

Immunotherapy Is Clinically Indicated in the Management of Allergic Asthma

IgE-mediated allergy is extremely common in asthma, both in children and adults. IgE-mediated allergic reactions are essential in the onset of the disease as well as for the occurrence of exacerbations. An allergen-based treatment is therefore of great importance for the management of allergic asthma.

Allergen-specific immunotherapy (SIT) is the practice of administering gradually increasing quantities of an allergen extract to an allergic subject to ameliorate the symptoms associated with the subsequent exposure to the causative allergen. The efficacy of SIT, using inhalant allergens in seasonal or perennial allergic rhinitis and asthma, is evidence based. Guidelines and indications for specific SIT have been published in 1998 in a WHO position paper (1) and refined in a 2001 ARIA (Allergic Rhinitis and its Impact on Asthma) document (2).

The major objectives of SIT in asthma are, in the short term, to reduce the allergic triggers precipitating symptoms, and, in the long term, to decrease bronchial inflammation and nonspecific bronchial hyperreactivity when bronchial remodeling is not prominent.

Besides anti-IgE therapy, SIT is the only current immunomodulatory treatment of allergic asthma. Asthma has been associated with a helper T cell type 2 (Th2)-like immune response and several nonspecific immunomodulatory approaches have been unsuccessfully tested (3). The mechanisms of SIT are complex but it was convincingly shown to act by modifying Th2 cell responses either by immune deviation (increase in Th0/Th1) or T cell anergy (decrease in Th2/Th0) or more likely both (4). These immunomodulatory effects were correlated with the efficacy of SIT, at least in grass pollen allergy (5). Moreover, anti-inflammatory effects of SIT were still observed, albeit reduced, one year after SIT cessation (6).

Efficacy of SIT in allergic asthma is evidence based. "Evidence-based medicine" is an increasingly important concept that has become a new paradigm in medicine (7). It is based on randomized controlled trials and meta-analyses of randomized clinical trials. Several placebo-controlled randomized controlled trials have found that SIT is effective in asthma and rhinitis induced by pollens, mites, animal danders, and a few mold species (strength of recommendation A on a scale ranging from A [evidence based] to D [opinion based] (7) (for review *see* references 1, 2, and 8). A systematic review of the Cochrane collaboration (8) examined 54 randomized controlled trials of SIT in asthma involving more than 1,000 patients. This meta-analysis confirmed the efficacy of SIT in asthma. In particular, it emphasized the clinically useful outcomes of decreased symptom scores and medication requirements as well as improved allergen and nonspecific bronchial hyperresponsiveness. Importantly, the results of the meta-analysis were homogeneous and the number of patients studied was greater than 1,000, making its interpretation strongly valid. However, only selected patients benefit from SIT, which was found to be ineffective in an unselected group of children with allergic asthma (9).

Specific immunotherapy acts on several sites of the allergic reaction. Allergic diseases usually affect multiple organs, and, asthma and rhinitis often co-exist (2). The indications for SIT in

allergic asthma and rhinitis have been separated in some guidelines (10). This artificial separation has led to unresolved issues (11, 12) because the allergen-induced IgE-mediated reaction has not been considered to be a multiorgan disease. It is therefore important to consider SIT on the basis of allergen sensitization rather than on the basis of the target organ, and to discuss the efficacy of SIT on combined lung and nose symptoms.

The safety of specific immunotherapy in asthma limits its use. Subcutaneous SIT is burdened with a risk of inducing systemic side effects including asthma. These systemic reactions are usually mild when the appropriate protocol is used, but they represent a general limitation to the use of SIT in patients with severe asthma. Specific immunotherapy should not be administered to patients with asthma who are receiving adequate pharmacotherapy and in whom the FEV₁ is under 70% of predicted values (1). However, recommendations for minimizing SIT risks have been proposed (10) and shown to reduce bronchial reactions in patients with asthma.

Indications for SIT in asthma are based on efficacy, safety, and costs. They conform to the WHO position paper published in 1998 (1) and recently updated (2). It is clear that safety concerns reduce the needs for SIT in asthma because pharmacotherapy is usually effective and safe in patients with mild to moderate asthma, and SIT should not be administered to patients with severe asthma. However, many patients with mild to moderate asthma are still uncontrolled despite optimal pharmacologic treatment (13, 14) and most, if not all, patients with asthma have rhinitis. Specific immunotherapy is highly effective in rhinitis (15). Specific immunotherapy is therefore a current treatment of asthma and should be considered for patients with moderate to severe rhinitis and mild to moderate asthma. Such a global approach in considering SIT for patients with allergy is largely validated and shown to be effective in asthma (16).

Specific immunotherapy should be initiated with a limited list of standardized allergens because it is ineffective to use multiple allergens (8, 9). As many patients are polysensitized, SIT applies to a small, but still relevant, number of patients with allergy.

In future, SIT may be used in the secondary prevention of asthma. Specific immunotherapy is the only treatment that may alter the natural course of allergic diseases (17). Specific immunotherapy with pollen extracts in children with rhinitis prevents the onset of persistent asthma (18). Moreover, SIT in monosensitized young children was found to reduce the onset of new sensitizations (19, 20). More studies are needed, however, to determine how SIT may modify the allergic disease or impair progression to asthma.

In conclusion, SIT is a current treatment for some highly selected patients with allergic rhinitis and mild to moderate asthma. The optimal candidate for SIT in asthma is the patient with moderate to severe rhinitis and mild to moderate asthma induced by a few selected seasonal or perennial allergens. In these patients it is highly effective and has an important place in therapy. Specific immunotherapy might also be an important treatment in future for the secondary prevention of asthma.

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Immunotherapy Is Not Clinically Indicated in the Management of Allergic Asthma

When immunotherapy was introduced by Noon in 1911 and for most of the 50 years that followed, it was about the only game in town. Not so in the new millennium. To be clinically indicated today, immunotherapy for asthma must be more effective or less toxic, or both, than alternative therapies. Or it must possess some unique advantages that can't be found elsewhere. This is the burden of proof to which I hold my worthy opponent.

So, how effective is immunotherapy, and compared with what? If you look at modern clinical trials of immunotherapy, where symptom indices, pulmonary function, and medication requirements were carefully monitored, the size of the therapeutic effect, if observed at all, is invariably modest (1, 2) and quantitatively comparable to effects observed with any of a number of bronchodilators (3) and cromolyn-like drugs (4).

One illustrative example of this is the collaborative study of immunotherapy for ragweed asthma (5). This careful study observed patients for asthma flares during one ragweed season followed by randomization to high-dose ragweed injections or placebo for the next two years. Morning peak flow measurements during the ragweed season after one year of treatment improved 5.1% ($p = 0.06$); symptom scores did not change, although medication use declined significantly ($p = 0.01$). After two years of treatment the results were even more modest. Numerous clinical studies have documented comparable degrees of effectiveness for drugs such as anti-leukotrienes, salmeterol, and nedocromil.

No published studies have demonstrated a steroid-sparing effect for allergen immunotherapy. A randomized study of perennial allergic asthma in children done at Johns Hopkins showed no difference in the requirement for either inhaled or oral steroids between immunotherapy and placebo groups (6). A di-

rect comparison of inhaled steroids and immunotherapy has not been done, and is not likely to be done because of ethical and logistic constraints. So my first conclusion is that immunotherapy, although effective in model systems, produces modest clinical benefits comparable to what is readily achieved with bronchodilators and nonsteroidal antiallergy drugs.

The next issue is safety. Review of available data through 1992 has indicated that at least three to five individuals die as a result of immunotherapy mishaps each year in the United States (7). The British experience suggests that about 75% of immunotherapy deaths occur in patients with asthma (8), indicating that asthma is a strong risk factor for a fatal outcome from systemic reactions. This observation has led to guidelines that mandate prescreening subjects with asthma before immunotherapy injections.

I am sure that almost all qualified allergy specialists adhere to these guidelines, but the real world is a bit different. Injections are not always under the direct supervision of a qualified specialist, and dosing errors, which are responsible for as many as half of systemic reactions to immunotherapy, can be minimized but probably not eliminated. On the other hand, alternative pharmacotherapies, including inhaled steroids, have remarkably little acute toxicity, and no directly attributable mortality.

Immunotherapy could be clinically indicated in allergic asthma if it possessed advantages or benefits not obtainable with alternative treatments. Immunologic specificity is a distinctive feature of immunotherapy but such specificity is a double-edged sword. If important treatment allergens are omitted the clinical result will be suboptimal. And unlike pharmacotherapy, immunotherapy provides no protection against nonallergic asthma triggers such as viral infections, irritants, and exercise.