
Specific immunotherapy in rhinitis and asthma

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Objective: The primary objective of this review is to discuss the efficacy of immunotherapy on combined lung and nasal symptoms, as well as data suggesting that allergen-specific immunotherapy (SIT) may, by altering the natural course of allergic disease, have a preventive effect on rhinitis and asthma.

Data Sources: A review of literature published on allergen-specific immunotherapy in the treatment of allergic rhinitis and asthma was performed. The review represents a synthesis of these sources and the expert opinion of the author.

Study Selection: The expert opinion of the authors was used to select the relevant data for the review.

Results: Epidemiologic studies have consistently shown that asthma and rhinitis often co-exist in the same patients, and rhinitis often precedes the onset of asthma. SIT has been shown to be effective as a curative treatment for these allergic diseases, but there is increasing evidence indicating that SIT also may have a preventive effect. A study of children monosensitized to house dust mites showed that immunotherapy altered the natural course of allergy in preventing the development of additional sensitizations.

Conclusions: At present, SIT seems to be the only treatment that may modify the course of the disease, either by preventing the development of new sensitivities or by altering the natural history of asthma. When SIT is introduced to patients with only allergic rhinoconjunctivitis, it may stop the development of asthma. SIT should be started early in the disease process, as soon as allergy has been diagnosed, to modify the spontaneous long-term progress of the allergic inflammation and disease.

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INTRODUCTION

Allergen specific immunotherapy (SIT) 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 (IT) was introduced to treat “pollinosis,” also known as allergic rhinitis, by Noon and Freeman in 1911.¹ There is good evidence that IT using inhalant allergens to treat seasonal or perennial allergic rhinitis and asthma is clinically effective. Guidelines and indications for SIT with inhalant allergens were published in 1998 by World Health Organization² following several other guidelines.

Allergic diseases usually affect multiple organs, and asthma and rhinitis often co-exist. The indications of SIT in allergic asthma and rhinitis have been separated in some guidelines.² This artificial separation has led to unresolved issues,^{3,4} possibly because the allergen-induced IgE-mediated reaction has not been considered to be a multi-organ disease. It is therefore important to consider SIT based on the allergen sensitization rather than on the target organ, and to discuss the efficacy of IT on combined lung and nasal symptoms.

Allergen SIT may have a preventive effect and act on the natural course of the disease. However, we need more studies to fully appreciate this effect.

OBJECTIVES OF IT IN ASTHMA

Asthma is a multifactorial and complex disease in which allergic factors and nonallergic triggers interact and

result in bronchial obstruction and inflammation. The inhalation of allergens leads to a complex activation of various cell types and the release of pro-inflammatory mediators. However, two different situations seem to exist. Although very few pollen grains can reach the lower airways, these allergens, carried on submicronic particles, frequently induce asthma via an IgE-mediated mechanism. Pollen-induced allergic reactions prolonged over several days almost always lead to nonspecific bronchial hyperreactivity (BHR) which is usually transient in patients only allergic to pollens, lasting from a few weeks to a few months after the end of the pollen season. In contrast, house dust mites and other perennial allergens induce a long-sustained inflammation of the bronchi leading to a variable degree of BHR, and symptoms are attributable to allergens, inflammation, and BHR. It has been shown that patients with chronic asthma present airways remodeling.⁵ Inflammation and airways remodeling may be involved in the accelerated decline of the pulmonary function characterized by a poorly reversible bronchial obstruction appearing after some decades of ongoing chronic asthma.⁶ Therefore, it is proposed that immunologic and anti-inflammatory treatments should be associated; but after a long course of the disease, inflammation becomes a major cause of symptoms, suggesting that the immunologic treatment should then be replaced by anti-inflammatory drugs. However, the airways remodeling in asthma patients may differ according to the etiology of the disease. It has been shown recently that patients with intrinsic asthma have a steeper rate of decline of the pulmonary function than those with extrinsic asthma.⁷

The natural history of asthma in children is not completely known but a large proportion of children with epi-

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sodic mild asthma will outgrow their symptoms within several years, whereas in those with a more severe form of the disease, asthma will persist later in life.⁸

These considerations suggest that 1) SIT may be more rapidly effective in patients allergic to grass pollen than in those sensitized to perennial allergens; 2) after a long course of the disease, patients with perennial asthma may have permanent airways abnormalities which can not be reversed by SIT; and 3) grass pollen allergy may be an adequate model to study the effects of SIT in patients with normal bronchi, whereas SIT in mite allergy may be used to examine the effects of the treatment in patients with a variable degree of bronchial inflammation and damage.

The major objectives of immunologic treatment are, in the short term, to reduce the allergic triggers precipitating symptoms, and, in the long term, to decrease bronchial inflammation and BHR when it is not too severe and when bronchial damage is not prominent. Further, at present, SIT seems to be the only treatment that might modify the course of the disease either by preventing the development of new sensitivities or by altering the natural history of asthma.

ASTHMA AND RHINITIS CO-EXIST IN THE SAME PATIENTS

The nasal and bronchial mucosa present similarities.^{9,10} Epidemiologic studies¹¹⁻¹⁴ have consistently shown that asthma and rhinitis often co-exist in the same patients. Many patients with allergic rhinitis have increased bronchial sensitivity to methacholine or histamine.¹⁵⁻¹⁷ There is a temporal relationship between the onset of allergic rhinitis and asthma, with rhinitis frequently preceding the development of asthma. Rhinitis more often appears before asthma in the case of occupational allergy to high molecular weight agents and small mammals.

Pathophysiologic studies have strongly suggested a relationship between rhinitis and asthma. The recent progress achieved in the cellular and

molecular biology of airways diseases has clearly documented that inflammation plays a critical role in the pathogenesis of asthma and rhinitis. A growing number of studies show that the inflammation of nasal and bronchial mucosa is sustained by a similar inflammatory infiltrate, which is represented by eosinophils, mast cells, T-lymphocytes, and cells of the monocytic lineage.^{5,18} The same pro-inflammatory mediators (histamine, CysLT), Th2 cytokines (interleukin [IL]-4, IL-5, IL-13, and granulocyte-macrophage colony-stimulating factor),¹⁹⁻²¹ chemokines (RANTES and eotaxin),^{22,23} and adhesion molecules²⁴⁻²⁶ seem to be involved in nasal and bronchial inflammation of patients with rhinitis and asthma. However, there are very few studies which have compared the nasal and bronchial mucosa in the same patients. In these, differences exist in the extent of the inflammatory indices, eosinophilic inflammation, and epithelial shedding being more pronounced in the bronchi than in the nose of the same patients suffering from asthma and rhinitis.²⁷ Inflammatory cells evaluated by sputum induction are present not only in the airways of patients with asthma but also in the airways of patients with seasonal allergic rhinitis, outside of season.²⁸ Airway remodeling exists microscopically in most, if not all, asthmatic patients⁵ but might not be so clearly evident in rhinitis. Endobronchial allergen challenge in patients with allergic rhinitis leads to an asthmatic response with recruitment of inflammatory cells and pro-inflammatory mediators.²⁹

These data have led to the concept that upper and lower airways may be considered as a unique entity influenced by a common, evolving inflammatory process, which may be sustained and amplified by interconnected mechanisms. Thus, it is important to consider asthma, rhinitis, and conjunctivitis as a single entity when IT is prescribed.

IT ALTERS THE COURSE OF ALLERGIC DISEASES

Although drugs are highly effective and usually without important side effects, they only represent a symptomatic treatment, whereas SIT is the only treatment that may alter the natural course of the disease.²

Long-term efficacy of SIT after it has been stopped has been documented for subcutaneous SIT.³⁰⁻³² Durham et al³² conducted a randomized, double-blind, placebo-controlled trial of the discontinuation of IT for grass-pollen allergy in patients in whom 3 to 4 years of this treatment had previously been shown to be effective. Scores for seasonal symptoms and the use of rescue antiallergic medication remained low after the discontinuation of IT, and there was no significant difference between patients who continued IT and those who discontinued it. However, in the study of Naclerio et al,³¹ 1 year after discontinuation of ragweed IT, nasal challenges showed partial recrudescence of mediator responses although reports during the season seemed to indicate continued suppression of symptoms. Long-term efficacy has yet to be documented for local SIT.

SIT has been used for the curative treatment of allergic diseases but there is increasing evidence indicating that SIT may have a preventive efficacy. Allergic sensitization usually begins early in life, and symptoms often start within the first decade. It has been shown that SIT is less effective in older patients than in children, and that inflammation and remodeling of the airways in asthma patients present a poor prognosis for an effective SIT. Further, if SIT is used as a preventive treatment, it should be started as soon as allergy has been diagnosed.³³

To determine whether SIT with standardized allergen extracts can prevent the development of new sensitizations, a prospective nonrandomized 3-year followup study was carried out in a population of asthmatic children under age 6 whose only allergic sensitivity was to house dust mites.³⁴ In this study, 22 children monosensitized to

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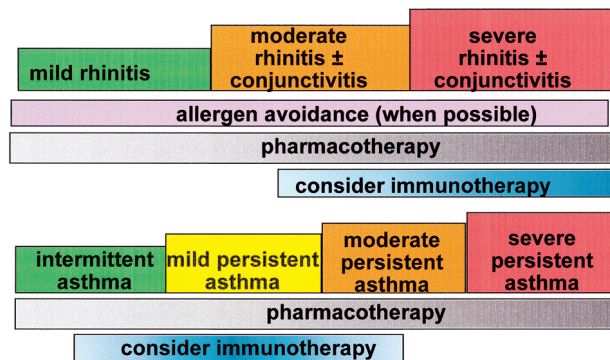


Figure 1. Indications of allergen SIT in rhinitis and asthma

house dust mites, who were receiving SIT with standardized allergen extracts, were compared with a control group of 22 other age-matched subjects monosensitized to house dust mites. Approximately 45% of the children receiving SIT did not develop new sensitivities whereas none of the children in the control group remained free of new sensitivities. This study suggested that SIT in children monosensitized to house dust mites alters the natural course of allergy in preventing the development of new sensitizations.

When SIT is introduced to patients with only allergic rhinoconjunctivitis, it may stop the development of asthma. The early study of Johnstone³⁵ with several different allergens showed that 28% of children receiving SIT developed asthma, compared with 78% of placebo-treated children who developed asthma. To answer the question, “does allergen SIT stop the development of asthma?” the Preventive Allergy Treatment (PAT) study has been started in children ages 7 to 13.³⁶ This study is a multicenter study taking place in Austria, Denmark, Finland, Germany, and Sweden. Results to date show that after 2 years of SIT, a significantly greater number of children in the control group developed asthma as compared with the active SIT group.

It is therefore proposed that SIT should be started early in the disease process to modify the spontaneous long-term progress of the allergic inflammation and disease.^{2,37,38}

EFFICACY OF SUBCUTANEOUS IT IN RHINITIS AND ASTHMA

Evidence-Based Medicine:

Randomized Controlled Trials in Rhinitis and Asthma

Randomized controlled trials in rhinitis and asthma (Table 1) have found that allergen SIT was effective in asthma induced by pollens, mites, and molds (evidence Ia, strength of recommendation A)⁴⁰; in rhinoconjunctivitis because of different pollen species (evidence Ib, strength of recommendation A)²; in rhinitis attributable to house dust mites (evidence Ib, strength of recommendation A)²; and in *Alternaria*-induced rhinitis (evidence Ib, strength of recommendation A).²

INDICATIONS OF IT IN ASTHMA AND RHINITIS

The treatment of allergic diseases is based on allergen avoidance, pharmacotherapy, allergen IT, 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. IT, where appropriate, should be used in combination with other forms of therapy with the hope that the patient will become as symptom-free as is medically possible.

Allergen IT 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 IT. Contraindications for inhalant allergen and venom IT may be absolute or relative.³⁷ Patient selection is important and efficacy must always be balanced against the risk of side effects. The necessity for initiating allergen IT 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 (Table 2).

Table 1. Classification Schemes of Statements of Evidence

Category of evidence	
Ia:	Evidence for meta-analysis of randomized controlled trials
Ib:	Evidence from at least one randomized controlled trial
IIa:	Evidence from at least one controlled study without randomization
IIb:	Evidence from at least one other type of quasi-experimental study
III:	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV:	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both
Strength of recommendation	
A:	Directly based on category I evidence
B:	Directly based on category II evidence or extrapolated recommendation from category I evidence
C:	Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D:	Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence

From Shekelle et al.³⁹

Table 2. Considerations for Initiating Immunotherapy

Presence of a demonstrated IgE-mediated disease
Positive skin tests and/or serum specific IgE
Documentation that specific sensitivity is involved in symptoms
Exposure to the allergen(s) determined by allergy testing related to appearance of symptoms
If required, allergen challenge with the relevant allergen(s)
Characterization of other triggers that may be involved in symptoms
Severity and duration of symptoms
Subjective symptoms
Objective parameters e.g. work loss, school absenteeism
Pulmonary function (<i>essential</i>): exclude patients with severe asthma
Monitoring of the pulmonary function by peak flow
Response of symptoms to non-immunologic treatment
Response to allergen avoidance
Response to pharmacotherapy
Availability of standardized or high quality vaccines
Contraindications
Treatment with β -blocker
Other immunologic disease
Inability of patients to comply
Sociologic factors
Cost
Occupation of candidate
Impaired quality-of-life despite adequate pharmacologic treatment
Objective evidence of efficacy of immunotherapy for the selected patient (availability of controlled clinical studies)

From the WHO Position Paper on Allergen Vaccines.²

CONCLUSION

In allergic rhinitis, IT is reserved for patients who experience a long course of the disease during the year, and/or patients who have severe symptoms and/or patients who require a substantial pharmacologic treatment. In asthma, IT is reserved for those patients with a mild disease usually well controlled by drugs, although the addition of drugs to control nasal and bronchial symptoms may increase potential side effects. Thus, it seems that the indications of IT are rather limited in asthma. However, because most asthmatic patients have persistent rhinitis, the indication of IT is largely supported in patients with moderate-to-severe rhinitis and mild asthma (Fig 1).

The use of allergen IT requires specialist evaluation, especially in children, because there are special problems and questions in this age group. IT started early in the disease process may modify the spontaneous long-term progress of the allergic inflammation and disease.^{37,38} IT is rarely started before the age of 5 years.

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