

Immunotherapy in children

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Purpose of review

Specific allergen immunotherapy although being performed for almost 100 years, is still being addressed in clinical trials. In children the sublingual allergen application has gained considerable interest.

Recent findings

Controlled long-term trials suggest that specific allergen immunotherapy has the capacity to modify the natural history of allergic airway disease by reducing the incidence of new sensitivities non-specifically, reducing allergic symptoms years after discontinuation and preventing the incidence of asthma. The current evidence on sublingual immunotherapy is not sufficient to recommend this mode of treatment in clinical practice yet.

Summary

Specific allergen immunotherapy should be considered in children in whom IgE-mediated allergic symptoms cannot be adequately controlled by symptomatic treatment.

Keywords

immunotherapy, allergic rhinitis, asthma

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Introduction

Specific allergen immunotherapy, which was introduced almost 100 years ago, still remains controversial. While this treatment is extensively practised in the USA and several European countries, it is almost neglected in other countries. The majority of chest physicians treating asthma in patients of all age groups tend to be sceptical and do not consider this mode of treatment, even in cases when allergens appear to be the main trigger factors [1–3].

Allergic diseases of the upper or lower airways frequently develop in childhood and remain prevalent throughout the first decades of life. In the majority of cases, immunoglobulin E-mediated sensitization to indoor or outdoor allergens is initiated between the ages of 2 and 20 years. Once sensitized, individuals are at risk of developing symptoms on exposure to seasonal or perennial allergens. From preschool age to adolescence, low-dose allergen exposure has been demonstrated to not only induce acute symptoms, but also to contribute to the development of nonspecific nasal or bronchial hyperresponsiveness and thus to a chronification of the disease process.

The pathophysiology of allergic airway disease in childhood is not different from that in adulthood. The clinical picture, however, is quite obviously dominated by allergens as trigger factors, as long as secondary problems contributing to chronic inflammation such as bacterial infections or remodelling of the airway have not yet become manifest.

Over the past few years the results of a variety of important studies have been published, adding evidence to the large number of controlled trials which have recently been reviewed by several experts, including the Cochrane library group [4,5*]. Here I will focus on these recent contributions.

Immunotherapy as a causal treatment

In contrast to pharmacotherapeutic interventions, it seems that besides allergen avoidance specific immunotherapy applied by subcutaneous injections of allergens is the only causal treatment controlling the disease process and providing symptomatic improvement long after discontinuation. This long-lasting clinical effect of immunotherapy with grass pollen allergen extract was impressively documented by Durham and colleagues [6,7*]. They followed a cohort of patients with seasonal allergic rhinoconjunctivitis for several years after

discontinuation of treatment, together with a control group without intervention and continuous treatment. Along with other studies [8], these authors confirmed earlier Scandinavian reports which documented the long-term benefits of specific immunotherapy with regards to symptoms upon allergen exposure, usage of medication and local inflammation, even several years after treatment was discontinued. These studies seem to indicate that immune intervention can be considered to be a causal treatment since clinical tolerance is induced to the relevant allergens. This process is associated with changes in the nasal mucosal cytokine responses to allergen exposure, with a shift in the T helper 2 to T helper 1 cytokine balance in favour of a T helper 1 response. [9••].

Specific immunotherapy reduces the incidence of new sensitivities to nonrelated allergens

The incidence of specific sensitizations to indoor or outdoor allergens is particularly high during the first decade of life, when after a sufficiently long period of exposure immunoglobulin E antibodies are produced and children will convert from skin test negativity to positivity. In a previous study by Des Roches *et al.* [10•] it was reported that during allergen injection immunotherapy the likelihood of developing new sensitivities which had not been observed at baseline was significantly reduced in the immunotherapy group compared with the control group. More recently, Pajno *et al.* [11] studied a large cohort of 134 children aged 5–8 years who had intermittent asthma with or without rhinitis and a single sensitization to mite allergen as demonstrated by skin test. The presence of alleviated serum-specific immunoglobulin E was also demonstrated. Seventy-five of these children received specific immunotherapy with a mite allergen extract and the rest served as controls. After an observation period of 6 years, more than 75% of the specific immunotherapy group showed no additional sensitization compared with 33% in the control group. Both studies suggest that an early application of specific immunotherapy offers the possibility of modifying or at least delaying the natural course of immunoglobulin E-mediated disease of the respiratory tract. Recently, these observations were confirmed in a large cohort of pollen-allergic children who had received immunotherapy over 3 years [12••]. Obviously, in addition to an allergen-specific effect, subcutaneous immunotherapy in children has an additional immunomodulatory effect that is not related to the allergen injected.

Immunotherapy modifies the natural history of allergic airway disease

From longitudinal birth cohort studies it is known that, especially in the first decade of life, there is significant comorbidity between upper and lower airway manifesta-

tion. This contributes to the fact that approximately one-third of 7-year-old children with established seasonal allergic rhinoconjunctivitis report associated asthmatic symptoms during the pollen season. Obviously, allergic rhinoconjunctivitis and allergic asthma are different manifestations of the same disease. Older observations suggested that children who had received specific immunotherapy treatment for pollen allergy early in life were much less likely to develop seasonal asthma symptoms. A Swedish study demonstrated that specific immunotherapy treatment had the potential to reduce bronchial hyperresponsiveness in patients with mild-to-moderate asthma [13]. In a group of 44 patients with severe summer hay fever, of whom 36 reported seasonal chest symptoms and 28 had seasonal bronchial hyperresponsiveness, Walker [14] was recently able to demonstrate a specific immunotherapy with grass pollen extracts that could reduce seasonal asthma symptoms as well as bronchial hyperresponsiveness and improve quality of life.

A recent multicentre trial involving more than 200 children with birch and grass pollen allergy suggests that, in children with rhinoconjunctivitis without asthma, specific immunotherapy treatment is able to reduce the risk for later development of asthma [12••]. It is plausible that if immunotherapy improves the symptoms from one part of the airways – the nose – it also has the potential to give the same immunologic response in another part – the lungs. This recent study indicates that specific immunotherapy has the potential to change the natural course of the allergic disease, which was first suggested by Johnstone and Dutten in 1968 [15].

Specific immunotherapy is effective in asthma

While the majority of researchers seem to agree that immunotherapy is effective in rhinitis, the role of this intervention in asthma remains highly controversial. It is generally accepted that the inhalation of allergen may lead to an inflammatory process involving the release of proinflammatory mediators in the lower airways; however, the majority of chest physicians seem to prefer the use of long-term antiinflammatory drugs to specific allergen vaccination. A metaanalysis performed by Abramson *et al.* [5•], which was recently updated, assessed the overall efficacy of allergen-specific immunotherapy upon asthma symptoms, medication requirements, lung function, non-specific bronchial hyperresponsiveness and allergen-specific bronchial hyperresponsiveness. In addition, the efficacy of mite, pollen and animal dander immunotherapy was compared. The authors were able to confirm that allergen-specific immunotherapy can significantly reduce asthma symptoms and medication requirements. While there was no consistent effect of immunotherapy on lung

function, patients randomized to immunotherapy were significantly less likely to develop increased nonspecific bronchial hyperresponsiveness and significant reductions of allergen-specific bronchial hyperresponsiveness. The authors conclude that the homogeneous results of the studies published indicate that specific immunotherapy can contribute to improved asthma control.

In a recent article, Adkinson [1] challenges this conclusion, pointing out that no published studies thus far have demonstrated a steroid sparing effect for allergen immunotherapy and that immunotherapy provides no protection against nonallergic asthma triggers such as viral infections, irritants and exercise. His own study [16•] in asthmatic children who had received a broad spectrum of up to seven different allergen sources included in an immunotherapy protocol failed to demonstrate an effect on partial or complete remission rates in addition to pharmacotherapy. One might conclude from this report that studies using multiple allergens for immunotherapy do not seem suitable to assess the efficacy of specific immunotherapy in asthma.

Recently, in young pollen-allergic adults, a rapid cluster regiment of grass pollen injection immunotherapy followed by 2 years of maintenance treatment was found to be highly effective in reducing hay fever and asthma symptoms as well as seasonal increases in airways responsiveness [17]. This effect was accompanied by marked improvement in quality of life and patient satisfaction. The effect of immunotherapy on nonspecific bronchial hyperresponsiveness obviously depends on the methods applied. A recent study with Austrian children [18] indicates positive effects on bronchial hyperresponsiveness if cold air challenge tests are performed.

Taking all recently published data together, specific allergen immunotherapy for asthma in childhood should be considered preferably early in life and applied to children with mild-to-moderate asthma which is induced by a few selected seasonal or perennial allergens. Immunotherapy should not be confined to asthmatic children in whom pharmacotherapy fails.

Allergen immunotherapy shows additive effects with anti-immunoglobulin E

In recent years, recombinant humanized antibodies have been developed against the epitope of the FC fragment of the immunoglobulin E molecule, which binds to the high-affinity FC ϵ receptor of basophils and mast cells. These antibodies have been shown to be effective in the treatment of seasonal allergic rhinoconjunctivitis and asthma. The obvious difference in the mode of action of the intervention by anti-immunoglobulin E and specific allergen immunotherapy [19•,20–22] stimulated a recent placebo-controlled study in a paediatric cohort with

concomitant allergies to birch and grass pollen [23•]. All children were treated with either a birch or grass pollen extract and received in addition an injection of placebo or anti-immunoglobulin E. Allergen-specific immunotherapy provided a significant reduction in symptoms and medications only for the relevant part of the pollen season, whereas anti-immunoglobulin E – as expected – led to a nonspecific additional improvement. This first study of a combined intervention indicates that there will be new avenues for immunomodulation and immunointervention in the future, which by combining several modes of treatment in selected cases may lead to a higher degree of safety as well as efficacy of specific allergen vaccination.

Sublingual immunotherapy in children

The use of sublingual immunotherapy has also attracted considerable attention [24,25,26•,27–29]. After oral immunotherapy was repeatedly proposed over several decades, particularly for children, the possibility of achieving desensitization by giving high doses of allergen topically has recently generated increasing interest. In experimental animals it is well known that immunoglobulin-E responses to allergens can be reduced by prior oral administration of the allergen. It was suggested that allergens should be given sublingually to allergic humans and retained in the buccal region in order to allow a local allergen take-up after administration. Extensive studies of sublingual immunotherapy in adults as well as in children suggest that it has a certain degree of efficacy in allergic diseases, it is highly accepted by patients, and is obviously associated with a reduced need for medical supervision. Still, the results of the different studies are hard to compare, since doses are not always clear, there are often problems with the design and the power of the study, there are baseline differences between the active and placebo group and, most importantly, there are no consistent results as far as clinical and immunological endpoints are concerned. In contrast to subcutaneous immunotherapy, there is no information about long-term benefits. Without doubt, sublingual immunotherapy in children requires further evaluation before it can be recommended for use in clinical practice.

Conclusion

There is evidence in the literature that for selected children with allergic diseases of the upper or lower airways, specific immunotherapy offers beneficial effects by modifying the natural history of the disease and preventing progression from rhinitis to asthma. It appears that specific immunotherapy is particularly valuable in children and adolescents with a narrow spectrum of sensitizations and a lack of secondary changes of the affected organs. In the years to come we still need to elucidate which patients benefit most

from immunotherapy. Obviously, monocomponent immunotherapy is more effective than the use of multiple allergens to which a patient reacts. Further studies are needed to assess the length of treatment for the best duration of effect, as well as the cost-effectiveness aspects of immunotherapy compared with established and new pharmacological treatments.

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