How Strong is the Evidence That Immunotherapy in Children Prevents the Progression of Allergy and Asthma?

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Abstract and Introduction

Abstract

Purpose of Review: The purpose of this review is to describe the scientific evidence that specific immunotherapy can prevent the development of asthma in patients suffering from rhinoconjunctivitis as well as reduce the number of new allergies developing.
Recent Findings: Proposed strategies for the prevention of the development of allergic rhinoconjunctivitis and asthma include allergen avoidance, pharmacological treatment (antihistamines and steroids) and specific immunotherapy. Long-term follow-up on immunotherapy studies demonstrates that specific immunotherapy for 3 years shows persistent long-term effects on clinical symptoms after termination of treatment and long-term, preventive effects on later development of asthma in children with seasonal rhinoconjunctivitis. It is so far the only treatment for allergic diseases that has been shown to be able to prevent worsening of disease and development of asthma. Also, specific immunotherapy seems to reduce the development of new allergic sensitivities as measured by the skin prick test as well as specific IgE measurements.
Summary: Specific immunotherapy is the only treatment that interferes with the basic pathophysiological mechanisms of the allergic disease and thereby carries the potential for changes in the long-term prognosis of respiratory allergy. Specific immunotherapy should be recognized not only as first-line therapeutic treatment for allergic rhinoconjunctivitis, but also as secondary preventive treatment for respiratory allergic diseases.

Introduction

Symptoms of allergic rhinitis and asthma are caused by an exacerbation of continuously ongoing inflammation driven by natural immunological mechanisms. This reaction causes antigen-mediated activation of mast cells, basophils and eosinophils.

Understanding the complexity of the allergic disease is crucial in order to offer the patient with allergy the optimal treatment that interacts with the basic immunological condition as well as the symptomatology. The optimum treatment of allergy increases quality of life by reducing the primary symptoms and the need for medication, but the treatment should also influence the basic immunological allergy syndrome by changing the immunological condition. Symptomatic drugs may decrease symptoms; however, the diagnostic tools available offer excellent possibilities for treating the patient in a specific way and changing the natural course of the systemic disease. The treatment of inhalant allergy, together with education of the patient, should include avoidance of allergens,

elimination treatment, treatment of symptoms and allergen specific immunotherapy (SIT) as the treatment of the immunological cause of the allergic disease.

Allergy, Rhinitis and Asthma

A close relation exists between allergic rhinitis and allergic asthma,[1,2] and the comorbidity of upper and lower airway diseases is carefully described.[3] A European survey covering 7000 allergy patients showed that 80% of patients with typical asthma symptoms also reported nasal symptoms and 40% of rhinitis patients reported coexisting asthma.[4] Allergic rhinitis is a major risk factor for later development of asthma.[5-7] More than 20% of all rhinitis patients develop asthma later on in life.[8-11] Many rhinitis patients have increased bronchial hyperresponsiveness (BHR) during and as well as outside the pollen season.[12-15] Even when exposure to allergens is below the level that usually leads to symptoms, allergic patients have a persistent minimal level of ongoing inflammation.[16]

Rhinitis, asthma and BHR are closely related, and a systemic pathway, involving the bloodstream and bone marrow, contributes to the cross-talk between upper and lower airways.[17] This is the basis for the diagnosis of the allergic patient and the choice between treatments available.[18] How close the connection is between rhinitis, asthma and BHR should be further described, although knowledge from epidemiological surveys underlines this relation. Allergic sensitivities usually increase with age from childhood to adulthood and monosensitized children are likely to become polysensitized with time,[19] and being sensitized to one allergen source also increases the risk of appearing with more allergic sensitivities over time.[20]

Allergen Specific Immunotherapy

SIT is the only treatment that interferes with the basic pathophysiological mechanisms of the allergic disease.[21]

Intensive research has led to important knowledge about clinical efficacy, safety, influence on specific as well as nonspecific objective parameters, basic immunological mechanisms and inflammation which has then again resulted in recommended dosing of the major allergen.[22]

SIT acts by influencing basic immunological mechanisms,[23] thus resulting in the suppression of the seasonal increase in eosinophilia;[24] late-phase reactivity is reduced,[25] and a shift from a T helper 2 to T helper 1-like response is initiated and maintained.[26-29]

Evidence for Prevention Of Asthma

The 14-year long-term follow-up study in children by Johnstone and Dutton[30] investigated SIT for prevention of exacerbation and development of asthma. A highly significant reduction in the number of patients with asthma was reported at the time of follow-up, which corresponded to the time of the children's 16th birthday. Only 22% of the placebo-treated children were free of asthma compared with 72% of the SIT-treated children. The children were initially treated for 4 years with individual mixtures of allergens and the clinical effect as well as the potential prevention of asthmatic symptoms were dose related, being strongest in children who received the highest doses of allergen. In children with allergy to grass and only suffering from allergic rhinitis, Bauer[31] demonstrated that fewer patients developed nonspecific BHR if treated with SIT. In this study the children were treated for 2 years with standardized grass pollen allergen extract. They reported reduced development of seasonal BHR to histamine, which after 2 years, treatment was highly significant.

In a study of the effect of immunotherapy in patients with allergic rhinoconjunctivitis caused by house dust mite

allergy, Grembiale *et al.*[32] selected children and adults with coexisting BHR for a 2-year placebo-controlled study. They found that immunotherapy reduced the provocative dose of metacholine four fold in actively treated patients compared with the placebo group. As a secondary outcome of the study they reported that none of the SIT-treated patients had developed symptoms of asthma during the 2-year study period.

The long-term asthma preventive potential of SIT was first described in the study by Jacobsen *et al.*[33] in which 36 adult patients received immunotherapy with standardized tree pollen allergen extracts for 2 years. During the long-term follow-up of 6 years after the termination of treatment it was found that none of the patients initially suffering from only rhinitis had developed asthma during the total study period of 8 years.

The Preventive Allergy Treatment (PAT) study[15] was the first prospective randomized controlled long-term follow-up study designed to show whether SIT can prevent the development of asthma in children suffering from seasonal allergic rhinoconjunctivitis caused by allergy to birch and/or grass pollen. SIT was given for 3 years after which the children were evaluated for the development of asthma. In total, 208 children, 6-14 years old, with grass and/or birch pollen allergy but without any other clinically important allergy were included in this study. After the initial season the children were randomized either to receive SIT for 3 years or to an open control group. Standardized allergen preparations were given every 6 ± 2 weeks. The contents of major allergen per maintenance injection corresponded to 20 µg Phl p V (grass) and 12 µg Bet v I (birch). The development of asthma was monitored through clinical evaluation, and metacholine bronchial provocation tests were carried out during the relevant season(s) and during winter.

Although patients with an indication of perennial or seasonal asthma were excluded, it was found as a consequence of the careful study examination that 20% of the children had mild asthma symptoms during the base pollen season(s) and that more than a third had a significant seasonal ongoing BHR as measured by metacholine challenge. Among those without asthma at baseline, the group treated with SIT had significantly less asthma after 3 years as evaluated by clinical symptoms (odds ratio = 2.52; $P<0.001$) and also less hyperresponsiveness to metacholine ($P<0.05$).

One study using sublingual immunotherapy (SLIT) has investigated the potential prevention of the development of asthma in children suffering from grass pollen allergic rhinoconjunctivitis.[34] In this open randomized trial children aged 5-14 years were treated for 3 consecutive years (4 months every year) sublingually with a standardized mixture of five grasses with a daily dose corresponding to 0.5 µg major group 5 allergen. The study reports that after 3 years of SLIT eight of 45 actively treated subjects and 18 of 44 controls had developed asthma, corresponding to a common relative risk of development of asthma in the control group of 3.80 ($P<0.05$).

Based on these studies the experimental evidence for prevention of asthma in patients with allergic rhinitis during the course of treatment is Ib for allergen SIT.[35] Together with the long-term clinical experience available, we regard SIT as an important treatment for the prevention of asthma in patients with allergic rhinitis.

Evidence for The Prevention Of New Allergies

Johnstone and Crump[36] reported in 1961 that subcutaneous immunotherapy (SCIT) could reduce the risk of development of allergic sensitivities as they found that no children developed new IgE sensitivities during a 4-year course of high-dose immunotherapy compared with 25% with new sensitivities in the control group. Several studies using SCIT have confirmed these findings. Two studies have shown the reduction in newly appearing sensitivities in children treated for house dust mite allergy. Monosensitized children treated for 3 years with SIT showed a significant reduction in new allergic sensitivities compared with nontreated controls. In the immunotherapy-treated group approximately 45% did not develop any new sensitivity at all, whereas none of the control patients remained free of the development of one or more new sensitivities as measured by the skin prick test and allergen specific IgE antibodies.[37] In 134 monosensitized asthmatic children allergic to house dust mites, 75 children were treated with a mixture of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* (50/50) for 3 years, and 63 children acted as controls. Three years after termination of immunotherapy,

66% of the control group children had developed one or more new sensitivities as measured by the skin prick test and specific IgE compared with only 25% with new sensitivities in the SIT group.[38]

For 4 years, 7182 monosensitized patients suffering from allergic rhinitis and/or asthma were treated with SCIT and 1214 were included as open controls treated only with symptomatic drugs. Almost half of the patients (44%) were monosensitized to either *D. pteronyssinus* or *D. farinae* and 53% were monosensitized to grasses or *Parietaria* and 3% to mugwort, olive or trees. After treatment, 68% of controls had developed one or more new sensitivities (skin prick test and specific IgE) compared with 27% with new sensitivities in immunotherapy-treated patients. At follow-up 3 years after termination of the treatment period, 75% of controls had developed new sensitivities compared with 25% in the active group.[39]

In a randomized open study with SLIT, 511 patients with allergic rhinitis with or without intermittent asthma were randomized to drugs only or drugs plus SLIT for 3 years. In this study SLIT appeared to prevent the onset of new allergic sensitizations as determined by skin prick testing. At the end of the treatment period, one or more new skin sensitizations appeared in 16 of 271 (5.9%) patients of the SLIT group and in 64 of 170 (38%) patients of the control group (P<0.001).[40]

The level of evidence for allergen SIT according to these studies is Ib for SCIT and IIA for SLIT.[35] Immunotherapy seems to reduce the development of new allergic sensitivities as measured by the skin prick test as well as specific IgE measurements. Although the exact mechanism for the reduced number of new sensitizations is not clear, the potential for the long-term prognosis of the disease should be taken into consideration. Also, a potential connection between development of new sensitizations and the development of asthma is of interest.

Evidence for Long-term Prevention

The 5 and 10-year follow-ups on the PAT study are the first prospective follow-up studies testing whether SIT can prevent the long-term development of asthma, and whether the clinical effects persist in children suffering from seasonal allergic rhinoconjunctivitis caused by allergy to birch and/or grass pollen as these children grow up. The total SIT period was 3 years, after which the children were evaluated for development of asthma. The patients were re-evaluated after a total of 5 years. The evaluation showed that immunotherapy reduces progression from allergic rhinoconjunctivitis to asthma after 3 years of SIT[15] and at the 5-year follow-up 2 years after SIT termination.[41**] The actively treated children had persistently significantly less asthma at the 5-year follow-up (odds ratio = 3.1; P<0.01). The significant improvements in allergic rhinoconjunctivitis symptom and medications scores as well as in the conjunctival sensitivity to birch and grass observed to persist at the 5-year follow-up also persisted at the 10-year follow-up. As at the 5-year follow-up, fewer actively treated subjects had developed asthma at the 10-year follow-up as evaluated by clinical symptoms (odds ratio = 2.5; 95% confidence interval = 1.1-5.9).[42**] The longitudinal treatment effect when adjusted for BHR and asthma status at baseline including all observations at 3, 5 and 10-year follow-up (all children with or without asthma at baseline, N = 189; 511 observations) was highly statistically significant (P = 0.0075). The odds ratio for no asthma was 4.6 (95% confidence interval = 1.5-13.7) in favor of SIT. This analysis also showed that BHR at baseline was associated with increased risk of later development of asthma (P = 0.002).

A potential association between development of new perennial allergic sensitivities and development of asthma was analyzed. Of those children who developed asthma during the 10-year follow-up, 30% (18 of 61) also developed a positive skin prick test to house dust mites compared with 17% (15 of 86) of the children who did not develop asthma. The difference was not significant. The same picture was demonstrated for development of sensitivity to cat or dog allergens.

The category of evidence for the long-term effect of SIT is Ib.[35] The preventive effect of a 3-year course of SIT on the development of asthma along with long-term clinical effects persisting at 10-year follow-up after

termination of the treatment in children with seasonal allergic rhinoconjunctivitis is an important indication for SIT. Since BHR in children with seasonal allergic rhinitis is significantly related to an increased risk for later development of asthma it could be considered to include evaluation of BHR in the indication of immunotherapy.

Discussion

Strategies for the prevention of the development of allergic rhinoconjunctivitis and asthma including allergen avoidance, pharmacological treatment (antihistamines and steroids) and SIT have been proposed. Allergen avoidance is not possible for grass and birch pollen allergy, and only a limited reduction in exposure can be achieved by modification of life habits. An inverse relationship between levels of allergen exposure in early life and allergy symptoms has been indicated in some studies, suggesting that exposure to high levels of allergen may provide protection against sensitization.[43-45] These aspects must be further investigated.

Prevention, addressing diseased children to prevent symptoms and further disease progression, involves traditional pharmacotherapy with antihistamines. Although antihistamines provide symptomatic relief and some disease control, these drugs do not modify long-term outcomes in children as the natural course of the disease is not altered.[46]

Preventive measures for worsening of asthma by early treatment with inhaled steroids in children with episodic wheezing have been suggested, but recent studies on the capacity of inhaled steroid therapy during early symptomatic episodes of wheezing to delay progression to persistent disease have failed to show any preventive potential.[47*,48]

The PAT study demonstrated that children with allergic rhinitis and BHR at baseline were those most likely to develop asthma, demonstrating that BHR may predict the risk for later asthma development. The study also investigated whether development of new perennial allergen sensitivities was associated with the development of asthma. Although data indicated that more children with asthma had developed sensitivity to house dust mites, the study cannot confirm this hypothesis and further investigations must be initiated.

Conclusion

Long-term follow-up on immunotherapy studies demonstrates that SIT for 3 years with high doses of standardized allergen extracts shows persistent long-term effects on clinical symptoms after termination of treatment and long-term, preventive effects on later development of asthma in children with seasonal rhinoconjunctivitis. It is so far the only treatment for allergic diseases that has been shown to be able to prevent worsening of disease and development of asthma. In this light, SIT should be recognized not only as first-line therapeutic treatment for allergic rhinoconjunctivitis, but also as secondary preventive treatment for respiratory allergic diseases.

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Abbreviation Notes

BHR = bronchial hyperresponsiveness; PAT = Preventive Allergy Treatment; SCIT = subcutaneous

immunotherapy; SIT = specific immunotherapy; SLIT = sublingual immunotherapy.

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