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Preventive Aspects of Specific Immunotherapy

Lars Jacobsen

Allergy, Hay Fever and Asthma

The existence of a link between hay fever and asthma has been described in several papers [1,2] and the co-morbidity of upper and lower airway diseases was recently carefully described by WHO [3]. In a European survey including 7000 allergy patients we found that 80% of the patients suffering from typical asthma symptoms also reported nasal symptoms and 40% of hay fever patients reported coexisting asthma [4]. Allergic rhinitis is a major risk factor for later development of asthma since 20% of all hay fever patients develop asthma later on in life [5,6]. Furthermore, rhinitis frequently precedes the onset of asthma [7,8]. Many hay fever patients have increased bronchial hyperresponsiveness during as well as outside the pollen season [9-11]. Development of bronchial hyperresponsiveness (BHR) and atopy may be significant factors influencing the increased prevalence of asthma seen over the last decades [9,12]. It has also been shown that even when exposure to allergen is below level that causes symptoms allergic patients have a constant minimal level of ongoing inflammation [13].

The connection between hay fever, asthma and BHR is close and relevant for the diagnosis of allergic diseases and the choice of optimal combination of treatments [14].

Clinical Benefits of Specific Immunotherapy

The documented efficacy of specific immunotherapy can be divided into 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

Eight to twelve 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 [15, 16].

Persistent Effect

Persisting and potential further increased benefits are achieved during a long-term treatment period for 3 to 5 years [17, 18]. Continuing the treatment for more than 12 months introduce non-specific efficacy parameters, seen as a decrease in the patient's non-specific bronchial hyperresponsiveness BHR [19]. A TH2/TH1 response back towards normal balance is achieved after a 12 months treatment period, and not after just 3 months despite documented symptomatic effects [20].

Long-Term Effect

Up to eight years persistent long term clinical effect after termination of 2-3 years SIT has been shown for grass pollen, tree pollen as well as animal hair and dander [21-24]. In one study none of the patients who initially suffered only from hay fever developed asthma during the treatment and follow up period [22]. 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 hyperresponsiveness during the 5-year follow up period [23]. A recently published, double-blind, placebo-controlled randomized 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 to 4 years was persisting at least 3 years after termination of SIT [24].

Preventive Effect

Prevention 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. it was demonstrated that fever patients only suffering from hay fever develop non-specific bronchial hyperresponsiveness if treated with SIT [25], and Johnstone showed in an uncontrolled long term study on the prevention potential of SIT a reduction in the number of children who developed asthma [26].

The preventive allergy treatment study (PAT) [27] 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 with pollen allergy but without asthma were included in the study. Allergy centers were involved in the study, but at inclusion all children were symptom free. During the initial season, two hundred and eighty children received either specific immunotherapy or placebo. The contents of major allergens (in units/ml) corresponded to the dose received symptomatically. Sodium cromoglycate was given during the development of asthma. The visual analogue scale was used during the relevant season. The study was terminated before the specific immunotherapy study period.

Before the start of the pollen season(s). A total of 151 children (n=151), the actively treated group was evaluated by clinical symptoms (p=0.05), and out of season symptoms of hay fever and conjunctivitis. Specific immunotherapy

Prevention of new

The first study that investigated the development of new sensitivities in children during immunotherapy compared to findings. In house dust immunotherapy, a significant group about half of the recent controlled studies on mites found that only 25% compared to 75% in sensitivities that developed within the sensitized patients it has been found that more allergies even in [31]. A large retrospective study of children suffering from rhinitis and conjunctivitis found that new allergies as well as three years after termination of treatment developed one or more new allergies. At follow up the controls had developed

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 six pediatric allergy centers were included in this study. All had moderate to severe hay fever symptoms, but at inclusion none reported asthma with need of daily treatment. After the initial season, two hundred and five children were stratified and randomized to receive either specific immunotherapy for three years or to an open control group. SIT depot preparations were given every six weeks ($\pm$ 2 weeks) for a total period of three years. The contents of major allergen per maintenance injection (Alutard SQ 100.000 SQ units/ml) corresponded to 20 μ g *Phl p* 5 (grass) and 12 μ g *Bet v* 1 (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 post-seasonal visual analogue scale. Methacholine bronchial provocation tests were carried out during the relevant season(s) and during winter. Conjunctival provocation tests were performed before specific immunotherapy and then every year at the same time during the study period.

Before the start of SIT, 20% of the children had mild asthma symptoms during the pollen season(s). Among those children without asthma before immunotherapy ($n=151$), 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 specific immunotherapy group as compared to 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 were published by Johnstone in 1961 [28]. He found that none of children during a 4 year course of immunotherapy developed new IgE sensitivities compared to 25% in the control group. Recent studies have confirmed these findings. In house dust mite monosensitized children treated for three years with immunotherapy, a significant reduction in new allergies were found and in the treated group about half of the patients did not develop any new sensitivities at all [29]. A recent controlled study including 138 monosensitized children allergic to house dust mites found that only 33% of the control children did not develop new sensitivities compared to 75% in the immunotherapy treated group. The majority of new sensitivities that developed were against various pollens [30]. Also for grass pollen monosensitized patients it has been shown that immunotherapy can reduce the risk for developing more allergies even five years after termination of a three year course of treatment [31]. A large retrospective study including more than 8000 monosensitized patients suffering from rhinitis and/or asthma has recently confirmed the reduced risk of developing new allergies as a result of specific immunotherapy for four years and at follow up three years after termination of the treatment. During treatment, 68% of controls had developed one or more new sensitivities compared to 27% in immunotherapy treated patients. At follow up three years after termination of the treatment period, 75% of controls had developed new sensitivities compared to 25% in the active group [32].

Conclusion

Besides the very significant clinical effect and long lasting benefits of specific immunotherapy it has been shown in several well controlled studies that immunotherapy do reduce the risk of developing new allergic sensitivities and do reduce the risk of developing asthma in children suffering from hay fever.

The immunological mechanism for the preventive capacity remains to be investigated. This investigation has to focus on the rationale for the immune system not being able to initiate new IgE responses 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.

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Discussion

Malling: I think that because clinically effective immunotherapy is mentioned some of the efficacy and the capacity of immunotherapy in discussing the application of immunotherapy in allergic diseases.

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Discussion

Malling: I think that these last aspects of immunotherapy are probably most important, because clinically effective treatment could be achieved by drugs. But you have mentioned some of the aspects that will not be achieved by drugs. That is the long-lasting efficacy and the capacity of prevention. I think, this is the most crucial aspect when discussing the applicability of immunotherapy in the whole concept of treating allergic diseases.