patients [99,100]. Both symptom improvement and reduction of medication requirements have been shown with SLIT [101]. Similar to SCIT, studies have shown that improvements in asthma symptoms caused by SLIT, although statistically significant, were small [102,103]. In addition, SLIT has been shown to interrupt the allergic march in atopic children. Marogna and colleagues [104] randomized 216 children to receive either medication alone or in combination with SLIT. After 3 years, 34.8% of control patients developed new allergen sensitizations compared with 3.1% of patients receiving SLIT. Patients given SLIT also had reduced bronchial reactivity and fewer developed mild persistent asthma compared with control patients. In a similar study, patients given SLIT for 4 to 5 years were statistically less likely to develop asthma compared with control patients. This effect was maintained for 4 to 5 years after discontinuation of therapy [105].

Immunologic changes following SLIT mirror those achieved with SCIT. These changes include reduction in skin reactivity to antigen, decreases in antigen-specific IgE, increase in antigen-specific IgG4, changes in T-regulatory cells, and tolerance to allergen [106,107].

A key advantage of SLIT compared with SCIT is safety. In one large review, local oral reactions were most common with SLIT, with prevalence of 0.68 per 1000 doses in some studies. There were 14 serious systemic reactions in 1,019,826 SLIT administrations resulting in the rate of severe reactions of 0.056% compared with 0.6% in patients who received SCIT [108]. Rare immunologic disorders such as eosinophilic esophagitis have been associated with SLIT; however, it is unclear whether there was a causal relationship or coincidental development of the diseases in the patients receiving SLIT [109]. The safety profile of SLIT has allowed SLIT dosing in Europe to be performed at the patient's home.

Although SLIT is not currently standard of care in the United States owing to lack of FDA-approved antigens, a rapidly growing number of American providers are offering it on an off-label basis. Given the similar efficacy, convenience of at-home dosing, no need for injection, and better safety profile, it is likely that SLIT will play a major role in the near future in the United States for treatment of allergic diseases.

OTHER ROUTES OF ADMINISTRATION

Intranasal, epicutaneous (transdermal), and intralymphatic injection routes have been used to deliver allergen immunotherapy in a limited numbers of studies. The intranasal route has been found to be effective, but many patients experienced bothersome side effects. Patients receiving transdermal delivery of antigen via a patch did not have significantly better symptom scores compared with patients receiving placebo via the same method. Intralymphatic injection of cat antigen resulted in improvement in symptoms after only 3 single injections over a 4-week period [110]. This improvement was similar to that achieved with conventional SCIT over a 3-year period. The effectiveness and safety of sublingual immunotherapy has reduced interest in intranasal and epicutaneous routes. More studies are needed to determine the efficacy and safety of this more invasive form of immunotherapy.

COMBINATION WITH ANTI-IGE THERAPY (OMALIZUMAB)

Many patients with unstable asthma are unable to tolerate reactions associated with immunotherapy despite optimal treatment with controller medication. Monoclonal antibody against soluble IgE (omalizumab) is highly effective in the treatment of difficult-to-control asthma [111]. Concurrent immunotherapy treatment with omalizumab has been shown to significantly decrease rates of systemic reactions, particularly with cluster and rush schedules [112,113]. Addition of omalizumab to conventional immunotherapy with birch and grass immunotherapy improved asthma control and reduced medication use compared with immunotherapy or omalizumab alone [114].

ADDITION OF IMMUNOREGULATORY ADJUVANTS

Immunotherapy results in changes in lymphocyte polarization from TH2 toward TH1, resulting in reduction and increase of allergen-specific IgE and IgG4 respectively [115]. Immunostimulatory oligonucleotide DNA sequences such as CpG motifs are found on bacteria cell walls and facilitate this TH2 to TH1 shift via toll-like receptors (TLRs). Addition of TLR9 agonist to ragweed antigen was shown to decrease allergic rhinitis symptoms after 6 doses in 25 adults [116]. However, a subsequent larger study did not yield similar results [6,117]. A TLR4 receptor agonist MPL (monophosphoryl lipid A) linked to grass pollen significantly reduced symptoms in a large multicenter study with patients who had grass-induced and tree-induced allergic rhinitis [118]. More studies are needed to assess efficacy and safety of these agents.

IMMUNOTHERAPY FOR FOOD ALLERGY

There is an unmet need to develop treatment modalities for food allergy, given its increasing prevalence. At present, avoidance and early treatment of severe systemic reactions with intramuscular adrenaline are the only recommended treatments [119]. Omalizumab and other agents such as Chinese herbs have been shown to be effective but are non-FDA approved and off-label [120]. Immunotherapy for food allergies was previously considered too dangerous and not effective. However, recent studies have shown that sublingual immunotherapy results in tolerance to foods including milk, egg, peanut, and hazelnut [6]. Moreover, immunologic changes such as reduction in skin reactivity and basophil activation were associated with these treatments, suggesting that there was real tolerance and not merely temporary saturation of IgE receptors, as in penicillin desensitization [121]. Reactions were noted in up to half of patients given peanut immunotherapy, although most were mild and attenuated with antihistamines and sodium cromolyn [122]. More studies are needed before immunotherapy can be adopted for treatment of food allergies.

IMMUNOTHERAPY FOR POLLEN FOOD ALLERGY SYNDROME

Pollen food allergy syndrome (PFAS) is a local-contact IgE-mediated reaction to fruits and vegetables localized to the mouth that rarely proceeds to systemic symptoms or anaphylaxis. PFAS rarely occurs in young children and develops in older children, teens, and adults. Sensitization does not occur in the gastrointestinal tract because fruit and vegetable antigen is easily broken down during digestion. Fruit and vegetable antigen has extensive cross reactivity with inhalant allergens such as between apples and birch pollen. Atopic patients who develop sensitization to inhalant allergens and develop respiratory disease, like allergic rhinitis, may cross sensitize to fruit and vegetable antigens. It is logical that immunotherapy for inhalant allergens would protect against PFAS. Small studies involving birch-sensitized patients with PFAS to apples showed reduced reactivity to the fruit after birch pollen immunotherapy [123,124]. PFAS is the most common type of food hypersensitivity in adults and older children; it currently has no treatment other than avoidance or cooking to denature the antigen. Thus immunotherapy may be a future modality to treat this more benign but troublesome disease.

SUMMARY

Immunotherapy remains an effective treatment of allergic diseases both as monotherapy and in synergy with other modern antiallergic therapies. Immunotherapy remains the only therapy that can afford a cure in a significant number of patients with allergies. It has evolved from its primitive beginnings from crude extracts to biologically standardized antigens. Concurrent immunotherapy has become more effective and patient populations likely to benefit more narrowly identified. Ongoing research will likely result in improved effectiveness, faster time to efficacy, improved safety, greater ease of administration, and expansion of the number of allergic diseases treated by immunotherapy.

References

- [1] Noon L. Prophylactic inoculation for hay fever. *Lancet* 1911;1:1572.
- [2] Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass pollen immunotherapy. *N Engl J Med* 1999;341:468–75.
- [3] Möller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002;109(2):251–6.
- [4] Des Roches A, Paradis L, Menardo JL, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol* 1997;99(4):450–3.
- [5] Pajno GB, Barberio G, De Luca F, et al. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy* 2001;31(9):1392–7.
- [6] Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011;127(Suppl 1):S1–55.
- [7] Varney VA, Gaga M, Frew AJ, et al. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs. *BMJ* 1991;302(6771):265–9.
- [8] Bødtger U, Poulsen LK, Jacobi HH, et al. The safety and efficacy of subcutaneous birch pollen immunotherapy – a one-year, randomized, double-blind, placebo-controlled study. *Allergy* 2002;57(4):297–305.
- [9] Ferrer M, Burches E, Peláez A, et al. Double-blind, placebo-controlled study of immunotherapy with *Parietaria judaica*: clinical efficacy and tolerance. *J Investig Allergol Clin Immunol* 2005;15(4):283–92.
- [10] Varney VA, Tabbah K, Mavroleon G, et al. Usefulness of specific immunotherapy in patients with severe perennial allergic rhinitis induced by house dust mite: a double-blind, randomized, placebo-controlled trial. *Clin Exp Allergy* 2003;33(8):1076–8.
- [11] Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of allergic rhinitis: an analysis of randomized, prospective, single- or double-blind, placebo-controlled studies. *Clin Ther* 2000;22(3):342–50.
- [12] Bielory L. Allergic and immunologic disorders of the eye. Part II: ocular allergy. *J Allergy Clin Immunol* 2000;106(6):1019–32.
- [13] Dreborg S, Agrell B, Foucard T, et al. A double-blind, multicenter immunotherapy trial in children, using a purified and standardized *Cladosporium herbarum* preparation. I. Clinical results. *Allergy* 1986;41(2):131–40.
- [14] Alvarez-Cuesta E, Cuesta-Herranz J, Puyana-Ruiz J, et al. Monoclonal antibody-standardized cat extract immunotherapy: risk-benefit effects from a double-blind placebo study. *J Allergy Clin Immunol* 1994;93(3):556–66.
- [15] Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2010;(8) CD001186.
- [16] Adkinson NF Jr, Eggleston PA, Eney D, et al. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med* 1997;336(5):324–31.
- [17] Creticos PS, Reed CE, Norman PS, et al. Ragweed immunotherapy in adult asthma. *N Engl J Med* 1996;334(8):501–6.
- [18] Golden DB, Moffitt J, Nicklas RA, et al. Stinging insect hypersensitivity: a practice parameter update 2011. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma & Immunology (AAAAI); American College of Allergy, Asthma & Immunology (ACAAI); Joint Council of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2011;127(4):852–4.e1–23.
- [19] Bonifazi F, Jutel M, Biló BM, et al. Prevention and treatment of Hymenoptera venom allergy: guidelines for clinical practice. EAACI Interest Group on Insect Venom Hypersensitivity. *Allergy* 2005;60(12):1459–70.
- [20] Hunt KJ, Valentine MD, Sobotka AK, et al. A controlled trial of immunotherapy in insect hypersensitivity. *N Engl J Med* 1978;299(4):157–61.

- [21] Reisman RE, Livingston A. Venom immunotherapy: 10 years of experience with administration of single venoms and 50 micrograms maintenance doses. *J Allergy Clin Immunol* 1992;89(6):1189–95.
- [22] Tracy JM, Khan FS, Demain JG. Insect anaphylaxis: where are we? The stinging facts 2012. *Curr Opin Allergy Clin Immunol* 2012;12(4):400–5.
- [23] Bilò MB. Anaphylaxis caused by Hymenoptera stings: from epidemiology to treatment. *Allergy* 2011;66(Suppl 95):35–7.
- [24] Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children—a 14-year study. *Pediatrics* 1968;42(5):793–802.
- [25] Purello-D'Ambrosio F, Gangemi S, Merendino RA, et al. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. *Clin Exp Allergy* 2001;31(8):1295–302.
- [26] Des Roches A, Paradis L, Paradis J. Immunotherapy for asthma. *N Engl J Med* 1997;336(26):1912.
- [27] Novak N, Bieber T, Leung DY. Immune mechanisms leading to atopic dermatitis. *J Allergy Clin Immunol* 2003;112(Suppl 6):S128–39.
- [28] Schäfer T, Heinrich J, Wjst M, et al. Association between severity of atopic eczema and degree of sensitization to aeroallergens in schoolchildren. *J Allergy Clin Immunol* 1999;104(6):1280–4.
- [29] Scalabrini DM, Bavbek S, Perzanowski MS, et al. Use of specific IgE in assessing the relevance of fungal and dust mite allergens to atopic dermatitis: a comparison with asthmatic and nonasthmatic control subjects. *J Allergy Clin Immunol* 1999;104(6):1273–9.
- [30] Takai T, Ikeda S. Barrier dysfunction caused by environmental proteases in the pathogenesis of allergic diseases. *Allergol Int* 2011;60(1):25–35.
- [31] Kato T, Takai T, Fujimura T, et al. Mite serine protease activates protease-activated receptor-2 and induces cytokine release in human keratinocytes. *Allergy* 2009;64(9):1366–74.
- [32] Bussmann C, Maintz L, Hart J, et al. Clinical improvement and immunological changes in atopic dermatitis patients undergoing subcutaneous immunotherapy with a house dust mite allergoid: a pilot study. *Clin Exp Allergy* 2007;37:1277–85.
- [33] Werfel T, Breuer K, Rueff F, et al. Usefulness of specific immunotherapy in patients with atopic dermatitis and allergic sensitization to house dust mites: a multi-centre, randomized, dose-response study. *Allergy* 2006;61:202–5.
- [34] Pajno GB, Caminiti L, Vita D, et al. Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: a randomized, double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2007;120:164–70.
- [35] Akdis CA, Akdis M. Mechanisms of allergen-specific immunotherapy. *J Allergy Clin Immunol* 2011;127(1):18–27.
- [36] Bacharier LB, Geha RS. Molecular mechanisms of IgE regulation. *J Allergy Clin Immunol* 2000;105(2 Pt 2):S547–58.
- [37] Sanderson CJ. Interleukin-5, eosinophils, and disease. *Blood* 1992;79(12):3101–9.
- [38] Gelfand EW. Inflammatory mediators in allergic rhinitis. *J Allergy Clin Immunol* 2004;114(Suppl 5):S135–8.
- [39] Creticos PS, Van Metre TE, Mardiney MR, et al. Dose response of IgE and IgG antibodies during ragweed immunotherapy. *J Allergy Clin Immunol* 1984;73(1 Pt 1):94–104.
- [40] Jutel M, Akdis M, Budak F, et al. IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. *Eur J Immunol* 2003;33(5):1205–14.
- [41] Larché M. Regulatory T cells in allergy and asthma. *Chest* 2007;132(3):1007–14.
- [42] Meiler F, Klunker S, Zimmermann M, et al. Distinct regulation of IgE, IgG4 and IgA by T regulatory cells and toll-like receptors. *Allergy* 2008;63(11):1455–63.
- [43] Joss A, Akdis M, Faith A, et al. IL-10 directly acts on T cells by specifically altering the CD28 co-stimulation pathway. *Eur J Immunol* 2000;30(6):1683–90.

- [44] Akdis CA, Blesken T, Akdis M, et al. Role of interleukin 10 in specific immunotherapy. *J Clin Invest* 1998;102(1):98–106.
- [45] Frew AJ, Powell RJ, Corrigan CJ, et al, UK Immunotherapy Study Group. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;117(2):319–25.
- [46] Dahl R, Kapp A, Colombo G, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;118(2):434–40.
- [47] Didier A, Malling HJ, Worm M, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007;120(6):1338–45.
- [48] Hedlin G, Graff-Lonnevig V, Heilborn H, et al. Immunotherapy with cat- and dog-dander extracts. V. Effects of 3 years of treatment. *J Allergy Clin Immunol* 1991;87(5):955–64.
- [49] Walker SM, Varney VA, Gaga M, et al. Grass pollen immunotherapy: efficacy and safety during a 4-year follow-up study. *Allergy* 1995;50(5):405–13.
- [50] Winther L, Malling HJ, Moseholm L, et al. Allergen-specific immunotherapy in birch- and grass-pollen-allergic rhinitis. I. Efficacy estimated by a model reducing the bias of annual differences in pollen counts. *Allergy* 2000;55(9):818–26.
- [51] Pichler CE, Helbling A, Pichler WJ. Three years of specific immunotherapy with house-dust-mite extracts in patients with rhinitis and asthma: significant improvement of allergen-specific parameters and of nonspecific bronchial hyperreactivity. *Allergy* 2001;56(4):301–6.
- [52] Walker SM, Pajno GB, Lima MT, et al. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. *J Allergy Clin Immunol* 2001;107(1):87–93.
- [53] Arvidsson MB, Löwhagen O, Rak S. Allergen specific immunotherapy attenuates early and late phase reactions in lower airways of birch pollen asthmatic patients: a double blind placebo-controlled study. *Allergy* 2004;59(1):74–80.
- [54] Durham SR, Ying S, Varney VA, et al. Grass pollen immunotherapy inhibits allergen-induced infiltration of CD4+ T lymphocytes and eosinophils in the nasal mucosa and increases the number of cells expressing messenger RNA for interferon-gamma. *J Allergy Clin Immunol* 1996;97(6):1356–65.
- [55] Osterballe O, Løwenstein H, Norn S, et al. Immunotherapy with grass pollen major allergens. Immunological results from a prospective 3-year double blind study. *Allergy* 1982;37(7):491–501.
- [56] Bousquet J, Van Cauwenberge P, Khaltaev N, et al. Allergic rhinitis and its impact on asthma. *Aria Workshop Group; World Health Organization. J Allergy Clin Immunol* 2001;108(Suppl 5):S147–334.
- [57] Stoloff SW. The National Allergy Survey Assessing Limitations (NASAL): patient and health care professional perspectives in allergic rhinitis. *J Fam Pract* 2012;61(Suppl 2):S1–33.
- [58] Nader ME, Abou-Jaoude P, Cabaluna M, et al. Using response to a standardized treatment to identify phenotypes for genetic studies of chronic rhinosinusitis. *J Otolaryngol Head Neck Surg* 2010;39(1):69–75.
- [59] Zeiger RS, Bird SR, Kaplan MS, et al. Short-term and long-term asthma control in patients with mild persistent asthma receiving montelukast or fluticasone: a randomized controlled trial. *Am J Med* 2005;118(6):649–57.
- [60] Malmstrom K, Rodriguez-Gomez G, Guerra J, et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. A randomized, controlled trial. *Montelukast/Beclomethasone Study Group. Ann Intern Med* 1999;130(6):487–95.
- [61] Lemanske RF Jr, Mauger DT, Sorkness CA, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med* 2010;362(11):975–85.
- [62] Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 2004;170(8):836–44.

- [63] Jones CA, Clement LT, Morpew T, et al. Achieving and maintaining asthma control in an urban pediatric disease management program: the Breathmobile Program. *J Allergy Clin Immunol* 2007;119(6):1445–53.
- [64] Bousquet J, Bachert C, Canonica GW, et al. Unmet needs in severe chronic upper airway disease (SCUAD). *J Allergy Clin Immunol* 2009;124(3):428–33.
- [65] Irwin RS, Richardson ND. Side effects with inhaled corticosteroids: the physician's perception. *Chest* 2006;130(Suppl 1):41S–53S.
- [66] National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. *J Allergy Clin Immunol* 2007;120(Suppl 5):S94–138.
- [67] The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343(15):1054–6.
- [68] Guilbert TW, Morgan WJ, Zeiger RS, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354(19):1985–9.
- [69] Kelly HW, Sternberg AL, Lescher R, et al. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med* 2012;367(10):904–12.
- [70] Harold S. Nelson Immunotherapy for inhalant allergens Middleton's Allergy Principles and Practice. 7th edition. St Louis(MO): Mosby, Elsevier; 2009. Chapter 95. p. 1657–77.
- [71] Desai M, Oppenheimer JJ. Medication adherence in the asthmatic child and adolescent. *Curr Allergy Asthma Rep* 2011;11(6):454–64.
- [72] Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. *J Allergy Clin Immunol* 2006;117:169–75.
- [73] Tankersley MS, Butler KK, Butler WK, et al. Local reactions during allergen immunotherapy do not require dose adjustment. *J Allergy Clin Immunol* 2000;106(5):840–3.
- [74] Kelso JM. The rate of systemic reactions to immunotherapy injections is the same whether or not the dose is reduced after a local reaction. *Ann Allergy Asthma Immunol* 2004;92(2):225–7.
- [75] Roy SR, Sigmon JR, Olivier J, et al. Increased frequency of large local reactions among systemic reactors during subcutaneous allergen immunotherapy. *Ann Allergy Asthma Immunol* 2007;99(1):82–6.
- [76] Greineder DK. Risk management in allergen immunotherapy. *J Allergy Clin Immunol* 1996;98(6 Pt 3):S330–4.
- [77] Bernstein DI, Wanner M, Borish L, et al. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. *J Allergy Clin Immunol* 2004;113:1129–36.
- [78] Bousquet J, Hejjaoui A, Dhivert H, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. Systemic reactions during the rush protocol in patients suffering from asthma. *J Allergy Clin Immunol* 1989;83:797–802.
- [79] Lockey RF, Nicoara-Kasti GL, Theodoropoulos DS, et al. Systemic reactions and fatalities associated with allergen immunotherapy. *Ann Allergy Asthma Immunol* 2001;87:47–55.
- [80] Toogood JH. Risk of anaphylaxis in patients receiving beta-blocker drugs. *J Allergy Clin Immunol* 1988;81:1–5.
- [81] Kaplan AP, Joseph K, Silverberg M. Pathways for bradykinin formation and inflammatory disease. *J Allergy Clin Immunol* 2002;109:195–209.
- [82] Ober AL, MacLean JA, Hannaway PJ. Life-threatening anaphylaxis to venom immunotherapy in a patient taking an angiotensin-converting enzyme inhibitor. *J Allergy Clin Immunol* 2003;112:1008–9.
- [83] Metzger WJ, Turner E, Patterson R. The safety of immunotherapy during pregnancy. *J Allergy Clin Immunol* 1978;61(4):268–72.
- [84] Shaikh WA. A retrospective study on the safety of immunotherapy in pregnancy. *Clin Exp Allergy* 1993;23(10):857–60.
- [85] Alvarez-Cuesta E, Bousquet J, Canonica GW, et al. Standards for practical allergen-specific immunotherapy. *Allergy* 2006;61:1–20.

- [86] Franklin W, Lowell FC. Comparison of two dosages of ragweed extract in the treatment of pollinosis. *JAMA* 1967;201:915-7.
- [87] Dolz I, Martinez-Cocera C, Bartolome JM, et al. A double-blind, placebo controlled study of immunotherapy with grass-pollen extract Alutard SQ during a 3-year period with initial rush immunotherapy. *Allergy* 1996;51:489-500.
- [88] Creticos PS, Marsh DG, Proud D, et al. Responses to ragweed-pollen nasal challenge before and after immunotherapy. *J Allergy Clin Immunol* 1989;84:197-205.
- [89] Malling HJ, Djurup R. Diagnosis and immunotherapy of mould allergy. VII. IgG subclass response and relation to the clinical efficacy of immunotherapy with *Cladosporium*. *Allergy* 1988;43:60-70.
- [90] Malling HJ. Diagnosis and immunotherapy of mould allergy. IV. Relation between asthma symptoms, spore counts and diagnostic tests. *Allergy* 1986;41:342-50.
- [91] Salvaggio JE, Burge HA, Chapman JA. Emerging concepts in mold allergy: what is the role of immunotherapy? *J Allergy Clin Immunol* 1993;92:217-22.
- [92] Kang BC, Johnson J, Morgan C, et al. The role of immunotherapy in cockroach asthma. *J Asthma* 1988;25:205-18.
- [93] Brown A. The perennial treatment of seasonal hayfever. *J Allergy* 1932;3:113-9.
- [94] Tari MG, Mancino M, Monti G. Immunotherapy by inhalation of allergen in powder in house dust allergic asthma—a double-blind study. *J Investig Allergol Clin Immunol* 1992;2:59-67.
- [95] Passalacqua G, Albano M, Pronzato C, et al. Long-term follow-up of nasal immunotherapy to *Parietaria*: clinical and local immunological effects. *Clin Exp Allergy* 1997;27:904-8.
- [96] Pajno GB, Vita D, Caminiti L, et al. Children's compliance with allergen immunotherapy according to administration routes. *J Allergy Clin Immunol* 2005;116:1380-1.
- [97] Warner JO. Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite. *Clin Allergy* 1986;16(5):387-8.
- [98] Penagos M, Compalati E, Tarantini F, et al. Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials. *Ann Allergy Asthma Immunol* 2006;97:141-8.
- [99] Penagos M, Passalacqua G, Compalati E, et al. Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. *Chest* 2008;133:599-609.
- [100] La Rosa M, Ranno C, André C, et al. Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized *Parietaria judaica* extract in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 1999;104(2 Pt 1):425-32.
- [101] Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005;60:4-12.
- [102] Calamita Z, Saconato H, Pela AB, et al. Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. *Allergy* 2006;61:1162-72.
- [103] Nieto A, Mazon A, Pamies R, et al. Sublingual immunotherapy for allergic respiratory diseases: an evaluation of meta-analyses. *J Allergy Clin Immunol* 2009;124:157-61.
- [104] Marogna M, Tomassetti D, Bernasconi A, et al. Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. *Ann Allergy Asthma Immunol* 2008;101(2):206-11.
- [105] Di Rienzo V, Marcucci F, Puccinelli P, et al. Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. *Clin Exp Allergy* 2003;33(2):206-10.
- [106] Cosmi L, Santarlasci V, Angeli R, et al. Sublingual immunotherapy with *Dermatophagoides* monomeric allergoid down-regulates allergen-specific immunoglobulin E and increases both interferon-gamma- and interleukin-10-production. *Clin Exp Allergy* 2006;36(3):261-72.

- [107] Bohle B, Kinaciyan T, Gerstmayr M, et al. Sublingual immunotherapy induces IL-10-producing T regulatory cells, allergen-specific T-cell tolerance, and immune deviation. *J Allergy Clin Immunol* 2007;120(3):707–13.
- [108] Cox LS, Larenas Linnemann D, Nolte H, et al. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol* 2006;117(5):1021–35.
- [109] Ridolo E, De Angelis GL, Dall'aglio P. Eosinophilic esophagitis after specific oral tolerance induction for egg protein. *Ann Allergy Asthma Immunol* 2011;106(1):73–4.
- [110] Senti G, Cramer R, Kuster D, et al. Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections. *J Allergy Clin Immunol* 2012;129(5):1290–6.
- [111] Milgrom H, Berger W, Nayak A, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics* 2001;108(2):E36.
- [112] Casale TB, Busse WW, Kline JN, et al. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2006;117:134–40.
- [113] Massanari M, Nelson H, Casale T, et al. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. *J Allergy Clin Immunol* 2010;125(2):383–9.
- [114] Kuehr J, Brauburger J, Zielen S, et al. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. *J Allergy Clin Immunol* 2002;109(2):274–8.
- [115] Till SJ, Francis JN, Nouri-Aria K, et al. Mechanisms of immunotherapy. *J Allergy Clin Immunol* 2004;113(6):1025–34.
- [116] Creticos PS, Schroeder JT, Hamilton RG, et al. Immunotherapy with a ragweed toll-like receptor 9 agonist vaccine for allergic rhinitis. *N Engl J Med* 2006;355:1445–55.
- [117] Dynavax reports interim TOLAMBA™ ragweed allergy results from DARTT Trial 01/08/2007 press release. 2007. Available at: <http://investors.dynavax.com/releasedetail.cfm?ReleaseID=231013>. Accessed October 9, 2012.
- [118] Drachenberg KJ, Wheeler AW, Stuebner P, et al. A well-tolerated grass pollen specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four preseasonal injections. *Allergy* 2001;56:498–505.
- [119] Burks AW, Jones SM, Boyce JA, et al. NIAID-sponsored 2010 guidelines for managing food allergy: applications in the pediatric population. *Pediatrics* 2011;128(5):955–65.
- [120] Kim EH, Burks W. Managing food allergy in childhood. *Curr Opin Pediatr* 2012;24(5):615–20.
- [121] Kim EH, Bird JA, Kulis M, et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. *J Allergy Clin Immunol* 2011;127(3):640–6.
- [122] Patriarca G, Nucera E, Roncallo C, et al. Oral desensitizing treatment in food allergy: clinical and immunological results. *Aliment Pharmacol Ther* 2003;17:459–65.
- [123] Bucher X, Pichler WJ, Dahinden CA, et al. Effect of tree pollen specific, subcutaneous immunotherapy on the oral allergy syndrome to apple and hazelnut. *Allergy* 2004;59:1272–6.
- [124] Hansen KS, Khinchi MS, Skov PS, et al. Food allergy to apple and specific immunotherapy with birch pollen. *Mol Nutr Food Res* 2004;48:441–8.