

PREVENTIVE ASPECTS OF SPECIFIC IMMUNOTHERAPY

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Symptoms of allergic respiratory diseases are caused by an exacerbation of an ongoing inflammatory process driven by immunological mechanisms related to an antigen-mediated activation of mast cells, basophils and eosinophils.

It is important to understand the complexity of the allergic disease in order to offer the patient optimal treatment. Allergic patients can be described in relation to the complex interaction between the allergic condition and the allergic disease. The optimum treatment of allergy reduces the primary symptoms and need for medication, but may also influence the basic allergy syndrome by changing the immunological cause of the disease. Symptomatic drugs may decrease symptoms; however, the efficient diagnostic tools available today offer excellent possibilities of treating the patient in a specific way to change the course of the disease. Optimal treatment of inhalant allergy should include avoidance of allergens, environmental allergen elimination, treatment of symptoms and immunotherapy as the treatment of the immunological cause of the allergic disease, together with education of the patient. Specific immunotherapy (SIT) is the only treatment that interferes with the basic pathophysiological mechanisms of the allergic disease.¹

Intensive research within the last decade has led to important knowledge about clinical efficacy, the influence on specific as well as non-specific objective parameters, basic immunological mechanisms and inflammation which has resulted in a recommended dose level of major allergen.² This recommended dose level is between 5 and 20 µg major allergen per maintenance dose injected. The fact that SIT acts by influencing basic immunological mechanisms has been documented in several studies. In birch pollen allergic asthmatics SIT resulted in a suppression of the seasonal increase in eosinophilic cationic protein.³ During a 4-year period of SIT, late-phase skin reaction following the clinical effect was reduced in the active-treatment group compared with the placebo group,⁴ and a shift from T-helper (TH)2- to TH1-like response was initiated and maintained as a consequence of long-term treatment with SIT.^{5,6}

ALLERGY, HAY FEVER AND ASTHMA

The connection between hay fever and asthma has been described in several papers^{9,10} and the comorbidity of upper and lower airway diseases was recently carefully described by WHO.¹¹ In a European survey covering 7 000 allergy patients we found that 80% of patients with typical asthma symptoms also reported nasal symptoms, and 40% of hay fever patients reported coexisting asthma.¹² Allergic rhinitis is a major risk factor for later development of asthma.^{13,14} More than 20% of all hay fever patients develop asthma later on in life,^{15,16} and it has been found that rhinitis frequently precedes the onset of asthma.^{17,18} Many hay fever

patients have increased bronchial hyperresponsiveness (BHR) both during and out of the pollen season.^{19,21} Development of BHR and atopy may be significant factors influencing the increased prevalence of asthma seen over the last decades.^{19,22} It has also been shown that even when exposure to allergens does not produce clinical symptoms, allergic patients have a constant level of ongoing inflammation.²³

Hay fever, asthma and BHR are closely related and a systemic pathway, involving bloodstream and bone marrow, contributes to the cross-talk between upper and lower airways.²⁴ This is important for the diagnosis of the allergic patient and the choice between the various combinations of treatments available.²⁵ How closely these different symptoms interrelate remains to be described, although it seems that the more knowledge obtained from epidemiological surveys, the closer the connection between upper and lower airway diseases appears to be. Allergic sensitivities usually increase with age, from childhood to adulthood, and monosensitised children are likely to become polysensitised with time.²⁶

CLINICAL BENEFITS OF SPECIFIC IMMUNOTHERAPY

The documented efficacy of SIT can be described at four levels:

- **Early effect**
 - reduction in symptoms/need for medication
- **Persisting effect**
 - reduction in symptoms/need for medication
 - reduction in hyperresponsiveness/late-phase response
- **Long-term effect**
 - persistently reduced symptoms/need for medication
 - persistently reduced hyperresponsiveness/late-phase response
- **Preventive effect**
 - prevention of new sensitivities and exacerbation of disease (rhinitis into asthma)

Early effect

At 8 - 12 weeks after initiation of the treatment, when patients have reached the maintenance dosage, they will experience a reduction in allergy symptoms and need for rescue medication.^{27,28}

Persistent effect

Persisting and potential further increased benefits are achieved during a long-term treatment period of 3 - 5 years.^{4,29} Continuing the treatment for more than 12 months introduces non-specific efficacy parameters, seen as a decrease in the patient's non-specific BHR.³⁰ A TH2/TH1 response towards normal balance is achieved after a 12-month treatment period, but not after 3 months despite documented symptomatic effects.⁶

Long-term effect

Up to 8 years' persistent long-term clinical effect after termination of 2 - 3 years of SIT has been shown for

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grass pollen and tree pollen, as well as animal hair and dander.^{29,31-33} In one study none of the patients who initially suffered from hay fever alone developed asthma during the treatment and follow-up period.³² Cat allergic patients with mild to moderate asthma not only reduced their reactivity to cat allergen following immunotherapy, but also reduced specific as well as non-specific BHR during the 5-year follow-up period.³⁴ A recently published, double-blind, placebo-controlled randomised long-term follow-up on grass pollen immunotherapy patients demonstrated that the clinical improvement as well as late-phase skin response to allergen challenge after a treatment period of 3 - 4 years had persisted for at least 3 years after termination of SIT.³³

Preventive effect

The preventive effect of SIT, i.e. 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 currently being investigated.

PREVENTION OF ASTHMA

In a study by Bauer *et al.*³⁵ it was demonstrated that fewer patients suffering from hay fever alone develop non-specific BHR if treated with SIT, and Johnstone and Dutton³⁶ showed a reduction in the number of children who developed asthma in an uncontrolled long-term study investigating the prophylactic potential of SIT.

The preventive allergy treatment study (PAT)³⁷ has been 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. Two hundred and eight children, 6 - 14 years old (mean 10.7 years), with grass and/or birch pollen allergy but without any other clinically important allergy, from 6 paediatric allergy centres were included in this study. All had moderate to severe hay fever symptoms but at the time of inclusion none reported asthma requiring daily treatment. After the initial season, 205 children were stratified and randomised to receive either SIT for 3 years or to an open control group. SIT depot preparations were given every 6 weeks (+/- 2 weeks) for a total period of 3 years. The contents of major allergen per maintenance injections (Alutard SQ 100.000 SQ units/ml) corresponded to 20 µg *Phl p V* (grass) and 12 µg *Bet v I* (birch). Both groups received symptomatic treatment limited to oral loratadine, topical levocabastine or sodium cromoglycate, and, in cases unresponsive to these drugs, nasal budesonide. The development of asthma was monitored through clinical evaluation and a postseasonal visual analogue scale. Methacholine bronchial provocation tests were carried out during the relevant season(s) and during winter. Conjunctival provocation tests were done before SIT and then every year at the same time during the study.

Before the start of SIT, 20% of the children had mild asthma symptoms during the pollen season. Among those without asthma before immunotherapy, the actively treated children had significantly less asthma after 3 years as evaluated by clinical symptoms (odds ratio 2.52; $p < 0.001$), visual analogue scale ($p < 0.001-0.05$) and out-of-season methacholine bronchial provocation test ($p < 0.05$). Symptoms of hay fever and conjunctival provocation test results improved significantly in the SIT group as compared with the control group.

PREVENTION OF NEW ALLERGIES

The first study that showed the capacity of immunotherapy to reduce the risk of development of new allergies was published in 1961.³⁸ Johnstone and

Crump found that none of the children undergoing a 4-year course of immunotherapy developed new IgE sensitivities compared with 25% in the control group. Recent studies have confirmed these findings. In house-dust mite monosensitised children treated for 3 years with immunotherapy, a significant reduction in the development of new allergies was found, and in the treated group about half of the patients did not develop any new sensitivities at all.³⁹ A recent controlled study including 138 monosensitised children allergic to house-dust mites found that only 33% of control children did not develop new sensitivities compared with 75% in the immunotherapy-treated group. The majority of new sensitivities that developed were against various pollens.⁴⁰ Among grass pollen monosensitised patients it has been shown that immunotherapy can reduce the risk for development of more allergies even 5 years after termination of a 3-year course of treatment.⁴¹ A large retrospective study including more than 8 000 monosensitised patients suffering from rhinitis and/or asthma has recently confirmed the reduced risk for new allergies as a result of SIT for 4 years and at follow-up 3 years after termination of the treatment. During treatment 68% of controls had developed one or more new sensitivities compared with 27% of 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.⁴²

MECHANISMS OF PREVENTION

Although much knowledge about the effects and mechanisms of immunotherapy is available and intensive research is ongoing, our understanding of the preventive capacity is not yet complete. The fact that allergy is a systemic condition that leads to typical respiratory symptoms could explain why immunotherapy can prevent exacerbation of the disease. Immunotherapy does not limit its anti-inflammatory potential to a single organ. Through a systemic reduction of the immune system's capacity to initiate the allergic cascade leading into a local inflammatory condition, immunotherapy could prevent hyperresponsiveness and inflammation from occurring in an organ. By changing the immune response in allergic patients towards a 'normalised' TH1 and T-regulatory cell response, symptoms that would have appeared under normal conditions are prevented, i.e. rhinitis does not develop into asthma.

It is not clear how the risk of developing new sensitivities is reduced. The immunological response to immunotherapy is specifically related to the antigen with which we treat the patient. A reduction in positive IgE sensitivities may not be related to an allergen-specific mechanism, but may be a consequence of reduced hyperresponsiveness. Allergen-induced hyperresponsiveness seems not to be related to only one organ type, but to have a systemic impact, and can occur in the nose, the lungs or the skin. Durham *et al.*⁴³ have shown that immunotherapy results in a smaller number of mast cells in the skin, and not only locally but also in peripheral blood it has been documented that the immunological response is pushed towards a TH1-like cytokine response.⁶ On the other hand, one could also speculate that the prevention of new allergies is indirectly the reason for the fact that pollen-induced rhinoconjunctivitis does not develop into asthma since asthma is very often caused by perennial allergies.

CONCLUSION

Besides the very significant clinical effect and long-lasting benefit of SIT, it has been shown in several well-controlled studies that immunotherapy does reduce the risk of developing new allergic sensitivities and

does reduce the risk of developing asthma for children suffering from hay fever.

The immunological mechanisms involved in prevention require further investigation, which needs to focus on the rationale for the inability to initiate a new IgE response, and the importance of reduced hyperresponsiveness in the nose, lungs and skin, as well as the impact of the basic influence of immunotherapy on the T-cell response. Time of onset seems to be a very important factor when estimating the prophylactic potential of immunotherapy. The studies described in this paper show a prophylactic potential in children as well as adults. It is important that in all studies referred to, the severity of the allergic symptoms were described as mild to moderate. Allergic respiratory diseases often progress in severity over time in the individual patient. Therefore it is important to consider immunotherapy early in the development of the allergic disease when the prophylactic potential is optimal, and the majority of symptoms are caused by IgE-mediated reactions and inflammation.^{1,44} The preventive capacity of immunotherapy also seems to be related to duration of treatment. A 3 - 5 year course of high-dose allergen administration has been shown to prevent exacerbation of allergic diseases and development of new allergic sensitivities.

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