

Allergen immunotherapy: Therapeutic vaccines for allergic diseases

A WHO position paper

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The World Health Organization and various allergy, asthma, and immunology societies throughout the world met on January 27 through 29, 1997, in Geneva, Switzerland to write guidelines for allergen immunotherapy. Over the ensuing year, the editors and panel members reached a consensus about the information to include in the WHO position paper "Allergen immunotherapy: Therapeutic vaccines for allergic diseases." The historical term allergen extract was changed to allergen vaccine to reflect the fact that allergen vaccines are used in medicine as immune modifiers. The document summarizes the scientific literature and rationale for the appropriate use of such therapy to treat allergic rhinoconjunctivitis, allergic asthma, and Hymenoptera hypersensitivity. It also includes recommendations to improve safety, discusses new techniques being developed that may result in better efficacy and less risk, and offers recommendations for areas of additional and necessary research. (*J Allergy Clin Immunol* 1998;102:558-62.)

Allergen immunotherapy is the practice of administering gradually increasing quantities of an allergen extract to an allergic subject to ameliorate the symptoms associated with subsequent exposure to the causative allergen. Allergen immunotherapy was introduced to treat "polli-

nosis," or allergic rhinitis, by Noon and Freeman in 1911.¹ For the past 80 years, immunotherapy has been used to treat allergic diseases caused by inhalant allergens and Hymenoptera venoms. Venom immunotherapy is accepted as the standard of care for Hymenoptera-induced systemic allergic reactions. There is good evidence that immunotherapy with inhalant allergens used to treat seasonal or perennial allergic rhinitis and asthma is clinically effective.

Guidelines and indications for immunotherapy with inhalant allergens, venoms, or both were proposed in 1987² and have been published within the past years by the World Health Organization (WHO),^{3,4} the European Academy of Allergy and Clinical Immunology (EAACI),^{2,5,6} the International Consensus Report on Asthma,⁷ the Global Strategy for Asthma Management and Prevention,⁸ the International Consensus Report on Rhinitis,⁹ the British Society for Allergy and Clinical Immunology,¹⁰ the American Academy of Allergy, Asthma and Immunology (AAAAI), and the American College of Allergy, Asthma and Immunology (ACAAI).¹¹

These reports provide guidelines for a better understanding of the use of allergen immunotherapy. However, none of them represent a consensus report of experts from various parts of the world where such therapy is used,^{3,5,10-12} and some only address specific issues on one of the target organs in relation to asthma^{7,8} or rhinitis.⁹

Physicians and scientists from several countries convened at the WHO headquarters in Geneva, Switzerland on January 27 to 29, 1997 to review the science of and indications for allergen immunotherapy to treat allergic diseases. New forms of therapy currently under development that may prove to be safer and more effective than conventional treatments were also discussed.

Vaccines are used in medicine as immune modifiers. So too is allergen immunotherapy. Knowledge gained from studies of allergic mechanisms, such as the importance of T_{H1} and T_{H2} cells, cytokine regulation of the immune responses, and specific inhibition or ablation of pathogenic immune responses by means of tolerance induction, may be applicable to a variety of allergic and other immunologic diseases. This is especially true for autoimmune diseases such as juvenile diabetes mellitus and multiple sclerosis. Thus the concepts used and the scientific data that support the use of allergen immunotherapy to treat allergic diseases are now being

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applied scientifically for other immunologic diseases. The panel therefore entitled this position statement "Allergen immunotherapy: Therapeutic vaccines for allergic diseases" to indicate that vaccines (allergen extracts) that modify or downregulate the immune response for allergic diseases are part of this broad-based category of therapies presently used and being developed to treat other immunologic and infectious diseases.

ALLERGEN STANDARDIZATION

The quality of the allergen vaccine is critical for both diagnosis and treatment. When possible, standardized vaccines of known potency and shelf-life should be used. The most common vaccines used in clinical allergy practice are now available as standardized products or are pending standardization. However, there are many vaccines currently being marketed (many of which are only used occasionally), and it is neither feasible nor economic to standardize all of them. The measurement of major allergens for standardization is now a realistic and desirable goal that should be encouraged.^{13,14} Allergen vaccines should be distributed, provided their potency, composition, and stability have been documented as either (1) vaccines from a single source material; (2) mixtures of related, cross-reacting allergen vaccines, such as grass-pollen vaccines, deciduous tree-pollen vaccines, related ragweed-pollen vaccines, and related mite vaccines; or (3) mixtures of other allergen vaccines, provided that stability data¹⁵ and data on clinical efficacy are available. Where mixtures are marketed, the relative amounts of each component of the mixture should be indicated.

MECHANISMS

Immunotherapy is specific to the antigen administered.¹⁶ The mechanisms of immunotherapy are complex and may differ depending on the allergen (venoms or inhalant allergens) and the route of immunization. Whereas earlier work focused on circulating antibody,^{17,18} newer studies suggest that immunotherapy acts by modifying T-cell responses either by immune deviation (increase in T_{H0}/T_{H1}), T-cell anergy (decrease in T_{H2}/T_{H0}), or more likely both.¹⁹⁻²¹ Systemic and local increases in $CD8^+$ cells have also been observed. Immunotherapy also reduces inflammatory cell recruitment and activation and mediator secretion.^{22,23}

EFFICACY OF SUBCUTANEOUS IMMUNOTHERAPY

Controlled studies demonstrate that allergen immunotherapy is effective for patients with stinging insect hypersensitivity,²⁴ allergic rhinitis/conjunctivitis, and allergic asthma. Immunotherapy is effective treatment for many pollen species, including grasses, ragweed, *Parietaria* species, and mountain cedar.⁵ Immunotherapy with house dust mite vaccines is effective for treatment of asthma²⁵ and rhinitis. Fewer studies have found that immunotherapy is effective for patients allergic to cats,²⁶ *Alternaria* species,²⁷ and *Cladosporium* species.²⁸ A metaanalysis of clinical trials of allergen

immunotherapy demonstrated that it is effective for treatment of asthma.²⁹

Immunotherapy dosing raises contrasting efficacy and safety issues. Low-dose immunotherapy is ineffective,³⁰ and high doses of allergen vaccines may induce a high and unacceptable rate of systemic reactions. Thus optimal doses using vaccines labeled either in biological units³¹ or in mass of major allergens³² have been proposed. The optimal dose is defined as the dose of allergen vaccine inducing a clinically relevant effect in the majority of patients without causing unacceptable side effects.^{33,34} The optimal dose should be the maintenance target dose for all patients.³¹ Doses of 5 to 20 μ g of the major allergen are optimal doses for domestic mites,^{31,34,35} cat dander,^{26,36} ragweed pollen,³⁷⁻³⁹ and Hymenoptera venoms.^{6,40} The majority of patients with allergic diseases can tolerate this target dose without difficulty. However, in selected individuals who have experienced reactions during their build-up treatment phase, a lower maintenance dose may be necessary. As with any therapeutic approach, the benefit-to-risk ratio must be carefully considered to determine whether immunotherapy should be continued.

Immunotherapy and allergen avoidance are the only treatments that may affect the natural course of allergic diseases. The use of allergen immunotherapy requires specialist assessment, especially in children, because there are special problems and questions in this age group. Immunotherapy started early in the disease process may modify the spontaneous long-term progress of the allergic inflammation and disease.^{5,41} Immunotherapy is rarely started before the age of 5 years.

SAFETY OF SUBCUTANEOUS IMMUNOTHERAPY

The major risk of allergen immunotherapy is anaphylaxis,⁴²⁻⁴⁵ and asthma appears to be a significant risk factor for systemic reactions.^{46,47} Therefore allergen immunotherapy should be administered by or under the close supervision of a trained physician who can recognize early symptoms and signs of anaphylaxis and administer emergency treatment.

INDICATIONS FOR SUBCUTANEOUS IMMUNOTHERAPY

The treatment of allergic diseases is based on allergen avoidance, pharmacotherapy, allergen immunotherapy, and patient education. Physicians should know the local and regional aerobiology and be aware of the potential allergens in the patient's indoor and outdoor environments. Only physicians with a training in allergology can select the clinically relevant allergen vaccines for therapy. Immunotherapy, where appropriate, should be used in combination with other forms of therapy with the hope that the patient will become as symptom-free as medically possible.

Allergen immunotherapy is indicated for patients who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens and whose allergic symptoms

warrant the time and risk of allergen immunotherapy. Contraindications for inhalant allergen and venom immunotherapy may be absolute or relative.⁵ Patient selection is important, and efficacy must always be balanced against the risk of side effects. The necessity for initiating allergen immunotherapy depends on the degree to which symptoms can be reduced by medication, the amount and type of medication required to control symptoms, and whether effective allergen avoidance is possible.

The indications for venom immunotherapy are provided in the position paper of the EAACI.⁶ An absolute indication is a history of severe allergic systemic reactions with respiratory symptoms, cardiovascular symptoms, or both and positive diagnostic tests (skin tests, serum-specific IgE, or both).

The indications for immunotherapy in asthma and rhinitis have been separated in some guidelines,⁷⁻⁹ and this artificial separation has led to unresolved questions,^{48,49} possibly because the IgE-mediated reaction has not been considered as a multiple organ involvement. It is therefore important to consider immunotherapy on the basis of the allergen sensitization rather than on a particular disease manifestation.

Immunotherapy for treatment of allergic rhinitis/conjunctivitis is indicated (1) when antihistamines and topical drugs insufficiently control symptoms, (2) in patients who do not wish to receive pharmacotherapy, (3) when pharmacotherapy produces undesirable side effects (4) when the patient is concerned about long-term pharmacologic therapy, and (5) if the season is prolonged or polysensitized patients are exposed to several subsequent pollen seasons (ie, tree, grass, and weed pollen sensitivity).^{3,5} The risk/benefit ratio should be considered in every case.

Although efficacy of immunotherapy has been shown for treatment of allergic asthma, the risk of systemic reactions in patients with asthma has been considered a contraindication in the UK guidelines,¹⁰ although not in the other published national or international guidelines.⁷⁻⁹

Patients allergic to mites are candidates for mite allergen immunotherapy if they have significant symptoms of rhinitis or asthma when they are exposed to domestic mite allergens.

Avoidance is the treatment of choice for animal dander-induced allergic diseases. However, complete avoidance is often impossible because of exposure to animal allergens in environments in which animals are not present.⁵⁰ Immunotherapy may be prescribed for patients in whom avoidance of animal allergens is not fully effective, such as because of occupational exposure or refusal to evict an animal from the home.

For mold allergy, avoidance, when possible, of indoor mold allergens is the treatment of choice. Some studies have demonstrated clinical improvement when well-characterized vaccines of *Cladosporium* or *Alternaria* species have been used in the treatment of mold-induced allergy. Patients with positive immediate hypersensitivity test results and symptoms when exposed to other relevant

mold allergens may be considered for immunotherapy.

Vaccines of undefined allergens, such as house dust, bacteria, *Candida albicans*, and *Trichophyton* species, should not be used for immunotherapy.⁵

The duration of immunotherapy required to maintain improvement in clinical symptoms is still unknown. For those patients who respond to treatment, many clinicians advise 3 to 5 years of therapy. However, a decision on when to discontinue allergen immunotherapy should be individualized. Several studies suggest that venom immunotherapy may be discontinued after 3 to 5 years in most patients.

OTHER ROUTES OF IMMUNOTHERAPY

New routes of administration of immunotherapy are currently being explored, such as nasal, sublingual-swallow, or oral immunotherapy with high-allergen doses.⁵¹ On the basis of current studies, immunotherapy by the oral or bronchial route cannot be recommended. Properly controlled, well-designed studies making use of high-dose sublingual-swallow and intranasal immunotherapy provide evidence that this form of therapy may be a viable alternative to parenteral injection therapy in the treatment of allergic airways disease with doses ranging from 5 to 20 times greater than those of subcutaneous immunotherapy. Further studies need to be done to fully characterize the most appropriate patients, the optimal therapeutic target dose, and the degree of effectiveness as compared with conventional injection immunotherapy.

FUTURE VACCINES

New technologies and the improvement of our knowledge of the basic mechanisms of allergic diseases may completely alter the way allergen immunotherapy is used in the future. These advances should result in new, safer, and substantially more effective methods of manipulating the human immune response. These new approaches will be directed at every disease induced by antigens, such as asthma, as well as autoimmune diseases, such as type I diabetes and multiple sclerosis. For allergic diseases, several approaches may be used, such as the development of nonanaphylactic allergens, allergen fragments, or peptides for active immunotherapy,^{52,53} IgE-binding haptens of major allergens for passive saturation of effector cells and induction of blocking antibodies,⁵⁴ allergen-specific antibodies and antibody fragments for passive therapy in the allergic effector organs,^{55,56} plasmid DNA immunization,⁵⁷ and anti-IgE humanized monoclonal antibodies.⁵⁸

RESEARCH NEEDS

Future studies of immunotherapy are needed in the following areas:

1. cost-effectiveness,
2. quality-of-life and patient's satisfaction,
3. comparison with pharmacologic treatment for allergy,
4. "add-on" studies (eg, effect of immunotherapy added to treatment with topical therapy,

5. optimal duration,
6. reduction of the severity of asthma in terms of hospital admissions and emergency department visits,
7. decrease of the incidence of asthma in patients with allergic rhinitis and no asthma,
8. altering the natural course of the allergic rhinoconjunctivitis and/or asthma,
9. decreasing the long-term sequelae associated with allergic rhinitis and/or asthma,
10. long-term effects after cessation,
11. efficacy and safety for animal allergy (eg, dogs and horses),
12. efficacy and safety for occupational allergy (eg, laboratory animal allergy), and
13. efficacy and safety in children under 5 years of age.

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