New Horizons Session on Specific Immunotherapy (SIT)

Session 4: Practical considerations for SIT

When should SIT be started and why?

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Respiratory allergic diseases (rhinoconjunctivitis and asthma) have a high prevalence in Europe, where they affect more than 20% of the adult population (1, 2). The disease burden associated with IgE sensitisation in adults is likely to continue to increase for some time (3). The Danish National Institute of Health has reported a significant increase in hay fever and asthma in Denmark between 1987 and 2005, which was confirmed by Linneberg and colleges in the Copenhagen allergy study: an eight-year follow up study in the Capital Area of Denmark (4). Allergic disease and sensitisation to the most common airborne allergens was followed from 1990 to 1998; together with an increase in the number of people with respiratory allergic symptoms, the study identified a significant increase in allergic sensitisation (5, 6). Although, during recent years an increase in allergic symptoms has also been identified in children (7, 8), the prevalence appears to have reached a level of saturation, as shown in the Swiss SCARPOL study (9). The increase in allergies observed between 1990 and 1998 in the Copenhagen study, may reflect a cohort effect related to major life style changes implemented after 1950 (10), based on the observation that the number of people with allergic symptoms does not decrease with age, as was often observed in cross-sectional studies, due to the fact that allergy has a chronic nature and a persists for many years in the individual patient (11).

A link between hay fever and asthma is evident (12, 13). Many patients with allergic rhinitis also have asthma, and up to 75% of patients with asthma experience nasal symptoms (14, 15). Allergy often presents as a multi-organ disease (16). The clinical impact, as well as the importance of specific diagnostics, and a combined strategy for treatment of respiratory allergic diseases, has been carefully described in the recent ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines. Moreover, ARIA has also identified allergic rhinitis as the most important risk factor for development of asthma (17, 18).

A recent study calculated the total annual treatment cost of allergic rhinitis at 2,200 Euros per patient (19). Although this economic burden may not seem so high for individual patients with allergic rhinitis, with or without concomitant asthma, the huge number of already diagnosed patients and the expected increase will lead to a substantial economic burden on the health care system (20).

Understanding the complexity of the allergic disease is crucial in order to offer the patient with allergy the optimal treatment which is interacting with the basic immunological condition as well as the symptoms. The optimum treatment of allergy increases the quality of life by reducing the primary symptoms and the need for medication, but the treatment should also influence the basic immunological allergic condition by changing the pathophysiological immunologic reactions(21)

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

The diagnostic tools available together with a well defined history of allergic symptoms offers excellent possibilities for identification of the specific allergic trigger, treating the patient allergen specific and change the natural course of the systemic allergic diseases. Based on the diagnostic procedures the treatment of inhalant allergy should together with education of the patient include avoidance and elimination of allergens, treatment of symptoms and as the treatment of the immunological cause of the allergic disease - allergen specific immunotherapy (SIT)(22).

Immunotherapy is specific for the antigen administered and requires a complete allergy evaluation before it is initiated. Since allergens interact with nasal, bronchial, and ocular mucosa, it seems appropriate to consider the efficacy of immunotherapy by allergen species rather than by a specific allergic disease.

Allergen immunotherapy is indicated for patients who have demonstrated evidence of specific IgE antibodies to clinically relevant allergens. The rationale for prescribing allergen immunotherapy 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(23).

SIT for respiratory allergic diseases leads to significant decrease in symptoms as well as need for symptomatic medication, but SIT also have the capacity for long-term clinical effects and can prevent development of further allergies and symptoms. The treatment is acting on the basic immunological mechanisms responsible for symptoms and has the potential for persisting changes of the immune response.

Different levels of benefit from early reduction in symptoms over progressive clinical effect during treatment to long-term effects after termination of treatment and prevention of asthma is described in international guidelines. The efficacy of SIT increases the longer it is continued and immunological changes leads into potential long-term benefits. Only SIT has so far documented a long-term and preventive potential for development of asthma and further sensitivities to appear over time. Depending on clinical documentation available and study duration's different claims for efficacy are possible(24).

- Treatment of allergic symptoms: Short term clinical trials conducted to show efficacy in the first pollen season after start of specific immunotherapy or to show efficacy in perennial allergies after some months of treatment
- Sustained clinical effect: Maintenance of significant and clinically relevant efficacy during two to three treatment years
- Long-term efficacy and disease modifying effect: Sustained significant and clinically relevant efficacy in post treatment years
- Curing allergy: Sustained absence of allergic symptoms in post treatment years.

The allergic condition is driven by a subset of T-helper lymphocytes (Th2), which are characterized by the production of cytokines like IL-4, IL-5. The complex of immunological changes following SIT leads into potential curative effects. One mechanism by which immunotherapy suppresses the allergic response is by an increase in the production of specific non - IgE competitive antibodies, primarily IgG4. Allergen 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.

The 5 and 10 year follow up studies on children treated SCIT (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 and at the 5 year follow-up 2 years after SIT termination. The actively treated children had persistently significantly less asthma at the 5 year follow-up and 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 5-year follow-up, also persisted at the 10-year follow-up. The study also showed that BHR at baseline was associated with increased risk of later development of asthma(25,26).

SIT should be recognized not only as first line therapeutic treatment for allergic rhinoconjunctivitis but also as secondary preventive treatment for respiratory allergic diseases. In order to a achieve the optimal benefit from SIT it is important to initiate the SIT treatment early in the history of the individual patients

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