
Preventive aspects of immunotherapy: prevention for children at risk of developing asthma

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Objectives: This review describes the connection between hay fever and asthma in patients suffering from specific IgE-mediated allergy. The short-term and long-term benefits of allergen specific immunotherapy (SIT), including potential prevention of exacerbation of disease from hay fever into asthma, are discussed.

Data Sources: A review of literature on recent studies of SIT as treatment for allergic disease was conducted. Preliminary data emerging from the ongoing preventive allergy treatment study in Northern Europe are also presented.

Study Selection: The author's expert opinion was used to select relevant data.

Results: Treatment with allergenic vaccines (immunotherapy) resulted in decreased symptoms of allergic rhinitis, decreased development of new allergies, and less asthma in the treated group, compared with the untreated control group.

Conclusions: SIT performed with characterized and standardized allergen extracts in an optimal dosage has been shown to interfere with the basic mechanisms of the allergy, resulting in immediate symptomatic relief and offering the patient a long-lasting and preventive effect.

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INTRODUCTION

The number of people suffering from respiratory allergic diseases is increasing. Despite the fact that, in recent years, several new and potent drugs have been developed, the number of cases of asthma, as well as the severity of the disease, is increasing. For children, approximately 80% of all asthma is caused by Type I allergy, and for adults the rate corresponds to 50% or more.

THE LINK BETWEEN ALLERGY, HAY FEVER, AND ASTHMA

The connection between hay fever and asthma is evident.^{1,2} Many hay fever patients report seasonal lung symptoms, and >70% of asthma patients report nasal symptoms.^{3,4} Approximately 20% of all hay fever patients develop asthma later on in life.^{5,6} It has been found that up to 73% of hay fever

patients show bronchial hyperresponsiveness (BHR) outside the pollen season and almost 50% during the season.^{7–9} Rhinitis frequently precedes the onset of asthma^{4,10} and patients with allergic rhinitis and BHR have a high risk of developing asthma.¹¹ Development of BHR and atopy may be significant factors influencing the increased prevalence of asthma seen over the last decades.^{7,12} The connection between hay fever, asthma, and BHR is illustrated in Figure 1. How close these different symptoms go together remains to be documented.

It is important to understand the complexity of the allergic disease to offer the patient the optimal treatment. Allergic patients can be described in relation to the complex interaction between the allergic condition and the allergic disease. The disease can be hay fever and asthma. The allergic patient is sensitized to an allergen, but he will only experience his disease when exposed to that allergen. In contrast, a patient suffering from, for example, rhinoconjunctivitis does not know

whether his disease is caused by allergy, unless he is tested by one or more of the diagnostic methods available. The optimum treatment for allergy limits the primary symptoms and may also influence the basic allergy syndrome by changing the immunologic cause of the disease. By using medications that effect symptoms, clinical improvement occurs. However, the efficient diagnostic tools that are available today provide an excellent possibility to treat the patient in a specific way and change the course of the disease. The optimal treatment of inhalant allergy should include avoidance of allergens, elimination treatment, treatment of symptoms, and treatment of the immunologic cause of the allergic disease together with education of the patient (Fig 2).

THE SPECIFIC ALLERGY DIAGNOSIS AND TREATMENT

The diagnosis can only be made by using a combination of different tools. The most important methods for diagnosis of allergy are skin tests, performed with an optimal concentration of allergen extract, in vitro specific IgE tests, and, in case of doubt, relevant challenge tests. The information about time period for symptoms related to the biologic exposure sources indicates which allergen is important for the disease.

When the allergenic source responsible for the symptoms is known, avoidance or elimination treatment is compulsory. Absolute avoidance of pollen exposure is not possible, and it has been documented that exposure to pet allergens is hard to avoid. Although families may eliminate the pet from their homes, children in school environments are often exposed to lev-

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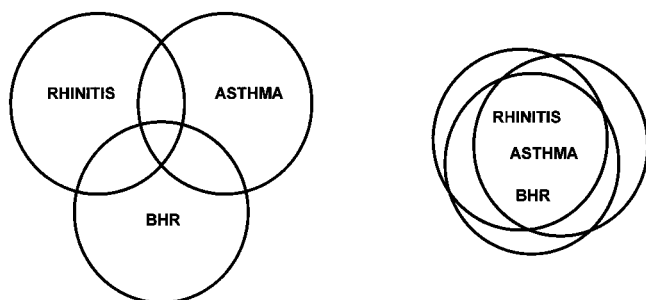


Figure 1. Illustration of the link between rhinitis, asthma, and BHR.

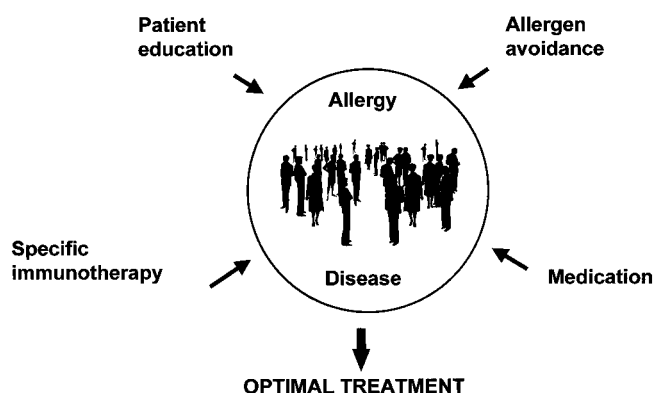


Figure 2. The concept of optimal treatment of the allergic patient.

els of allergens that give rise to sensitization, as well as symptoms.¹³

Specific immunotherapy (SIT) is the only treatment that interferes with the basic pathophysiologic mechanisms of the allergic disease.¹⁴ As is the case in many other pharmaceuticals, the exact mechanism of action is not described. Intensive research within the last decade has led to important information about clinical efficacy, influence on specific as well as nonspecific objective parameters, basic immunologic mechanisms, and inflammation, and has led to a recommended dose level of

major allergen.¹⁵ This recommended dose level is between 5 and 20 μ g of major allergen per maintenance dose injected. The fact that SIT is acting by influencing basic immunologic mechanisms has been documented in several studies. In birch pollen-allergic asthmatic patients, SIT resulted in a suppression of the seasonal increase in eosinophilic cationic protein.¹⁶ During a 4-year period of SIT, late-phase skin reaction was reduced in the active-treatment group compared with the placebo group following the clinical effect,¹⁷ and a shift from TH2 to TH1-

like response is initiated and maintained as a consequence of long-term treatment with SIT.^{18,19}

FOUR LEVELS OF CLINICAL BENEFITS

The documented efficacy of SIT can be described in four levels (Fig 3).

Early effect can be defined as the effects that the patients achieve immediately after the treatment has been initiated. Within 8 to 12 weeks after initiation of the treatment, when patients have reached the maximum dosage, these patients will experience clinical benefits when exposed to allergens.^{20,21}

Persisting effect can be defined as the persisting and potential further increased benefits that are achieved during a long-term treatment period of 3 to 5 years.^{17,22} Several studies have shown that continuing the treatment >12 months gives an additional clinical improvement of the patient's disease, introducing nonspecific efficacy parameters, as a decrease in the patient's nonspecific bronchial BHR.²³ It has recently been shown that the indirect beneficial TH2 and TH1 response back toward normal is achieved after a 12-month treatment period, not after just 3 months, despite documented symptomatic effects.¹⁹

Long-term clinical effect after termination of 2 to 3 years of SIT has been shown for grass pollen and tree pollen as well as animal hair and dander (Table 1). In one followup study on grass pollen-allergic patients, it was shown that patients suffering from rhinoconjunctivitis, with or without mild-to-moderate seasonal asthma, consistently experienced significantly decreased symptoms during seasonal exposure 5 years after termination of SIT.²⁴ A similar study with birch pollen-allergic patients showed effect after 2 years of SIT on asthma and hay fever symptoms as well as on nasal sensitivity.²⁵ This study confirms that the clinical effect persists for a period of at least 6 years after termination of SIT. The patients had significantly fewer symptoms comparable with the level at the termination of SIT, despite

- **Early effect**
 - effect achieved after initiation of SIT
- **Persisting effect**
 - effect persisting during SIT
- **Long-term effect**
 - effect after termination of SIT
- **Preventive effect**
 - prevention of new sensitivities and exacerbation of disease

Figure 3. Documented efficacy levels of SIT.

Table 1. Follow-up studies with characterized, standardized allergen extracts

Author	Allergen (species)	Dose (μ g)	Patients (N)	Time (months)	Followup (years)
Mosbech ²⁴	Grass	20	35	28	6
Jacobsen ²⁶	Birch	12	32	36	6
Durham ²⁸	Grass	20	36	36 & 48	3
Hedlin ²⁷	Cat/dog	15 & 8	32	36	5

the fact that exposure during the followup season was 75 times higher than at the season of inclusion. None of the patients who initially suffered only from hay fever developed asthma during the study period.²⁶ Hedlin et al²² found that cat-allergic patients with mild-to-moderate asthma not only reduced their reactivity to cat allergen, but also reduced specific as well as nonspecific hyperresponsiveness. The followup study 5 years after termination of SIT showed the effect was persistent with regard to exposure to cats as well as nonspecific hyperresponsiveness.²⁷

A recently published, double-blind, placebo-controlled, randomized long-term followup study on grass pollen immunotherapy patients demonstrated that the clinical improvement achieved after a treatment period of 3 to 4 years persisted at least 3 years after termination of SIT.²⁸

The preventive effect of SIT, ie, the potential to change the natural course of the allergic disease by preventing the exacerbation from hay fever to asthma and the onset of new sensitivities, is being investigated. In a study by Bauer et al²⁹ it was demonstrated that fewer patients suffering only from hay fever develop nonspecific BHR if treated with SIT, and Johnstone³⁰ showed, in an uncontrolled long-term study on the preventive potential of SIT, a reduction in the number of children who developed asthma.

The ongoing preventive allergy treatment study has been designed to show whether SIT can prevent the development of asthma in children suffering from allergic rhinoconjunctivitis caused by allergy to birch and/or grass pollen. More than 200 children, ages 6 to 14 years, are included in the preven-

tive allergy treatment multicenter study in 6 centers in Austria, Denmark, Finland, Germany, and Sweden. They all had positive skin tests with birch and/or grass pollen circulating specific IgE antibodies to the relevant allergens, and a positive conjunctival provocation test. The patients had no clinically important allergies to other pollens or perennial allergens. The children were randomized to the active treatment group and received immunotherapy with birch and/or grass pollen for 3 years. Maintenance injections were given every 6 weeks ($\pm$ 2 weeks). The content of major allergen in maintenance injections corresponds to 20 μ g (grass *Phl p*V) and 12 μ g (birch, *Bet v*I; Alutard SQ, ALK-Abelló, Hørsholm, Denmark). The control group was treated with optimal symptomatic medication. The patients were included in the study from 1992 to 1994. A high degree of BHR during seasonal exposure at the 0-season (inclusion) was found. Based on the 0-season level of BHR and the revision of the clinical diagnosis of asthma, it was found that several patients had mild asthma. Among those patients without any clinical sign of asthma before initiation of SIT, the actively treated children had significantly less asthma after 2 years as evaluated by clinical symptoms, visual analog scale and methacholine bronchial provocation test than controls. Symptoms of hay fever and conjunctival provocation test results improved in the SIT group compared with the control group. In conclusion, these preliminary results support the hypothesis that SIT in children with allergic rhinoconjunctivitis has a preventive effect on later development of asthma.

CONCLUSION

Specific allergy treatment in the form of SIT performed with characterized and standardized allergen extracts in an optimal dosage is, so far, the only treatment for allergic diseases that has been shown to interfere with the basic mechanisms of the allergy and to offer the patient a long-lasting and preventive effect.

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