The future of the treatment of allergies

Jocelyne JUST, MD PhD

Service de Pédiatrie orienté en Pneumologie et Immuno Allergologie Clinique Hôpital d'Enfants Armand-Trousseau - 26, Avenue du Dr. Arnold Netter 75571 PARIS Cedex 12 - France

Introduction

In industrial countries, the prevalence of allergic diseases has increased dramatically during the past 20 years. The precise factors explaining this increase (outdoor & indoor air pollution, passive smoke inhalation, etc.) are unknown. Environmental allergen levels play a major role.

In order to deal with this allergic component, allergen evictiion and specific immunotherapy (SIT) have been proposed. SIT is now considered to be a specific treatment for respiratory allergies. It induces increased tolerance to allergens by modulating immune responses, in particular the Th1/Th2 balance (Th2 skew in allergic patients) (1). SIT appears to be a promising treatment, since new indications and new modes of administration have recently been proposed. Early introduction of respiratory allergy treatment by SIT (or other “vaccinations” under study) may change the natural history of this disease in children.

Mode of action

Airway inflammation is considered to be a constant feature in the pathophysiology of asthma. This includes an allergic component in more than 80% of school-age asthmatic children. Studies indicate that SIT influences the Th1-Th2 balance by inducing true anergy or by the commutation of Th2 lymphocytes to the Th1 or Th0 type, by increasing IL-10 or by reducing cytokine release, as well as the number and activity of inflammatory cells within the organs (2, 3).

Efficacy of SIT in respiratory allergies

Many studies, in particular reviews (4) and meta-analyses (5) including double-blind placebo-controlled randomized studies (DBPCRS) in asthma have shown the efficacy of SIT by subcutaneous injections in respiratory allergies. Overall, randomized studies have shown that SIT is beneficial in allergic rhinitis, with a 30 % improvement over placebo. Noteworthy, however, most of these studies have been conducted in adults. A meta-analysis published by Abramson et al., including 62 randomized studies published prior to 1998, gives a synthetic view of the efficacy of subcutaneous SIT in asthma. Most studies involved house dust mite (n = 28), pollen (n = 15), and animal dander (n = 9). In 5 studies multiple-allergen SIT was administered, and in 2, cladosporium. The results were expressed in 2 manners, according to the type of variables analysed : quantitative (scores, PD20) or qualitative (improvement, unchanged, deterioration). Regarding quantitative data, there was a significant decrease in symptom and medication-consumption scores, as well as non-specific PD20. This meta-analysis thus demonstrates the efficacy of subcutaneous SIT on asthma symptoms, medication consumption, and specific and
non-specific bronchial hyper-responsiveness. However, no significant changes were observed regarding spirometric data.

Indications for SIT

SIT is currently indicated as curative therapy for respiratory allergies, similar to allergic environmental control. In initial forms of allergy, such as allergic rhinitis or early stages of asthma, SIT conveys preventive effects by modifying disease severity and bronchial hyper-responsiveness as well as avoiding further allergic sensitizations as the child grows older (6-8).

Future perspectives

For satisfactory results, indications for SIT should be chosen very carefully. Its efficacy also depends on the quality of the allergenic extracts. However, enhanced allergenicity increases the risk of severe anaphylactic reactions, which explains the hesitations in SIT use in childhood asthma.

One of the problems with SIT by the injectable route is its relative invasiveness, constraints and long duration of treatment, combined with potential systemic syndromic reactions. Various other modes of administration have thus been proposed, such as the bronchial, oral, nasal and sublingual routes. The oral and sublingual routes are the most commonly used. The cumulative doses of allergens administered should be 200- to 500- fold greater than the subcutaneously injected route. There has been some discussion regarding the efficacy and tolerance of the sublingual route. According to the WHO, 1/ the oral route is not recommended since treatment efficacy cannot be evaluated prior to 1-year's treatment and due to the high risk of severe side effects; 2/ the efficacy of the sublingual route has, on the other hand, been demonstrated in allergic conjunctivitis, and seasonal and perannual rhinitis (9). Only few studies have been conducted in childhood asthma (9-11). Bousquet et al. (11) have reported significant improvement in the global symptom and medication score without any significant difference between the active treatment and the placebo groups regarding adverse effects. Three studies in asthmatic children (9, 10, 12) have shown a significant decrease in medication score as well as symptom score (decreased asthma crises and nocturnal symptoms), in favor of the treatment group (13).

Kuehr and co-workers (14) have shown that the effect of SIT may be potentialized by its combined use with a “passive” non-specific treatment of respiratory allergy: anti-IgE monoclonal antibodies. In their study, in 221 children aged 6 to 17 years with allergic rhinitis and multiple sensitizations to various types of pollen, anti-IgE and SIT together induced a greater protective effect when compared to SIT alone. This was observed during the hay fever season corresponding to the allergens included in the SIT, as well as during periods not covered by the specific treatment. In the future, this type of treatment may help extend the indications of SIT to patients sensitized to multiple allergens.

Engineering of genes coding for the allergens and/or the use of allergenic proteins may lead to the fulfillment of the following 2 requirements: the purity and stability of allergens, resulting in the elimination of the risk of anaphylaxis. It will be possible to synthesize allergen-derived peptides (recombinant peptides) having retained the
sites (epitopes) recognized by T-lymphocytes, whose target IgE-interacting epitopes have been deleted (15). The “future allergenic extracts” will be synthetized according to techniques based on genetic manipulations currently applied to vaccines. Fragments of known allergen DNA (cloned from genomic DNA libraries) will be incorporated in plasmids or viral vectors. The use of other DNA fragments which can induce a non-specific Th-1 type lymphocytic response has been proposed. These are immunostimulant sequences (ISS) composed of repeated sequences with a high cytosine dinucleotide and non-methylated guanine (also known as CpG motifs) content. These CpG motifs are found in bacteria which have the capacity to induce the secretion of cytokines by antigen-presenting cells, driving the response to antigens toward a Th-1 profile.

Références

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