

E. Valovirta

Pediatrician,
Pediatric Allergist
Turku Allergy Center, Finland

Revisión

Preventive allergy treatment by subcutaneous allergen specific immunotherapy

The purpose of this review is to highlight important and interesting articles about the preventive aspects and capacity of allergen specific subcutaneous injection immunotherapy. The preventive capacity of subcutaneous immunotherapy in suppression of the development of new IgE-sensitisations and the progression of the allergic disease into more severe one is an interesting topic in the field of allergen specific immunotherapy. Allergen-specific immunotherapy, the subcutaneous administration of increasing doses of allergen extracts, is the only specific and curative approach towards the treatment of IgE-mediated allergy. Immunotherapy affects the natural course of allergic disease, and induces prolonged clinical remission when the treatment is continued for several years, which has raised the question of whether it should be considered earlier in the management of allergic diseases.

Key words: Prevention. Allergen specific injection immunotherapy. Asthma.

Tratamiento alergológico preventivo mediante inmunoterapia subcutánea específica de alérgeno

El objetivo de la presente revisión es resaltar artículos importantes y de interés acerca de los aspectos y de la capacidad preventiva de la inmunoterapia específica de alérgeno administrada por vía subcutánea. La capacidad preventiva de la inmunoterapia subcutánea en la supresión del desarrollo de nuevas sensibilizaciones mediadas por IgE y de la progresión de la enfermedad alérgica hacia formas más graves constituye un tema de gran interés en el campo de la inmunoterapia específica de alérgeno. La inmunoterapia específica de alérgeno, es decir, la administración por vía subcutánea de dosis crecientes de extractos alérgicos, es el único planteamiento terapéutico específico y curativo en las enfermedades alérgicas mediadas por IgE. La inmunoterapia modifica el curso natural de la enfermedad alérgica e induce una remisión clínica prolongada cuando el tratamiento se mantiene durante varios años; esto ha planteado la pregunta acerca de si esta modalidad de tratamiento debería tenerse en cuenta más precozmente en el manejo terapéutico de las enfermedades alérgicas.

Palabras clave: Prevención. Inmunoterapia parenteral específica de alérgeno. Asma.

Correspondencia:
Erkka Valovirta
Turku Allergy Center
FIN-20610 Turku, Finland
e-mail: erkka.valovirta@allergia-
keskus.net

INTRODUCTION

In the Interim Report of Prevention of Asthma and Allergy¹ by World Health Organisation (WHO) and the International Association of Allergology and Clinical Immunology – World Allergy Organisation (IAACI-WAO) it is stated that "allergen immunotherapy has been shown to effect a Th-2 to Th-1 switch in response to allergen, and early employment of this therapeutic intervention has been shown to interrupt the expansion of allergic sensitisation from a single allergen to multiple allergens and is currently tested in the context of interruption of progression from allergic rhinitis to asthma". Already in the Position Paper² on Immunotherapy by European Academy of Allergology and Clinical Immunology from the year 1993 it was suggested that allergen specific injection immunotherapy has a possibility of preventing further development of severe disease and the development of new IgE sensitisations. In the WHO Position Paper Therapeutic Vaccines for Allergic Diseases from the year 1998³ it was stated for the first time that allergen specific immunotherapy influences on the IgE-mediated inflammation as a whole. In the Consensus Statement on the Treatment of Allergic Rhinitis⁴ from the year 2000 it is discussed that allergic reaction has multiple organ involvement and immunotherapy should be considered based on allergen sensitization rather than on a particular disease manifestation. In this report it is also suggested that immunotherapy should be introduced to the patients at the early phase in the course of allergic disease. In an early report from 1968, Johnstone and Dutton⁵ observed that young rhinitic patients receiving injection immunotherapy were less likely over a long time to develop asthma subsequently. This article received important criticisms due to its intrinsic methodological biases, and it was therefore not considered strong enough to support the prophylactic effect of immunotherapy. Although the level of evidence for the preventive capacity of subcutaneous immunotherapy is still incomplete, there is increasing amount of scientific data giving evidence of the preventive aspects.

THE LINK BETWEEN ALLERGIC RHINITIS AND ASTHMA

The international document entitled Allergic Rhinitis and Its Impact on Asthma ARIA⁶ highlights the concept that upper and lower airways may be considered as a unique entity influenced by a common inflammatory process,

which may be sustained and amplified by interconnected mechanisms. Thus, it is important to consider asthma, rhinitis and conjunctivitis as a single entity when immunotherapy is prescribed. The connection between hay fever and asthma is evident^{7,8}. Approximately 30% of patients with perennial rhinitis have lung symptoms and signs of asthma, and >70% of asthma patients have nasal symptoms⁹. Rhinitis frequently precedes the onset of asthma^{9,10}. Patients with allergic rhinitis and bronchial hyperresponsiveness (BHR) have a high risk of developing asthma¹¹. It is reported that 25 to 43% of the patients experiencing rhinitis develop asthma within 10 years^{10,12}.

CAN IMMUNOTHERAPY FOR ALLERGIC RHINITIS PREVENT THE ONSET OF ASTHMA?

The preventive effect of subcutaneous immunotherapy, ie, the potential to change the natural course of the allergic disease by preventing the exacerbation from allergic rhinitis to asthma has been investigated. In the study by Bauer¹³ it was demonstrated that fewer patients suffering only from hay fever develop nonspecific BHR if treated with injection immunotherapy. In the study on effects of immunotherapy in allergic rhinitis individuals with BHR by Grembiale et al¹⁴ there was a 4-fold increase in the provocative dose of metacholine in the bronchial provocation test after 2 year of immunotherapy with house dust mite in the immunotherapy group in a double blind placebo controlled setting. There were no change in the placebo group. In the study by Walker et al¹⁵ it was observed that there were no change in the airway metacholine PC20 (provocation concentration producing a 20% fall in the forced expiratory volume in one second, FEV1.0) in the group treated with grass pollen immunotherapy compared with an almost 3 doubling-dose decrease in the placebo-treated group.

The study by Johnstone and Dutton⁵ with several different allergens showed that 28% of children receiving immunotherapy developed asthma, compared with 78% of placebo-treated children who developed asthma. In this study it was used a mixture of non-standardized allergens for injections.

In the study by Jacobsen et al¹⁶ the results of 36 adult patients receiving immunotherapy with standardized tree pollen extracts for 3 years show after the period of 6 years that none of the rhinitis patients developed asthma during the study period, ie, during 9 years.

To answer the question "Does allergen specific injection immunotherapy stop the development of asthma in children suffering from allergic rhinoconjunctivitis induced by birch and/or timothy pollen allergy?" the Preventive Allergy Treatment (PAT) Study has been started in 1992 in children aged from 7 to 13 years¹⁷. The results show that children treated actively with the standardized birch and/or timothy pollen extracts had significantly fewer asthma symptoms after 3 years of treatment compared to the control group as evaluated by clinical diagnosis. In the active group, also the metacholine bronchial provocation test results improved significantly.

It is documented in several studies that injection immunotherapy is acting by influencing basic immunological mechanisms¹⁸⁻²⁰. It is possible that when immunotherapy improves the symptoms from one part of the airways, ie, the nose, it also has the potential to give the same immunologic response in another part, ie, lungs.

PREVENTION OF NEW IgE-MEDIATED SENSITIZATIONS BY SPECIFIC IMMUNOTHERAPY

To determine whether injection immunotherapy with standardized allergen extract can prevent the development of new sensitizations, a prospective nonrandomized 3-year follow-up study was carried out in a population of asthmatic children under the age of 6 years whose only allergic sensitivity was to house dust mites²¹. In this study 22 children monosensitized to house dust mites, who were receiving immunotherapy with standardized allergen extracts, were compared with a control group of 22 other age-matched subjects to house dust mites. Approximately 45% (10 out of 22) of the children receiving immunotherapy did not develop new sensitivities whereas none of the children in the control group remained free of new sensitivities measured by skin prick testing and by the measurement of allergen specific IgE antibodies in sera.

In the large retrospective survey²² of 8396 patients monosensitized to mites, grass, olive, *Compositae*, *Corylaceae-Betulaceae* or *Parietaria*, it has been shown that specific immunotherapy for 4 years reduced new sensitizations in these monosensitized subjects suffering from respiratory allergic diseases rhinitis and asthma statistically significantly compared to the control group without any injection immunotherapy.

The prevention of new sensitizations in asthmatic children monosensitized to house dust mites by specific immunotherapy has been evaluated in a recent study by Pajno et al²³. In this study 134 children aged from 5 to 8 years were divided in the immunotherapy and control group who were treated only with symptomatic medication. Immunotherapy was given for 3 years and the follow up was in total 6 years. At the end of the study, statistically significantly less children in the immunotherapy group developed new IgE-mediated sensitizations compared to the control group.

The mechanisms that explain the lower rate of new sensitizations in children given immunotherapy are unclear. One of the most intriguing field of research centres on the possible action of immunotherapy on the regulation of the Th1: Th2 -balance, lymphocyte function and responsiveness to allergen, and the production of cytokines and interferon-gamma (IFN-gamma). Immunotherapy has been shown to alter the production of cytokines and IFN-gamma, and in addition to that, to decrease the number of mast cells in the skin²⁴.

SPECIFIC IMMUNOTHERAPY – THE INDUCTION OF NEW IgE-SPECIFICITIES?

An issue that recently has gained attention is the question of whether the administration of allergen extracts in the course of subcutaneous immunotherapy can induce IgE reactivities and clinically relevant sensitizations to new allergens²⁵. In the publication by Moverare et al²⁶ they report the development of new IgE reactivities to allergenic components in pollen extracts during specific immunotherapy. The authors monitored 24 children and adults who were treated with birch pollen rush immunotherapy for up to three years. At the beginning of the study all patients had IgE to major birch pollen allergen Bet v 1, but only three had detectable Ig E to recombinant birch pollen allergens rBet v 2 and/or rBet v 4. However, IgE reactivities to new allergen components were observed by immunoblotting in 65% of patients after one to three years in addition to the original IgE-reactivities. These data are in keeping with the recent study by Ball et al²⁷ showing that patients receiving one year grass pollen immunotherapy develop new immune responses not only to new epitopes but also to the new allergens in the administered extract. These results upraise the question of the quality of allergens and allergen extracts both in the diagnosis and treat-

ment of allergic diseases. The answer is the use of hypoallergenic recombinant allergens.

CONCLUSION

Allergen specific subcutaneous injection immunotherapy has been used for the curative treatment of allergic diseases but there is increasing evidence in the highly selected patients indicating that immunotherapy may have a preventive efficacy, both in the development of asthma in patients with allergic rhinitis and in the development of new IgE-mediated sensitizations. For the purposes of everyday clinical practice it is important in the future studies to evaluate if there are some special characteristics of those patients who would get the best benefits from immunotherapy, not only to relief the symptoms of the allergic diseases and to give a long-lasting effect, but, especially, the characteristics of those in whom prevention of the development of asthma could happen.

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