

EFFICACY OF IMMUNOTHERAPY

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Immunotherapy has its roots in the advances of immunology, which occurred at the end of the 19th and the beginning of the 20th century. The original, incorrect concept was that allergic rhinitis and conjunctivitis were caused by toxins released by pollen particles. It was believed that protective antibody, or antitoxin, would develop when subjects with these diseases were vaccinated, or immunized, with pollen vaccines. Behring and Kitasato introduced this concept by inducing protection from diphtheria and clostridia bacterial toxins.

The evolving concept of anaphylaxis, beginning with Portier and Richet in 1902, and astute clinical observations of human allergic disease directed investigators to conclude that the mechanism responsible for clinical allergy is a hypersensitivity reaction, not exposure to exogenous toxins. Immunotherapy is a form of immunomodulation that decreases the hypersensitivity response to allergens. During the succeeding decades, the clinical experience and majority of clinical trials attest to the efficacy of immunotherapy.

IMMUNOLOGIC EFFECTS

Immunotherapy is not desensitization, as clinical improvement occurs despite the persistence, and occasional increase, of specific IgE antibody.²⁵ The mechanism by which immunotherapy is effective in allergic disorders remains incompletely defined. The following hypotheses are partially supported by clinical and scientific data.

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"Blocking Antibody"

Immunotherapy induces allergen-specific IgG, or "blocking antibody," which competes with IgE for allergen binding (Fig. 1).^{76, 86, 127} Specific IgG may inhibit inherent enzymatic activity of allergens that promote airway inflammation.^{131a} There are a few studies demonstrating clinical improvement in the absence of an increase in allergen-specific IgG, but the bulk of evidence shows an inverse correlation between reduced symptom-medication scores and serum levels of specific-IgG^{24, 48, 114}; however, within study populations, particularly of allergic rhinitis and asthma, some individuals with a significant increase in specific-IgG fail to improve. The role of IgG in diminishing allergic symptoms has been better established in insect venom sensitivity than in inhalant allergy.³⁰

Decrease in IgE

Immunotherapy results in a gradual reduction of allergen-specific IgE, although IgE levels increase initially in response to treatment (Fig. 2).^{25, 30} Studies with seasonal pollen immunotherapy, such as ragweed, also show a decrease in the characteristic postseasonal rise in IgE (see Fig. 2); however, symptoms often improve before the levels of specific-IgE have decreased or even when the levels have increased.²⁵ Thus, since there is no clinical correlation with specific-IgE levels, IgE monitoring during immunotherapy is generally not of value.

Modulation of Mast Cells and Basophils

Immunotherapy modulates target cell function and number, reducing mediator release from mast cells and basophils despite allergen combining with specific-IgE on their surfaces.⁸² Such an effect has been demonstrated by a decrease after immunotherapy of histamine release from peripheral blood basophils following *in vitro* allergen challenge. This effect occurs prior to a decrease in specific-IgE or an increase in specific-IgG. A decrease in skin test and nasal reactivity prior to changes in IgE and IgG antibody levels probably results from this reduction of mediator release from mast cells and basophils despite allergen-IgE interaction on cell membranes.^{23, 101} In addition to the activation of mast cells and basophils, the number of these cells in affected tissues and skin is decreased by immunotherapy (Table 1).^{35, 96} The reduction in mast cell/basophil activation and number suppresses the inflammatory, late-phase allergic response following allergen exposure. This anti-inflammatory effect of immunotherapy is due to a net reduction of inflammatory cell recruitment by chemoattractants of the activated mast cells or basophils (Fig. 3).^{45a, 103, 104}

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Figure 1. Semilogarithmic plot of serum antiragweed IgG levels in arbitrary (arbit.) units at entry in study (February 21–March 12), preseason (July 21–August 6), and postseason (October 10–27). Ragweed immunotherapy was administered according to two different schedules after study entry, and a placebo injection was given to a third group as a control. Horizontal dashed lines designate the median value. (*From Van Metre TE Jr, Adkinson NF Jr, Amodio FJ, et al: A comparison of immunotherapy schedules for injection treatment of ragweed pollen hay fever. J Allergy Clin Immunol 69:181, 1982; with permission.*)

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Figure 2. Semilogarithmic plot of serum antiragweed IgE levels (ng/mL) at entry in study (February 21–March 12), preseason (July 21–August 6), and postseason (October 10–27) for each patient in study. Ragweed immunotherapy was administered according to two different schedules after study entry, and a placebo injection was given to a third group as a control. Horizontal dashed lines designate the median values. Levels of the placebo group rose from median of 132 ng/mL at study entry to 141 ng/mL before season and to 243 ng/mL after season. IgE rise across season was statistically significant ($P = 0.007$), unlike the treated groups where no trans-seasonal rise was observed ($P > 0.3$). (From Van Metre TE Jr, Adkinson NF Jr, Amodio FJ, et al: A comparison of immunotherapy schedules for injection treatment of ragweed pollen hay fever. *J Allergy Clin Immunol* 69:181, 1982; with permission.)

Table 1. EFFICACY OF IMMUNOTHERAPY ON NASAL METACHROMATIC CELLS IN PATIENTS WITH PERENNIAL ALLERGIC RHINITIS

Group	No. of Basophils and Mast Cells		
	First Month	Third Month	Sixth Month
Control (n = 11)	1,025 ± 261	1,070 ± 295	930 ± 168
Treated (n = 14)	1,295 ± 280	456 ± 140*	237 ± 92†

*Values represent mean ± standard error.

†Statistically significant ($P < 0.05$) reduction compared with before immunotherapy.

From Otsuka H, Mezawa A, Ohnishi M, et al: Changes in nasal metachromatic cells during allergen immunotherapy. Clin Exp Allergy 21:115–119, 1991; with permission.

Modulation of Lymphocyte Subsets and Other Regulatory Cells

Immunotherapy alters regulatory cells, in part by increasing T-lymphocyte suppressor activity.¹²⁰ IgE production, maturation of select mast cell populations, macrophage activation, mediator release from mast cells and basophils, and bone marrow cellular responses are regulated by T lymphocytes.¹²⁰ Alteration of regulatory T-cell function occurs

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Figure 3. The results of a study of ragweed immunotherapy on eosinophil recruitment in the nasal mucosa. The eosinophil number was assessed microscopically with samples acquired by nasal brushing. Subjects were treated with either 2 µg of Amb a I (the major allergen in ragweed, also referred to as antigen E) or 24 µg of Amb a I per injection. The data show a reduction in the number of nasal eosinophils with immunotherapy and the effect is dependent on dose and duration of treatment. This eosinophil reduction occurred with natural, seasonal exposures and provocative challenge with allergen. (*Statistically significant difference compared with no immunotherapy.) (From Furin MJ, Norman PS, Creticos PS, et al: Immunotherapy decreases antigen-induced eosinophil migration into the nasal cavity. J Allergy Clin Immunol 88:27–32, 1991; with permission.)

following immunotherapy.^{31, 34, 39} Cytokine production by T cells is altered by immunotherapy with a decrease in interleukin-4 (IL-4), associated with the T-helper 2 (T_H2)-like subset, and an increase in IL-2, IL-12, and gamma interferon, associated with the T_H1-like subset (Fig. 4).^{37, 71, 92, 111} T_H2-type cells are linked with allergic, humoral immune responses whereas T_H1-type cells are connected with delayed hypersensitivity. Alveolar macrophages, platelets, mononuclear cells, and vascular endothelial cells also produce factors that release histamine, and probably other mediators, from mast cells and basophils.^{24, 25, 25a, 102} The severity of asthma and bronchial hyperreactivity correlates with the magnitude of spontaneous production of histamine-releasing factors by lymphocytes.²⁶ Immunotherapy results in decreased production of histamine-releasing factors following allergen challenge.⁷⁰ Thus, immunotherapy modulates these complex, regulatory cellular networks to reduce the atopic diathesis.

PROOF OF EFFICACY

Rhinoconjunctivitis

Noon and Freeman first reported in 1911 that immunotherapy is effective for hayfever. The clinical application of immunotherapy grew rapidly during the first half of the 20th century despite the absence of controlled trials. This may be attributed to the high prevalence of allergic diseases, approximately 20% of the population, the previously limited availability of effective pharmacologic therapy, and the apparent benefit of immunotherapy. Several clinical reviews summarize the immunotherapy efficacy data for allergic rhinitis (see article by Moss and Bush elsewhere in this issue).^{8, 20, 72, 135}

Clinical Trials

A variety of clinical trials, with variable blinding and control groups, have been done for seasonal and perennial allergic rhinitis since 1954. Thirty of the 35 best designed, double-blind trials demonstrate efficacy (see article by Moss and Bush).*

The majority of the controlled trials with immunotherapy demonstrate beneficial clinical effects in both seasonal and perennial allergic rhinitis. The efficacy data are most convincing for grass, ragweed, birch, mountain cedar, and *Cladosporium*-triggered allergic rhinitis. The data are inconclusive or not available for rhinitis due to dust mite, cockroach, cat, dog, rodent and additional trees, grasses, weeds, or molds. Laboratory tests, particularly an increase in specific-IgG or a decrease in specific-IgE, generally correlate with the clinical improvement. Nasal or conjunctival challenge and skin test reactivity tend to decrease with

*References 7, 9, 10, 11, 14, 18, 24, 25, 26, 33, 34, 36, 38, 40, 43, 58, 66, 67, 81, 83, 95, 109, and 130.

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Figure 4. The influence of immunotherapy on the production of IL-4, an important cytokine regulating the production of IgE and eosinophils. Subjects were allergic to house dust mite (Der f, *circle*) or grass pollen (Lol p, *square*). T cells were isolated and stimulated in vitro with either allergen or tetanus toxoid as a control. Ten subjects with allergic rhinitis received immunotherapy for a mean of 5 years. These treated subjects were compared with a similar population of 10 subjects with allergic rhinitis who were not treated with immunotherapy. Data are shown for the treated subjects with allergen (A) and tetanus toxoid (B). IL-4 production after allergen incubation decreased with immunotherapy, but there was no effect on the response to tetanus toxoid. The subjects not treated with immunotherapy had no change in allergen or tetanus toxoid response. The decrease in IL-4 production was dependent on the duration of immunotherapy. (From Secrist H, Chelen CJ, Wen Y, et al: Allergen immunotherapy decreases interleukin 4 production in CD4+ T cells from allergic individuals. Reproduced from The Journal of Experimental Medicine, 1993, vol 178, pp 2123–2130 by copyright permission of The Rockefeller University Press.)

therapy, with the delayed or late-phase skin response showing the most consistent decrease; however, the many exceptions indicate that there is not a specific test to confirm clinical benefit. Symptom improvement remains the standard response variable. Treatment of rhinitis with immunotherapy may reduce the likelihood of the development of asthma or the development of additional allergen sensitivity.^{60, 63, 123} The available cost-benefit analyses show reduced overall health costs with allergen immunotherapy (see article by Bernstein elsewhere in this issue).^{5, 32}

Asthma

Twenty-one of 28 double-blind, placebo-controlled studies of asthma demonstrate clinical improvement following immunotherapy; 3 did not report clinical outcome and 4 did not show improvement (see article by Moss and Bush).^{*} One study demonstrates less improvement during the second year of immunotherapy than in the first year.²⁴

A meta-analysis of 20 double-blind, placebo-controlled asthma studies published between 1966 and 1990 shows benefits from immunotherapy.¹ The odds ratio for symptomatic improvement with immunotherapy is 2.7 (95% confidence interval 1.7–4.4). The odds ratio for a reduction in needed medication following house dust mite immunotherapy is 4.2 (95% confidence interval 2.2–7.9). This meta-analysis concludes that 36 subsequent, negative-controlled trials would be necessary to determine that immunotherapy is not of value in the treatment of asthma. Combining asthma immunotherapy studies for analysis has limitations, and information not used in this analysis may strengthen the conclusions for beneficial effects of immunotherapy in asthma.¹⁶

A review of 15 dust-mite immunotherapy studies of asthma concluded that the cumulative data support the efficacy of immunotherapy.⁴¹ The treatment was judged beneficial in eight trials, equivocal in two trials, and ineffective in five trials. Patients with mild to moderate asthma were deemed to more likely benefit than subjects with severe asthma.

The study of Johnstone, published in 1961, does not meet criteria for being double-blind but is of significance because of its 4-year duration.⁶⁵ Two-hundred children with asthma were randomized to low-dose immunotherapy (1:10 million w/v), medium-dose immunotherapy (1:5000 w/v), high-dose immunotherapy (1:250 w/v), or placebo. Wheezing with exertion was subsequently reported in 54% of the children receiving placebo and the low-dose immunotherapy, 31% of those treated with the medium dose and 9% of those receiving high dose. Similar differences among the groups were reported following respiratory infection.

In summary, the majority of controlled trials demonstrate beneficial effects in both seasonal and perennial allergic asthma. Studies in which

*References 2, 4, 10, 12, 17, 24, 28, 33, 41, 53, 54, 55, 56, 86, 95, 103, 109, 119, 122, 127, 128, and 130.

specific-IgG was measured usually demonstrate an increase when clinical improvement was noted, but not always. Bronchial challenges with allergen generally show less sensitivity to allergen following immunotherapy, and the late-phase asthma response is less frequent and severe.^{124, 125} Immunotherapy may reduce the possibility of the treated subject becoming sensitive to additional allergens and the development of asthma in atopic populations.^{29, 123} The data show convincing benefit of immunotherapy for grass-pollen, ragweed-pollen, birch-pollen, mountain-cedar-pollen, and dust-mite-triggered asthma. Data show probable benefit for asthma associated with cat, *Cladosporium*, and *Alternaria* allergy. Asthma efficacy data are limited or not available for dog, rodent, horse, cockroach, and additional mold or pollen immunotherapy.¹³¹ As compared with the treatment of allergic rhinitis, there are fewer trials showing efficacy and more trials not showing benefits with immunotherapy of asthma. This may be explained by the difficulties of designing and performing such studies in asthma, by the lower prevalence of seasonal versus perennial asthma, by the effect of nonallergic factors which aggravate asthma (viral infections, sinusitis, pollutants, irritants, air temperature and humidity changes, esophageal reflux), and by coexisting diseases, such as chronic obstructive lung disease, which contribute to symptoms. The available cost-benefit analysis shows reduced total health care costs with immunotherapy.³²

Insect Sting Anaphylaxis

A double-blind, placebo-controlled trial of venom and whole-body extract immunotherapy in individuals with a history of anaphylactic reactions to Hymenoptera sting demonstrates that only venoms prevent reactions to sting challenge (see article by Golden elsewhere in this issue) (Fig. 5).⁶⁰ Previous, uncontrolled trials using whole-body vaccine suggest effectiveness of whole-body vaccine immunotherapy, but this was not confirmed when treated subjects were purposely stung under controlled conditions. The use of venoms facilitates the study of immunologic responses of Hymenoptera-hypersensitive individuals undergoing immunotherapy. Specific-IgG usually increases with venom immunotherapy, and the higher maintenance doses are associated with higher levels of specific-IgG.^{13, 61, 134} Specific-IgE generally increases initially and decreases after 3 years or more of treatment^{47, 50, 75}; however, determination of specific-IgG or specific-IgE antibody levels does not permit prediction of the risk of anaphylactic reactions to stings in subjects who discontinue immunotherapy.^{48, 61, 75} Several large studies demonstrate excellent safety for immunotherapy using these standardized venom vaccines.^{47, 73, 134}

Imported fire ant sensitivity is more prevalent than other Hymenoptera sensitivity in areas in which the imported fire ant is endemic.^{44, 68} The available studies confirm clinical benefit with imported fire ant whole-body vaccine immunotherapy, which has been shown to contain the venom-specific allergens^{45, 62, 107, 132}; however, treatment failures have

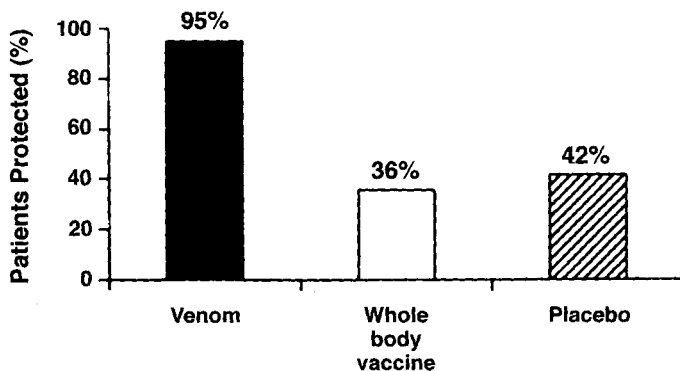


Figure 5. The beneficial effects of venom immunotherapy compared with whole-body insect vaccines and placebo. Systemic anaphylaxis was prevented in 95% of the subjects treated with venom immunotherapy compared with 36% and 42% of the subjects treated with whole-body vaccines and placebo, respectively. The reduction with whole-body vaccines and placebo is caused by the natural variation in the allergic sensitivity to the venoms. These data do not apply to whole-body vaccines from the imported fire ant, which have been shown to contain sufficient venom allergens for use in immunotherapy. (Data from Hunt KJ, Valentine MD, Sobotka AK, et al: A controlled trial of immunotherapy in insect hypersensitivity. *N Engl J Med* 299:157, 1978.)

been reported, and no double-blind trial (comparing whole-body vaccine, venom, and placebo) has been done.^{73, 74, 99}

Food Allergy

There are no clinical studies indicating that food immunotherapy, either oral or by injection, has a role in the management of allergic individuals. One group of investigators demonstrated efficacy with immunotherapy in peanut-sensitive subjects⁹⁴; however, more data are needed before such therapy can be recommended for routine clinical use. Food immunotherapy in highly allergic individuals may have a greater risk for severe, life-threatening reactions than inhalant immunotherapy.^{89, 90}

Ineffective Methods of Immunotherapy

Low-dose immunotherapy, such as that recommended by Rinkel, has been used by some physicians for treatment of allergic disease (see article by Terr elsewhere in this issue).¹¹² A skin test endpoint titration to select a "safe" dose of allergen vaccine is used for low-dose treatment programs. The skin test endpoint is defined as the fivefold dilution of allergen vaccine that induces a positive intradermal skin test reaction sufficient to cause the wheal size to increase by 2 mm compared to the previous dilution. Administration of the determined dose is claimed to

relieve symptoms within minutes. The dose is repeated at intervals to maintain improvement, and the prolonged increase of dosage over weeks is allegedly not required. Local and systemic reactions rarely, if ever, occur because of the small amount of allergen administered. A large, placebo-controlled study of low-dose therapy (Rinkel method), using mixed allergens administered over 2 years, failed to demonstrate clinical benefit.⁵⁷

The idea that the pathogenesis of rhinitis and sinusitis is caused by bacteria in the nasopharynx led to the hypothesis that immunization with bacterial extracts, derived from culture of the respiratory tract of the treated subject, would be beneficial.⁸⁵ Such bacterial vaccines were advocated for the treatment of recurrent rhinitis and sinusitis during the early part of the 20th century. This treatment was also advocated for asthma that was aggravated by respiratory infections. These vaccines are not effective for the treatment of asthma or any other respiratory tract disease, and their continued use is not justified.^{42, 64}

Dose Dependence of Immunotherapy

Clinical and immunologic improvement of allergic disease is more likely with a greater amount of administered allergen, within certain limits. A comparison of two doses of allergen extract for treatment of ragweed hay fever demonstrates improvement only with the higher dose (up to 0.5 mL of 1:50 w/v extract).⁴³ A comparison of high-dose ragweed immunotherapy (11 μ g of antigen E) with low-dose Rinkel immunotherapy (0.001 μ g of antigen E) demonstrates beneficial clinical and immunologic responses only in the high-dose group.²⁶ Increasing the dose of immunotherapy beyond a certain level does not result in further improvement, as shown by a ragweed study providing improvement with a twofold, but not a fivefold, increase in dose.²⁵ Studies of immunotherapy for asthma led to similar conclusions. For example, improvement with immunotherapy in asthma due to cat allergen correlates positively with the dose of allergen administered.^{4, 77, 93, 119, 128} The improvement has been assessed both by clinical symptoms and bronchial challenge with cat allergen. The optimal dose of 7 μ g of house dust allergen minimized reactions while improving asthma.⁵⁴ Comparison of several studies with venom immunotherapy demonstrates that a 100 μ g maintenance dose is 96% to 100% effective following sting challenge, whereas a 50 μ g maintenance dose is 79% effective.⁴⁹ Thus, the data consistently indicate that clinical improvement following immunotherapy is dependent on the dose administered.

Duration of Immunotherapy

Inhalant Allergy

There are no data to identify the optimal duration of inhalant immunotherapy. General recommendations are that maintenance immu-

notherapy be administered until symptoms have improved to a satisfactory level for one year, until symptom improvement is noted in three consecutive annual seasons, or until 3 to 5 years of maintenance immunotherapy have been completed.^{51, 135} Relapse of symptoms after discontinuation of immunotherapy occurs in up to 55% of treated subjects.²⁸ Recrudescence is less common, as duration of treatment increases from 12 to 96 months and as specific skin test reactivity decreases.²⁸ If no improvement is noted after a trial of 12 to 24 months, it is unlikely that additional therapy will be of value.

Hymenoptera Hypersensitivity

There is no consensus to define guidelines concerning the optimal duration of immunotherapy for Hymenoptera hypersensitivity (see article by Golden). Various investigators have proposed or presented data supporting three approaches: (1) measure specific-IgG to the venom used and discontinue immunotherapy when a concentration of 5 $\mu\text{g/mL}$ or more is reached^{118, 50}; (2) repeat the measurement of specific-IgE, either in vitro or by skin testing, and discontinue when the level decreases from the initial level or the specific-IgE disappears¹⁰⁵; (3) discontinue without testing after immunotherapy has been given for a time period of 3 to 5 years.^{47, 110} It is possible that all of these approaches have clinical utility. Application of clinical judgment with use of some of the above guidelines is generally the course of action. Therapy can be discontinued when the skin or in vitro specific-IgE tests become negative. More data are necessary to determine when therapy can be safely discontinued in subjects whose level of specific-IgE remains detectable.⁷³

Summary

1. The beneficial effects of immunotherapy are limited to the allergens administered.^{90, 109} Nonspecific reduction of allergic sensitivity or symptoms does not occur. Conflicting information exists as to whether bronchial hyperreactivity improves with immunotherapy.^{24, 56, 78, 83, 90, 111} There may be some beneficial effects in decreasing hypersensitivity to allergens that cross-react antigenically with the allergens administered.
2. Improvement is dose dependent, although most available studies have not addressed this issue. Available data indicate that approximately 4 to 12 μg of an allergen is required for maintenance immunotherapy.⁵¹
3. Immunotherapy is most likely to benefit subjects who are highly sensitive; however, such subjects are also at highest risk for anaphylaxis associated with immunotherapy.^{74, 108, 118}
4. Available cost-benefit analyses show reduced overall health care costs with immunotherapy.

Additional studies are needed to address the following:

1. The value of additional standardized allergen vaccines needs to be better defined with respect to improving efficacy and reducing side effects of immunotherapy in a cost-effective manner.
2. The appropriate maintenance dose for all allergens should be determined. Comparisons among studies are possible only if the amount of allergen administered is clearly identified.
3. Multiple-allergen immunotherapy needs additional study because most allergic subjects are sensitive to many allergens, and the general rule is to administer multiple allergens per vial for treatment.
4. Better outcome data are needed to compare pharmacologic management with immunotherapy. Such studies should assess the most cost-effective therapy, incorporating the risk-benefit ratios of pharmacotherapy and immunotherapy, the long-term anatomic and physiologic results and lifestyle issues. Additional information concerning the natural history of allergic disease, particularly chronic asthma and the development of asthma in atopic populations, is needed to make these assessments.
5. Additional studies are needed to explore the efficacy of immunotherapy in populations below 6 and over 50 years of age.
6. The optimal duration for immunotherapy needs to be better defined. Ideally a confirmatory monitoring test should facilitate the decision to terminate therapy.

CLINICAL APPLICATIONS OF IMMUNOTHERAPY

Indications

Box 1 suggests some considerations for using immunotherapy (see article by Moss and Bush).²⁴ The symptoms or disease process should be consistent with known immunologic mechanisms (i.e., allergic asthma, allergic rhinoconjunctivitis, insect sting anaphylaxis). Chronic urticaria, eczema, and food allergy have not consistently improved following immunotherapy, but treatment of severe atopic dermatitis with immunotherapy is a consideration in selected cases. Specific-IgE for appropriate allergens must be documented, and symptoms should correlate with exposure to those specific allergens selected for immunotherapy. An exception to this recommendation, although not accepted by all investigators, is that individuals with anaphylaxis following Hymenoptera envenomation by a species of stinging insect other than imported fire ants or harvester ants should be treated with all venoms against which the individual has specific-IgE. The correlation of symptoms with allergen exposure and sensitivity requires a knowledge of the environment of the subject, as well as a familiarity with the quality and reliability of allergen testing reagents used to document sensitivity.

The association of symptoms with exposure may be difficult to document with perennial asthma and rhinitis. The severity and duration of symptoms should be of sufficient degree to justify immunotherapy.

Box 1. Considerations for Initiating Immunotherapy

Presence of IgE-mediated disease amenable to immunotherapy

- Allergic rhinitis
- Asthma with allergic triggers
- Anaphylaxis following Hymenoptera stings

Documentation of specific sensitivity

- Association of allergen exposure and symptoms
- Presence of specific-IgE to allergen
 - Skin tests
 - RAST tests or other in vitro tests
 - Provocation challenge

Symptoms of sufficient duration and severity

- Two seasons of seasonal symptoms despite avoidance measures and pharmacologic therapy
- Perennial symptoms failing trials of avoidance measures and chronic pharmacologic therapy
- Anaphylaxis following Hymenoptera stings except children with reactions limited to cutaneous anaphylaxis or urticaria

Availability of quality allergenic vaccines

Absence of significant social or logistical barriers

- Travel and time
- Cost
- Risk versus benefit
- Facilities and personnel to treat anaphylaxis

Absence or minimal underlying medical conditions or medications that could complicate immunotherapy administration

- Beta blocker therapy, particularly in subject with asthma
- Initiation of treatment during pregnancy
- Autoimmune disease
- Unstable asthma
- Advanced age
- Significant heart disease
- Contraindication to epinephrine administration

Perennial symptoms should be associated with a high degree of allergic sensitivity coupled with a failure of avoidance measures and chronic, safe pharmacologic therapy. Significant seasonal symptoms should be present for at least two seasons despite the appropriate use of safe, pharmacologic therapy and appropriate avoidance measures. Occasionally immunotherapy should be considered earlier if symptoms are particularly severe.

Quality allergen vaccines are a prerequisite for testing and treat-

ment. Progress has been made to improve allergen vaccines, but certain extracts, notably molds, have been difficult to standardize (see article by Løwenstein elsewhere in this issue).^{104, 115}

The age of the subject is a factor in that studies showing benefits with immunotherapy have been limited, for the most part, to children older than 6 years old and adults younger than 50 years old.²¹ This should not be construed to mean that immunotherapy is not beneficial in older and younger age groups, but instead that there are limited data proving benefit.

Spontaneous improvement does occur in some allergic individuals, of all age groups, and this confuses interpretation of induced clinical improvement. Older adults with asthma may have a component of fixed obstructive lung disease that will not benefit from immunotherapy.

Allergen Selection

Allergens selected for immunotherapy should be those to which exposure results in significant symptoms and to which significant sensitivity has been documented using available testing and treatment reagents. The treating physician should be knowledgeable concerning the local environment to permit association of symptoms with known allergens. Challenge studies are seldom performed and allergens for immunotherapy should not be chosen solely based on skin tests or in vitro testing. Potential outdoor allergens consist primarily of plant-derived materials (particularly pollen from wind-pollinated plants), fungal products (particularly mold spores), and airborne wings and body parts from insects (see article by Weber).¹⁹ The seasons for pollen exposure in temperate climates are spring for trees, spring and summer for grasses, and fall for weeds. Numerous exceptions do occur, and in the deep southern regions of North America there is a great deal of overlap of these seasons. Airborne mold spores generally are detected when temperature and humidity are increased, with very high levels occurring in the Gulf Coast states and associated with farming activities in the Midwest. Indoor allergens are perennial, although there are changes in levels of dust mite allergen which correlate with seasonal environmental changes.¹⁹ Indoor allergens are derived from house dust mites, storage mites, fur-bearing animals, insects, and mold spores. Selected occupations are exposed to significant allergen concentrations, as in wood working, certain chemical industries, animal husbandry, animal research, and agriculture and food processing. Heating and air conditioning systems may become contaminated with various potential allergens, most notably mold. Clinical acumen, inspection and knowledge of the environment, and experience are needed to accurately determine the important allergens in a selected environment.

Inhalant allergen immunotherapy is generally administered as a mixture of allergens. Ideally, the number of allergens in a mixture should be less than 10 although a great deal of variation is typical. There is a decrease in potency of pollen allergens, particularly grass pollen extracts,

when mixed with mold spore and cockroach extracts. This is primarily due to proteolytic enzymes in the mold spore, especially *alternaria* and *cladosporium*, and cockroach extracts.^{69, 88} These enzymes potentially degrade or inactivate the other allergens.

Other Forms of Immunotherapy

Local Nasal Immunotherapy

Local nasal aeroallergen immunotherapy is an alternative form of immunotherapy using an aqueous solution of allergen to spray on the nasal mucosa at specified time intervals.^{27, 126, 133} This form of treatment has been shown to be clinically effective, with some studies demonstrating systemic immunologic changes with treatment.⁴⁶ Other reports show decrease in nasal sensitivity to allergen challenge and decrease in symptoms with natural exposure but no alteration in skin test sensitivity or levels of specific-IgG or specific-IgE.^{4a, 97} The risk of anaphylactic reactions is less than with traditional immunotherapy, and administration is facilitated because the patient self-administers the extract. The primary side effects are nasal pruritus, congestion, and sneezing, which are of sufficient severity in some subjects to result in discontinuation. Sufficient long-term trials are not yet available to permit recommending this form of therapy.

Oral Aeroallergen Immunotherapy

Oral immunotherapy with birch pollen extract has been shown to be efficacious, using various dosage schedules.^{6, 49, 121, 129} Trials with sublingual administration of allergen vaccines suggest that low-dose therapy with dust mite or grass-maize vaccine is efficacious in allergic rhinitis and asthma.^{121, 129} No adverse effects were described. A double-blind, placebo-controlled trial of sublingual standardized cat immunotherapy for the treatment of asthma demonstrates no benefit with this form of treatment.⁸⁹ Both oral immunotherapy and sublingual immunotherapy are of uncertain efficacy, and additional studies are needed.

Alum-Precipitated Allergen Vaccines

Modifications of aqueous vaccines, by precipitation of proteins with aluminum hydroxide, results in a product that produces less systemic reactions than aqueous allergen vaccines.^{54, 111} This modification permits a more rapid increase in the dosage of the treatment, and fewer total injections are required before benefits are realized.⁸⁰ Equivalent clinical and immunologic changes with ragweed alum-precipitated vaccines required half as many injections as did aqueous ragweed vaccines. Cat and grass have also been studied, and other alum-precipitated vaccines would presumably be of equivalent efficacy. Although systemic reactions

are decreased, some treated subjects experience prolonged local reactions following administration of alum-precipitated vaccines.¹²⁶ Alum-precipitated products are currently limited in diversity and should not be mixed with aqueous extracts.

Before alum precipitation, allergens can be extracted with pyridine to further reduce the potential for systemic reactions following administration. Alum-precipitated pyridine grass vaccines have been shown to be efficacious, but other allergens, such as ragweed, are denatured by the pyridine treatment and rendered ineffective.¹²⁶ The use of alum-precipitated pyridine vaccines is limited and largely unproven.¹¹¹

Modified Aeroallergen Vaccines

Polymerization or aggregation of the proteins of an aqueous vaccine reduces the allergenicity while preserving the immunogenicity of the product. Two methods of such modification have accomplished this goal—formalin-treated allergens (allergoids) and glutaraldehyde-treated allergens (polymerized allergen extracts).^{79, 91} Regimens using these vaccines permit completion of an immunotherapy program with 10 to 15 weekly injections with less than 1% occurrence of systemic reactions.^{51, 91, 126} One trial of immunotherapy with polymerized vaccines demonstrates clinical improvement lasting for at least 4 years following a course of treatment.⁵² The possibility of long-term side effects, although none have been documented, has hindered commercial development of this effective modification of immunotherapy. These products offer the potential for a major advance in the treatment of inhalant allergic disorders.

Identification and synthesis of immunodominant T-cell epitopes provide the possibility of administering specific immunotherapy with less risk of anaphylaxis. The T-cell epitopes lack the tertiary structure of the native allergen, which reduces the potential for binding to specific-IgE and provoking allergic symptoms. This strategy has been applied to cat allergic subjects with asthma and was effective.⁷⁷ However, anaphylaxis and delayed reactions with respiratory symptoms occurred but at a lower rate than would have occurred with equivalent efficacy using a native allergy vaccine. Peptide vaccines offer the potential of safer vaccines requiring fewer injections for efficacy (see article by Mohapatra).

SUMMARY

Immunotherapy has stood the test of time and is an important treatment modality for subjects suffering from inhalant allergic diseases and Hymenoptera sting hypersensitivity. In contrast to pharmacologic therapies, immunotherapy offers the possibility of addressing the fundamental pathophysiologic process of allergy—the release of mast cell and basophil mediators upon contact with specific allergens.

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