Chapter 41
Allergy Immunotherapy

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Introduction

Allergic diseases have increased in prevalence over the last 30 years, affecting as many as 40–50 million people in the United States. Allergen immunotherapy has been a therapeutic option for over 100 years and its use is supported by multiple placebo-controlled trials. Allergen immunotherapy alters the course of allergic diseases through either a series of injections of extracts composed of clinically relevant allergens or sublingual tablets containing clinically relevant allergens The term "allergen extract" has been replaced by "allergen vaccine" by the World Health Organization to reflect that allergen vaccines are used in medicine as immune modifiers. The preferred term for therapy is allergen immunotherapy.

Indications

Allergen immunotherapy is used in the treatment of allergic rhinitis, allergic asthma, atopic dermatitis (with aeroallergen sensitization), and stinging insect venom hypersensitivity. The diagnosis of these diseases is made by history and physical exam supported by testing to confirm IgE sensitization. Skin testing by prick or

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Table 41.1 Immunotherapy

Currently indicated	Allergic rhinitis
	Allergic asthma
	Venom allergy
	Atopic dermatitis with aeroallergen sensitization
Not indicated	Food allergy
	Chronic urticaria/angioedema
Relative contraindications	Unstable asthma (absolute contraindication)
	Concurrent use of beta-blockers or ACE inhibitors
	Severe coronary artery disease
	Malignancy
	Unable to cooperate/communicate clearly (very young children

intradermal method is the preferred objective assessment, but in vitro tests are an alternative, especially when skin testing is unable to be performed.

Candidates for venom or Hymenoptera immunotherapy include all patients who have experienced life-threatening allergic reactions or non-life-threatening systemic reactions to Hymenoptera stings. The risk of anaphylaxis for a venom-allergy patient from an insect sting is greater than the risk of anaphylaxis from immunotherapy. In patients younger than 16 years of age with only urticaria to Hymenoptera stings, immunotherapy is not generally recommended. However, in patients older than 16 years of age with only cutaneous reactions, immunotherapy is a recommended option. Venom immunotherapy is also indicated for patients who have recurrent bothersome large local reactions especially those with occupational exposure.

Immunotherapy is also effective for pollen, mold, animal dander, dust mite, and cockroach allergies. Symptomatic patients with allergic rhinitis and asthma despite allergen avoidance and pharmacotherapy are candidates for immunotherapy (Table 41.1). Other candidates include allergic rhinitis or asthma patients having undesirable adverse reactions to medications or those wishing to reduce or eliminate long-term pharmacotherapy. In addition to reducing symptoms to current allergens, immunotherapy may prevent the development of sensitization to new allergens or progression of allergic rhinitis to asthma, especially in children.

Mechanism

The exact mechanism of how subcutaneous immunotherapy works is not fully understood, but involves shifting a patient's immune response to allergen from a predominately allergic T-lymphocyte (TH2) response to a "non-allergic" T-lymphocyte (TH1) response. Lymphocytes of a TH2 phenotype typically produce

IL-4 and IL-5, cytokines needed for IgE production and eosinophil survival. Findings of increased production of IFN-γ and a decreased production of IL-4 and IL-5 have not, however, been consistently demonstrated after immunotherapy. What has been consistent is the increased production of allergen-specific IL-10. IL-10 causes a shift in allergen-specific IgE to allergen-specific IgG4. This change is orchestrated by regulatory T-cells which downregulate allergic immune responses in part through the release of IL-10 and TGF-β. With allergen immunotherapy, the seasonal increase in allergen-specific IgE is blunted, while protective allergen-specific IgG4 production is increased. However, these changes in IgE and IgG may not correlate with clinical efficacy, so periodic skin testing or in vitro IgE antibody measurements are not always useful in evaluating responses to immunotherapy. Sublingual immunotherapy also induces regulatory T-cells via cytokines released from Langerhans cells, myeloid dendritic cells, and macrophages.

Contraindications

Relative contraindications for immunotherapy include medical conditions that reduce patients' ability to survive a serious systemic allergic reaction, such as coronary artery disease or the concurrent use of β-blockers (including eye drops) or angiotensin-converting enzyme inhibitors (Table 41.1). Beta-adrenergic blocking agents may make the treatment of immunotherapy-related systemic reactions more difficult. Despite this, immunotherapy is indicated for patients with life-threatening stinging insect hypersensitivity receiving β-blockers. Allergen immunotherapy should not be initiated in asthmatic patients unless the patient's asthma is relatively stable with pharmacotherapy. Patients who are mentally or physically unable to communicate clearly, such as very young children, are not good candidates for immunotherapy as it may be difficult for them to report early symptoms of a systemic reaction. Pregnancy is not a contraindication for immunotherapy, but by custom immunotherapy is not initiated during pregnancy. If a patient becomes pregnant while already on immunotherapy, the dose is not increased during the pregnancy but maintained at the current level in an attempt to avoid anaphylactic reactions.

Dosing

Standard allergen immunotherapy is administered as a subcutaneous injection. The appropriate allergen extracts (vaccines) are selected based on the patient's clinical history, allergen exposure history, and the results of tests for allergen-specific IgE antibodies. The immunotherapy vaccine should contain only clinically relevant allergens. When preparing mixtures of allergen vaccines, the prescribing physician must take into account the cross-reactivity of allergens, the optimal dose of each constituent, and the potential for allergen degradation caused by proteolytic enzymes

Table 41.2 Conventional subcutaneous allergen immunotherapy

Buildup
1000–10,000-fold dilution starting dose (depending upon sensitivity)
Increase dose once to twice a week with at least 2 days in between injections
Maintenance achieved after 4–6 months
Maintenance
Therapeutic dose administered every 2–6 weeks
Therapy continued for 3–5 years

in the mixture. The efficacy of immunotherapy depends upon achieving an optimal therapeutic dose of each allergen in the vaccine.

Subcutaneous allergen immunotherapy dosing consists of two treatment phases: the buildup phase and the maintenance phase. The prescribing physician must specify the starting immunotherapy dose, the target maintenance dose, and the immunotherapy buildup schedule. The highest concentration of vaccine that is projected to provide the therapeutically effective dose is called the "maintenance" dose or concentrate. In general, the starting immunotherapy dose is 1000- to10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose may be even lower. Dilute concentrations are more sensitive to degradation and lose potency more rapidly than the more concentrated preparations. Thus, their expiration dates are much shorter and must be closely monitored.

The buildup phase involves injections with increasing amounts of allergens. The frequency of the injections can vary depending upon the protocol. The most common or "conventional" protocol recommends dosing once to twice a week with at least 2 days between injections (Table 41.2). It is customary to repeat or reduce the dose if there has been a substantial time interval between injections. Patients with greater sensitivity may require a slower buildup phase to prevent systemic reactions. With this schedule, maintenance is usually achieved after 3–6 months (Table 41.3). Alternative schedules such as "rush" or "cluster" immunotherapy rapidly achieve maintenance dosing and should preferably be administered by an allergist/immunologist because of an increased risk for systemic reactions. Allergen immunotherapy dosing schedules should be written by appropriately trained physicians, and primary care physicians should seek their advice if questions or issues arise during administration.

The maintenance phase begins when the effective therapeutic dose is achieved. This final dose is based on several factors including the specific allergen, the concentration of the extract, and how sensitive a patient is to the extract. Once maintenance is achieved, the intervals for injections range from every 2 to 6 weeks, but are individualized for each patient. Clinical improvement can be demonstrated shortly after the patient reaches their maintenance dose. If no improvement is noted after 1 year of maintenance therapy, a reassessment should be done. Possible

Table 41.3 Typical buildup schedule for conventional subcutaneous allergen immunotherapy

1:1000 (v/v)	0.05
	010
	0.20
	0.40
1:100 (v/v)	0.05
	0.10
	0.20
	0.30
	0.40
	0.50
1:10 (v/v)	0.05
	0.07
	0.10
	0.15
	0.25
	0.35
	0.40
	0.45
	0.50
Maintenance concentrate	0.05
	0.07
	0.10
	0.15
	0.20
	0.25
	0.30
	0.35
	0.40
	0.45
	0.50

reasons for lack of efficacy need to be evaluated, and if none are found, discontinuation of immunotherapy should be considered. Patients should be evaluated at least every 6–12 months while on immunotherapy by the prescribing physician. Duration of maintenance therapy is generally 3–5 years. Treatment may lead to prolonged clinical remission and persistent alterations in immunologic reactivity. The severity of disease, benefits from sustained treatment, and the convenience of treatment are all factors that are considered when deciding the length of therapy for each individual patient.

Many studies, from Europe, have shown that high-dose sublingual allergen immunotherapy (SLIT) is effective for certain patients. Some of the earlier studies suffered from inconsistencies including varying doses of allergen and multiple dosing regimens. More recently, several double-blind, placebo-controlled, randomized

control trials with standard dosing and time frames conducted in North America and Europe have demonstrated the effectiveness of SLIT in patients with allergic rhinitis. The positive results from these studies have led to the US Food and Drug Administration approval of two grass and one ragweed SLIT tablets in 2014 (Table 41.5). Dosing should be initiated 12–16 weeks prior to the allergen season and continued throughout the season (pre-seasonal/coseasonal) or continuously for a minimum of 2–3 years. Dosing is daily during the treatment phase with local side effects such as oral pruritis and throat irritation commonly noted especially early (during the first week) during treatment. The five-grass product (Oralair)® is available in two strengths (100 IR and 300 IR). For children and adolescents ages 10–17, the dose is increased over the first 3 days: on day 1, a 100 IR tablet is given; on day 2, two 100 IR tablets are given; on day 3 and following, the 300 IR tablet (same as for adults) is given. For the ragweed and timothy grass products, Ragwitek™ and Grastek®, children and adults take the same dose, a single tablet daily over the prescribed time period, with no buildup.

Recently, several studies have demonstrated the effectiveness of oral immunotherapy for food allergy (peanut, milk, egg) in children. In general, patients after therapy are able to tolerate higher levels of allergen without serious adverse reactions. It has been noted that with the daily treatment some patients develop eosinophilic esophagitis to the specific food that resolves with the discontinuation of the offending food. Several questions such as appropriate dosing and duration of treatment need to be answered before this therapy can be considered anything but experimental.

Safety

The greatest concern with allergen immunotherapy is safety. Local reactions at the injection site, such as redness, swelling, and warmth, are common. These reactions can be lessened with H1 antagonists prior to injections. Local reactions can be managed with treatments such as cold compresses or topical corticosteroids. Large, local, delayed reactions ($\geq$25 mm) do not appear to be predictors of developing severe systemic reactions and generally do not require adjustment of dosing schedules. However, some patients with a greater frequency of large local reactions (>10 % of injections) may be at increased risk for future systemic reactions and dosing adjustments may be necessary.

The incidence of systemic reactions, such as urticaria, angioedema, increased respiratory symptoms (nasal, pulmonary, ocular), or hypotension, ranges from 0.05 to 3.2 % per injection or 0.84–46.7 % of patients. Risk factors for systemic reactions include errors in dosing, symptomatic asthma, a high degree of allergen hypersensitivity, concomitant use of β-blocker medications, injections from new vial, and injections given during periods when allergic symptoms are active, especially during the allergy season. A recent survey of 1700 allergists reported that 58 % of responders had an event in which a patient received an injection meant for another patient and 74 % reported that patients had received an incorrect amount of vaccine.

These errors resulted in a multitude of adverse events including local reactions, systemic reactions, and even one fatality. Thus, it is extremely important to make sure patients are questioned about potential risk factors and the correct vials are used to administer immunotherapy injections.

It is unclear if premedication with antihistamines can reduce the frequency of systemic reactions in conventional immunotherapy, but in cluster or rush immunotherapy, premedication can reduce the rate of systemic reactions.

The incidence of fatalities due to immunotherapy is extremely low and appears to be lessening. From 1990 to 2001, fatal reactions occurred at a rate of 1 per 2.5 million injections, with an average of 3.4 deaths per year. Most fatal reactions occurred with maintenance doses of immunotherapy. Between 2008 and 2012, only one fatal reaction was noted with 23.3 million injection visits. The patient population at greatest risk was poorly controlled asthmatics. In many of the fatalities, there was either a substantial delay in giving epinephrine or epinephrine was not administered at all. The incidence of near-fatal reactions (respiratory compromise, hypotension, or both requiring epinephrine) is 2.5 times more frequent than fatal reactions. Overall systemic allergic reactions of any severity (grades 1–4) occurred at a rate of 8.0 reactions per 10,000 injection visits. Severe (grade 4) reactions were reported at a rate of 0.01 per 10,000 injections, or 35 reactions documented in 2012.

Adverse reactions associated with SLIT may be local or systemic. Local reactions are fairly common, affecting up to 75 % of SLIT patients. Isolated gastrointestinal symptoms associated with SLIT, e.g., nausea or gastrointestinal pain, may be considered local reactions due to swallowing the tablet. If gastrointestinal symptoms occur in conjunction with other systemic symptoms, they would be considered systemic reactions. Most SLIT local reactions occur shortly after treatment initiation and cease within 2 weeks without any medical intervention. The use of antihistamines in the treatment of a local reaction should be considered. Since SLIT generally is administered in a setting without direct medical supervision after the initial dose, patients should be given instructions regarding recognition and management of adverse reactions and when SLIT should be withheld (e.g., asthma exacerbation). Also, prescribing information for the three FDA-approved SLIT products recommends that patients have an epinephrine auto-injector.

Treatment of Anaphylaxis

Systemic allergic reactions can be life threatening and need to be treated rapidly. Most systemic reactions are limited to the skin, such as urticaria. Respiratory symptoms are seen alone or with skin manifestations in 42 % of systemic reactions. Epinephrine is the standard of care for severe systemic or anaphylactic reactions. Treatment of anaphylactic reactions includes placing a tourniquet above the injection sites and immediately injecting epinephrine 1:1000 intramuscularly, preferably into the anterolateral thigh. For adults, the dose is typically 0.2–0.5 cc, and for children, 0.01 mL/kg (max 0.3 mg dose) every 5–10 min as needed. For

convenience, subcutaneous injection at the arm (deltoid) is frequently used, but intramuscular injection into the anterolateral thigh produces higher and more rapid peak levels of epinephrine.

Subcutaneous Allergen Immunotherapy in General Practice

According to practice guidelines, subcutaneous allergen immunotherapy should be administered in a setting that permits the prompt recognition and management of adverse reactions. The preferred setting is the prescribing physician's office, especially for high-risk patients. However, patients may receive immunotherapy injections at another health-care facility if the physician and staff at that location are equipped to recognize and manage systemic reactions, in particular anaphylaxis. Informed consent should be obtained prior to administering allergen immunotherapy. A full, clear, and detailed documentation of the patient's immunotherapy schedule must accompany the patient when receiving injections at another health-care facility. Use of a constant uniform labeling system for dilutions may reduce errors in administration. The maintenance concentration and serial dilutions should be prepared and labeled for each individual patient. The American Academy of Allergy, Asthma and Immunology's recommended nomenclature and color-coded system is contained in Table 41.4.

Table 41.4 Subcutaneous allergen immunotherapy vaccine labeling

Dilution from maintenance	Dilution designation in volume per volume (V/V)	Color	Number
Maintenance	1:1	Red	1
10-fold	1:10	Yellow	2
100-fold	1:100	Blue	3
1000-fold	1:1000	Green	4
10,000-fold	1:10,000	Silver	5

Table 41.5 SLIT products

Product	Components	Regimens	Updose	Children
Oralair	Sweet vernal, orchard, perennial rye, Timothy, Kentucky blue grass	Pre-seasonal/coseasonal (start 4 months before onset of season)	First 3 doses	10–17
Grastek	Timothy grass	Pre-seasonal/coseasonal (start 3 months before season) or year-round	No	5–17
Ragwitek	Short ragweed	Pre-seasonal/coseasonal (start 3 months before season)	No	No

All three products are daily tablets indicated for allergic rhinitis/rhinoconjunctivitis with/without controlled asthma in patients with specific IgE antibodies to relevant allergens

A brief review of a patient's current health status is recommended prior to administration. It is important to assess any current asthma symptoms, increased allergic symptoms, any new medications, or any delayed reactions to the previous injection. In patients with asthma, peak expiratory flow rate measurements should be obtained prior to each injection. In general, immunotherapy injections should be withheld if the patient presents with an acute asthma exacerbation or if peak flow measurements are below 20 % of the patient's baseline values. Immunotherapy may need to be decreased or held if significant allergic symptoms are present prior to an injection.

Most severe reactions develop within 20–30 min after the immunotherapy injection, but reactions can occur after this time. Patients should wait at the physician's office for at least 20–30 min after the immunotherapy injection. In some cases, the wait may need to be longer depending upon the patient's history of previous reactions.

It is usual practice to reduce the dose of vaccine when the interval between injections is longer than prescribed. This reduction in dose should be clearly stated on the patient's immunotherapy schedule. Because of the potential of extract degradation over time, when new vials are started, the initial dose is decreased and then built back up to maintenance. When a systemic reaction occurs, the physician needs to decide if immunotherapy should be continued. This should be done in consultation with the physician who prescribed the immunotherapy. If the decision is to continue, the dose of the vaccine needs to be appropriately reduced to reduce the risk of a subsequent systemic reaction.

Efficacy and Outcomes

Once maintenance dosing is achieved for venom immunotherapy, 80–98 % of individuals will be protected from systemic symptoms upon sting challenges. Maintenance therapy is generally recommended for 3–5 years, with growing evidence that 5 years of treatment provides more lasting benefit. A low risk of systemic reactions to stings (approximately 10 %) appears to remain for many years after discontinuing venom immunotherapy. In children who have received venom immunotherapy, the chance of systemic reaction to a sting after discontinuation of immunotherapy is even lower.

The efficacy of subcutaneous and sublingual allergen immunotherapy for allergic rhinitis has been clearly demonstrated in a number of clinical trials and meta-analyses. These studies have shown significant improvements in symptoms, quality of life, medication use, and immunologic parameters. Subcutaneous allergen immunotherapy for allergic rhinitis has been shown to be beneficial for at least 3–6 years after completion of a 3-year course of treatment. Data from Oralair® clinical trials also showed sustained clinical benefits for at least 2 more years after 3 years of preseasonal/coseasonal therapy course.

The efficacy of immunotherapy for asthma has been assessed in many trials, but some studies have been difficult to interpret either because of the use of poor-quality allergen extracts or suboptimal study design. The risk/benefit ratio of

immunotherapy for asthma must always be considered. Currently, professional societies recommend that patients with asthma and FEV1 values less than 70 % should not receive immunotherapy. A Cochrane review in 2004 examined the role of subcutaneous allergen immunotherapy for asthma. This review of 75 trials with 3100 patients found a significant reduction in asthma symptoms and medication use and improvement in bronchial hyperreactivity associated with the administration of allergen-specific immunotherapy. The reviewers concluded that immunotherapy was effective in asthma and commented that one trial found that the size of the benefit was possibly comparable to inhaled corticosteroids. Because SLIT pivotal studies were not designed to study asthma, none of the 3 FDA-approved tablets list asthma as an indication. However, the pivotal SLIT tablet trials did include patients with controlled asthma, and beneficial effects on asthma symptoms were demonstrated in those studies.

Summary

Allergen immunotherapy has been a valuable tool in treating allergic rhinitis, asthma, and stinging insect hypersensitivity for decades. Although newer pharmacological agents continue to become available, immunotherapy is still the only available treatment that alters the natural course of allergic diseases. Even though there are some risks, these can be minimized when immunotherapy is given in an appropriate environment to carefully selected patients. Guidelines have been established to further reduce the risks by establishing a universal system of reporting dilutions and establishing appropriate dosing for subcutaneous allergen immunotherapy. Despite a large body of evidence demonstrating the positive therapeutic benefits of immunotherapy, only 3 million patients in the United States are receiving immunotherapy out of a potential 40–50 million allergic patients, many of whom could benefit from this therapy. Newer therapies, such as anti-IgE (omalizumab), when used with immunotherapy may improve the efficacy and safety profile of immunotherapy in the future. In addition, newer forms of immunotherapy such as T-cell peptides, epicutaneous immunotherapy, or adjuvants combined with allergens are currently under investigation.

Evidence-Based Medicine

Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. *J Allergy Clin Immunol*. 2011;127(1):64–71. This study evaluates the use of sublingual allergen immunotherapy versus placebo in 345 children, 5–17 years of age, with allergic rhinitis to grass. The children were treated with once-daily grass AIT (2800 bioequivalent allergen units, 75,000 standardized

quality tablet, approximately 15 mg of Phl p 5) or placebo starting 16 weeks before the 2009 grass pollen season. Treatment was well tolerated with no systemic reactions noted, while mild transient reactions such as oral pruritis and throat irritation were common. Even though 89 % of the patients were polysensitized, treatment with only grass SLIT improved symptom scores, medication use, and quality of life by 26 %.

Cox LS, Casale TB, Nayak AS, Bernstein DI, Creticos PS, Ambroisine L, Melac M, Zeldin RK. Clinical efficacy of 300IR 5-grass pollen sublingual tablet in a US study: the importance of allergen-specific serum IgE. *J Allergy Clin Immunol*. 2012 Dec;130(6):1327–34.e1. doi: 10.1016/j.jaci.2012.08.032. Epub 2012 Oct 31

- Four hundred seventy-three adults with grass-induced allergic rhinitis were randomized in a double-blind, placebo-controlled study to receive 300IR five-grass pollen sublingual tablet or placebo starting 4 months before and continuing through the pollen season. A combination of symptom and medication use was reduced 28 % in the treatment group compared to the placebo group during this time. In those patients with a higher baseline grass-specific IgE level of ≥0.1 kU/L, the improvement was 30 % as they made up the bulk of the patients. This study also had no anaphylactic events and oral pruritis and throat irritation were common.

Bibliography

1. Aaronson DW, Gandhi TK. Incorrect allergy injections: allergists' experiences and recommendations for prevention. J Allergy Clin Immunol. 2004;113:117–21.
2. Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma (cochrane review). In: The Cochrane library. Issue 2. Chichester: Wiley; 2004.
3. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens. J Allergy Clin Immunol. 2014;133(3):621–31. doi:10.1016/j.jaci.2013.12.1088. Review.
4. Amin HS, Liss GM, Berstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. J Allergy Clin Immunol. 2006;117:169–75.
5. Bernstein DI, Wanner M, Borrish 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.
6. Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. J Allergy Clin Immunol. 2011;127(1):64–71.e1–4. doi:10.1016/j.jaci.2010.11.034. Epub 2011/01/08. PubMed.
7. Cox LS, Casale TB, Nayak AS, Bernstein DI, Creticos PS, Ambroisine L, Melac M, Zeldin RK. Clinical efficacy of 300IR 5-grass pollen sublingual tablet in a US study: the importance of allergen-specific serum IgE. J Allergy Clin Immunol. 2012;130(6):1327–34.e1. doi:10.1016/j.jaci.2012.08.032. Epub 2012 Oct 31.
8. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, Nelson M, Weber R, Bernstein DI, Blessing-Moore J, Khan DA, Lang DM, Nicklas RA, Oppenheimer J, Portnoy JM, Randolph C, Schuller DE, Spector SL, Tilles S, Wallace D. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol. 2011;127(1 Suppl):S1–55. doi: 10.1016/j.jaci.2010.09.034. Epub 2010 Dec 3. Erratum in: J Allergy Clin Immunol. 2011 Mar;127(3):840.

9. Creticos PS, Maloney J, Bernstein DI, Casale T, Kaur A, Fisher R, et al. Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. J Allergy Clin Immunol. 2013;131(5):1342–9.e6. doi:10.1016/j.jaci.2013.03.019. PubMed.
10. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. AAAAI/ACAAI surveillance study of subcutaneous immunotherapy, years 2008–2012: an update on fatal and nonfatal systemic allergic reactions. J Allergy Clin Immunol Pract. 2014;2(2):161–7. doi:10.1016/j.jaip.2014.01.004. PMID: 24607043.
11. Golden DBK, Kagey-Sobotka A, Norman PS, et al. Outcomes of allergy to insect stings in children, with and without venom immunotherapy. N Engl J Med. 2004;351:668–74.
12. Li JT, Lockey IL, Bernstein JM, et al. Allergen immunotherapy: a practice parameter. Ann Allergy Asthma Immunol. 2003;90:1–40.
13. Lieberman P, Kemp SF, Oppenheimer J, et al. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol. 2005;115:S483–523.
14. Moingeon P. Update on immune mechanisms associated with sublingual immunotherapy: practical implications for the clinician. J Allergy Clin Immunol Pract. 2013;1(3):228–41. doi:10.1016/j.jaip.2013.03.013. Epub 2013 Apr 29.
15. Moller 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;109:251–6.
16. Polos R, Al-Delaimy W, Russo C, et al. Greater risk of incident asthma cases in adults with allergic rhinitis and effect of allergen immunotherapy; a retrospective cohort study. Respir Res. 2005;6:153–64.
17. Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of asthma: a meta-analysis of prospective, randomized, double-blind, placebo-controlled studies. Clin Ther. 2000;22:329–41.
18. 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;22:342–50.
19. Till SJ, Francis JN, Nouri-Aria K, et al. Mechanisms of immunotherapy. J Allergy Clin Immunol. 2004;113:1025–34.