

O V I D*

Full Text

[Results Display](#) [Main Search Page](#) [Help](#) [LOGOFF](#)
[PayPerView Account](#) [View Cart](#)



The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED 1812 • ISSN 0028-4793 • WWW.NEJM.ORG

Owned, published, and © copyrighted, 1999, by the MASSACHUSETTS MEDICAL
SOCIETY Volume 341(7), 12 August 1999, pp 522-524

[About this Journal](#)

[Table of Contents](#)

[Browse TOC](#)

[Find Citing Articles](#)

[Email Jumpstart](#)

[Save Article Text](#)

[Email Article Text](#)

[Print Preview](#)

Links

[Complete Reference](#)
[Catalogo Biblioteca ISS](#)

Outline

- REFERENCES

Recent History

Immunotherapy for Allergi...

GO

[Previous Page](#)

Immunotherapy for Allergic Rhinitis [Editorials]

Adkinson, N. Franklin Jr.

Johns Hopkins School of Medicine; Baltimore, MD 21224

Allergic rhinitis, or hay fever, afflicts 10 to 20 percent of people in the United States and northern Europe. The disease occurs either during the seasons of airborne pollens

and molds or throughout the year, triggered by indoor allergens such as dust mites, house pets, cockroaches, and molds. Allergic rhinitis usually starts in childhood, on average at about the age of 10 years. Like that of asthma, its prevalence is rising, especially in urban areas, for obscure reasons. Although many assume that allergic rhinitis is more of a nuisance than a clinically significant health problem, it is responsible for \$6 billion annually in health care costs in the United States, [1] and it frequently causes absence or poor performance at work and school. [2]

Management begins with efforts to prevent exposure to allergens (for example, through the use of air conditioning, restrictions on pets, and dust-mite abatement), supplemented by drug therapy. Older H_1 -receptor-antagonist drugs (such as diphenhydramine and chlorpheniramine) can have central nervous system effects, especially sedation, which can persist during the day even if the medications are taken only at bedtime. [3] Second-generation H_1 -receptor antagonists (such as fexofenadine and loratadine) control symptoms with little or no sedation in most patients who have mild or moderate rhinitis. Intranasal glucocorticoids need to be added for patients with more severe disease or year-round symptoms. With respect to young children, concern about the effect of intranasal glucocorticoids on growth and development may lead to the use of cromolyn sodium or nedocromil. Decongestants can help with nasal congestion or associated sinusitis. [4]

Noon [5] and Freeman [6] reported in 1911 that a majority of patients who had rhinitis in the spring had symptomatic improvement after receiving injections of a grass-pollen extract; many were "desensitized" by a factor of 100 as measured by conjunctival challenge. [7] Prolonged courses of injections of biologic extracts, popularly known as "allergy shots," remained the mainstay of therapy for allergic rhinitis until the development of clinically useful histamine H_1 -receptor antagonists in the 1940s. A

typical course of therapy consists of three or more years of subcutaneous injections of the highest or maintenance-level dose of grass-pollen extract at intervals of two to six weeks. Induction of clinical tolerance of the maximal dose is achieved by means of a series of weekly injections at escalating doses, usually given over a period of four to six months. Because of the risk of acute allergic reactions to the injections, standard care requires that the injections be supervised by a physician and that patients remain in a medical facility for at least 20 minutes after each injection. [8] Systemic allergic reactions, however, are uncommon. Numerous controlled trials have demonstrated the clinical efficacy of this therapy in both seasonal and year-round rhinitis. [4,7]

Since better medications are now available for allergic rhinitis, what is the role of immunotherapy? The logistics of comparing immunotherapy, which involves at least six months of prophylactic subcutaneous injections, with intranasal glucocorticoids administered daily during an allergy season, are formidable. Therefore, there have been no masked or placebo-controlled comparison trials. Despite the absence of evidence from such trials, immunotherapy continues to be an attractive therapeutic option for selected patients because it provides benefits that cannot be achieved with pharmacotherapy. First, immunotherapy offers a specific antidote for allergen-specific immune responses. It is therefore devoid of systemic toxic effects other than the risk of acute allergic reactions to injections and local swelling and tenderness at the injection site. Second, the reduced sensitivity to allergen induced by this therapy is systemically effective, so that allergic reactions in the upper and lower airways, conjunctivae, and skin are all diminished. Finally, allergen immunotherapy seems to alter the natural history of rhinitis and asthma.

One line of evidence that immunotherapy may alter the natural history of allergic respiratory disease is the persistence of clinical benefit long after therapy is

discontinued. The study reported by Durham et al. in this issue of the Journal [9] provides the best evidence to date that allergen immunotherapy has long-term, perhaps permanent, benefits. Their study clearly demonstrates that traditional allergen immunotherapy with a grass-pollen extract, administered for three to four years, induces a clinical remission that persists for at least three years after treatment is discontinued. This clinical remission is accompanied by persistent immunologic changes, including cellular desensitization and attenuated late-phase inflammatory responses on cutaneous challenge. Which of the immunologic changes are responsible for the persistent amelioration of symptoms remains to be sorted out.

Previous clinical studies have also suggested a long-term benefit of allergen immunotherapy. [10,11] Most studies of the outcome of the discontinuation of immunotherapy agree on two observations. First, there is considerable variation among patients with respect to the return of symptoms over time. And second, skin tests and mucosal challenge tests become increasingly positive after treatment is discontinued, though they rarely return to pretreatment values. Interestingly, recent studies of venom immunotherapy in patients who are allergic to insect stings also support the concept that three to five years of immunotherapy may induce long-lasting immunologic changes and reductions in risk. [12]

Other studies also suggest that allergen immunotherapy may alter the natural history of disease, especially if it is used early in the course of relatively mild respiratory allergy [13] and in patients who have restricted, rather than broad, allergic profiles. [14] A recent placebo-controlled study of immunotherapy in children with moderate-to-severe asthma found no overall benefit when immunotherapy was added to pharmacotherapy and environmental measures. [15] There was a strong trend,

however, toward a benefit of treatment in children who were younger or had less severe disease. An ongoing European study is now directly addressing the question of whether early immunotherapy for rhinitis can prevent the emergence of allergic asthma.

Except for the improved quality of extracts, allergen immunotherapy is still administered in a way that would be recognized by Noon [\[5\]](#) and Freeman. [\[6\]](#) Novel formulations for immunotherapy against specific allergens are now on the horizon. These may be better tolerated, less demanding in terms of the frequency and duration of treatment, and more efficacious. Promising candidates include therapy with anti-IgE monoclonal antibodies, peptide therapy aimed at inducing tolerance in allergen-specific T cells, and immunomodulatory adjuvants such as oligonucleotide sequences that shift immune responses away from the allergic T_H2 phenotype. [\[16\]](#)

Even as we look forward to improved formulations, the question remains, which patients should receive allergen immunotherapy for allergic rhinitis? The most common indication is poor tolerance or ineffectiveness of treatment with medications.

Immunotherapy with seasonal or year-round allergens can be expected to provide substantial relief of symptoms and reduction in medication requirements. [\[4,7\]](#) Patients with asthma are at greater risk for systemic allergic reactions than those with rhinitis; most fatal allergic reactions due to immunotherapy have occurred in patients with asthma. [\[17\]](#) Because of this increased risk and the lack of readily demonstrable benefits in patients with moderate-to-severe asthma, such patients should probably not receive immunotherapy.

Immunotherapy has the greater benefit relative to the investment of time and cost for patients who have rhinitis caused by known aeroallergens in more than one season or throughout the year. Allergen immunotherapy works best when environmental controls

are first implemented to minimize exposure to allergens, especially in the home. [\[4,14\]](#)

If patients sensitive to animal dander are unwilling to banish pets from their living quarters, allergen immunotherapy may be a waste of time and money.

Patients' preferences are also important. Patients with year-round symptoms or intense seasonal rhinitis may prefer immunotherapy, with visits to the doctor for injections every three to six weeks, to taking two or three medications each day. Patients with severe rhinitis may require supplemental medications while receiving immunotherapy, but others will be free of symptoms most of the time and require only occasional medications. For this reason, some patients who have excellent clinical results with immunotherapy are reluctant to stop treatment, even when it is reasonable to do so.

Allergen immunotherapy is a medical therapy that was widely used in the first quarter of this century and that is still in broad use in the last quarter. Although rarely curative, it provides substantial relief of symptoms and is safe for most patients who are likely to benefit. Although the lack of a clear understanding of which immunologic changes are driving symptomatic relief has hampered needed refinement in the technique, recent advances in immunology hold great promise for the future. [\[18\]](#)

N. Franklin Adkinson, Jr., M.D.

Johns Hopkins School of Medicine; Baltimore, MD 21224

REFERENCES

1. Ray NF, Baraniuk JN, Thamer M, et al. Direct expenditures for the treatment of allergic rhinoconjunctivitis in 1996, including the contributions of related airway illnesses. J Allergy Clin Immunol 1999;103:401-7. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)

2. Ross RN. The costs of allergic rhinitis. Am J Managed Care 1996;2:285-90. [\[Context Link\]](#)
3. Alford C, Rombaut N, Jones J, Foley S, Idzikowski C, Hindmarch I. Acute effects of hydroxyzine on nocturnal sleep and sleep tendency the following day: a C-EEG study. Hum Psychopharmacol Clin Exp 1992;7:25-35. [\[Context Link\]](#)
4. Dykewicz MS, Fineman S, Skoner DP, et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 1998;81:478-518. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
5. Noon L. Prophylactic inoculation against hay fever. Lancet 1911;1:1572-3. [\[Context Link\]](#)
6. Freeman J. Further observations on the treatment of hay fever by hypodermic inoculations of pollen vaccine. Lancet 1911;2:814-7. [\[Context Link\]](#)
7. Norman PS. Immunotherapy past and present. J Allergy Clin Immunol 1998;102:1-10. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
8. American Academy of Allergy, Asthma and Immunology Board of Directors. Guidelines to minimize the risk from systemic reactions caused by immunotherapy with allergenic extracts. J Allergy Clin Immunol 1994;93:811-2. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
9. Durham SR, Walker SM, Varga E-M, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999;341:468-75. [Catalogo Biblioteca ISS Full text \(pacchetto Ovid\)](#) [Bibliographic Links](#) [\[Context Link\]](#)
10. Naclerio RM, Proud D, Moylan B, et al. A double-blind study of the discontinuation of ragweed immunotherapy. J Allergy Clin Immunol 1997;100:293-300. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
11. Mosbech H, Osterballe O. Does the effect of immunotherapy last after termination of treatment? Follow-up study in patients with grass pollen rhinitis. Allergy 1988;43:523-9. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
12. Committee on Insects, American Academy of Allergy, Asthma and Immunology. The discontinuation of Hymenoptera venom immunotherapy. J Allergy Clin Immunol 1998;101:573-5. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
13. Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children - a 14-year study. Pediatrics 1968;42:793-802. [\[Context Link\]](#)
14. Bousquet J, Lockey R, Malling HJ, et al. Allergen immunotherapy: therapeutic vaccines for allergic disease. Ann Allergy Asthma Immunol 1998;81:401-5. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
15. Adkinson NF Jr, Eggleston PA, Eney D, et al. A controlled trial of immunotherapy for asthma in allergic children. N Engl J Med 1997;336:324-31. [Catalogo Biblioteca ISS Full text](#)

(pacchetto Ovid) Bibliographic Links [\[Context Link\]](#)

16. Platts-Mills TA, Mueller GA, Wheatley LM. Future directions for allergen immunotherapy. J Allergy Clin Immunol 1998;102:335-43. **Catalogo Biblioteca ISS Bibliographic Links** [\[Context Link\]](#)

17. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy and skin testing. J Allergy Clin Immunol 1987;79:660-77. **Catalogo Biblioteca ISS Bibliographic Links** [\[Context Link\]](#)

18. Rolland J, O'Hehir R. Immunotherapy of allergy: anergy, deletion, and immune deviation. Curr Opin Immunol 1998;10:640-5. **Catalogo Biblioteca ISS Bibliographic Links** [\[Context Link\]](#)

Accession Number: 00006024-199908120-00010

Copyright (c) 2000-2005 [Ovid Technologies, Inc.](#)

Version: rel10.2.0, SourceID 1.11354.1.53