Allergen-Specific Immunotherapy in the Treatment of Allergic Diseases

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Introduction

Other than environmental control, whose goal is to decrease allergen exposure, allergen-specific immunotherapy is the only intervention available to reduce symptoms of allergies. These treatments come in several forms, subcutaneous injections, nasal instillation or sublingual

Allergen extracts for immunotherapy should be purified, potent, and standardized since the success of immunotherapy depends of the antigen dose utilized. Immunotherapy is based on gradually increasing concentration of specific allergens up to reach effective dose for reducing the severity of the disease, even under natural allergen exposure.

Goals

The main aims of the allergen-specific immunotherapy are: to reduce responses to the inducer allergens, to decrease the inflammatory response and prevent the chronic persistent disease in the long term by inducing immunological changes or tolerance against administered allergens. Consequently, the patient is able to tolerate the allergen exposure, showing the reduction of allergic rhinitis and/or asthma symptoms.

General Indications for Allergen-Specific Immunotherapy

Allergen-specific immunotherapy, also called "allergy shots", is indicated for atopic patients, with allergic diseases mediated by IgE, as allergic rhinitis, moderate asthma and insect sting allergy.

Specific Indications for Allergen-specific Immunotherapy in Allergic Rhinitis

In allergic rhinitis, indication of allergen-specific immunotherapy should be considered when (1) patients show poor response to medications or allergen avoidance measures by environmental control; (2) the patient does not wish to continue exclusively on pharmacotherapy; (3) when patients present unacceptable side-effects of medications; (4) the patient do not wish to keep a long-term medications; (5) co-existence of allergic rhinitis and asthma, or (6) when the objective is to prevent asthma in children.

For the success of allergen-specific immunotherapy, the allergen choice should be based on the identification specific IgE antibodies by skin tests and/or serum, preferentially for prevalent allergens in the region. It is needed to evaluate the

clinical severity and administrate allergen extract from good precedence and adequate concentration individualized for each patients.

Mechanism of action

Overall, the mechanisms of action of immunotherapy are heterogeneous and several factors are involved such as, the nature of antigen, route of administration, duration of the treatment, site of the allergic disease as well as the use of adjuvants.

Immunotherapy is effective in allergic rhinitis and asthma by administering antigen, in up-dosing manner up to reach relatively high dose that stimulate the development of specific Th1 cells to allergen and decrease Th2 cells. The increase in IgG levels is dose- dependent and it occurs only after administration of sufficient amount of allergen. The immune response seems to belong to the IgG1 subclass in the early phase of the immunotherapy while IgG4 is a dominant subclass in the long-term immunotherapy. By continuation of immunotherapy, the levels of IgG antibodies specific to the allergen increase until to stabilize in a plato. IgG antibodies induced by immunotherapy may act as blocking antibodies by competing with IgE for allergen binding, blocking the specific IgE-dependent activation of mast cells.

Regarding IgE antibodies, immunotherapy initially induces an increase of total IgE antibodies and a long-term a decline in total and specific IgE, with no changes in immediate skin reactivity in the majority of the cases. However, the changes in the IgE antibodies concentration do not correlate with the clinical response to immunotherapy, especially in patients with respiratory allergy symptoms.

In an important study was concluded that the success of immunotherapy was associated with the increase in an IFN-α and IL-5 mRNA ratio produced by nasal mucosa cells, but these changes were not reflected by alterations in the peripheral blood T cells proliferation or in cytokines production before and after the immunotherapy.

An interesting double-blind placebo controlled randomized using SLIT enrolling 86 children with mild asthma, ranging from 5 to 12 years old, sensitized to the mite *Dermatophagoides pteronyssinus*, where 33 children had allergic rhinoconjunctivitis. In this study, 47 children received active sublingual immunotherapy and 39 children received placebo. After 6 months of sublingual immunotherapy, a significant reduction in symptom and medication scores as well as significant reduction of ECP (eosinophil cationic protein), IL-13, and PRL (prolactin) was observed. It is believed that sublingual immunotherapy modulates the synthesis of Th2-type cytokines and point out for decreasing the T cell activation.

Additionally, in a double blind placebo controlled study which was employed oral immunotherapy using grass pollen extract, the authors reported a significant reduction on medication and symptom scores, decrease of IL-5 mRNA production in the active group compared to the placebo group. No change in the IgE, IgG levels and skin prick test results was observed.

More recently, researchers have reported that the immunological basis for curing allergic disease with allergen immunotherapy is the development of CD4+,

CD25+ T regulatory cells, which in turn decrease in Th2 response would occur to the production of immunoregulatory cytokines as IL-10 e TGF-α more than increasing in Th1 response.

Contraindications

Immunotherapy is contraindicated in patients with severe asthma, coronary disease, malignancies, patients using beta-blockers, patients with basic alteration of the immune system, as immunodeficiencies and autoimmune disorders.

Side-effects

The risk of inducing systemic side-effects may accompany allergen immunotherapy and the patient should be informed of these risks. Then, the assistant physician or health care professional should be prepared for treating such systemic reactions. Local reactions are common but generalized urticaria may occur. Some patients can present with transient worsening of the clinical manifestation after allergen extract application. For this reason, it is important to adjust the dose of allergen extract administered. In the literature are reported few cases of anaphylaxis and/ or death. In patients with asthma is necessary a special attention due to the greater risk of development of severe adverse reactions.

Routes of administration of the Immunotherapy

Subcutaneous immunotherapy (SCIT), sublingual immunotherapy (SLIT), intranasal immunotherapy (INIT), oral immunotherapy (OIT).

Subcutaneous immunotherapy

Currently, the most used route for immunotherapy application is by subcutaneous injections and the time recommended is 3 to 5 years for obtaining the desired effects. The benefit of immunotherapy should be evaluated by clinical follow-up determining the intensity and frequency of symptoms and reduction in medication intake. Several studies have demonstrated the benefit of immunotherapy in allergic rhinitis by reducing new sensitizations and prevent the development of asthma in patients with allergic rhinitis.

In a double bind placebo, , randomized study involving 36 patients with moderate and severe persistent allergic rhinitis who received subcutaneous immunotherapy for 1 year, the authors observed clinical symptom amelioration and reduction of medication use. In addition, the authors reported reduction of the wheal size in the skin test when compared to the placebo group.

In a recent study with 72 patients at our institution, we observed that the group receiving subcutaneous immunotherapy with *D. pteronyssinus* associated to bacterial extract showed a tendency of lower systemic side-effects in comparison to the group that received mite extract only. It is possible to hypothesize that a Th1 stimulus induced by bacterial extract may be responsible for the protection of these patients because this fact did not occur in the group that received only *D. pteronyssinus* whole extract.

Sublingual immunotherapy

In a meta-analysis article and systematic review on sublingual immunotherapy for allergic rhinitis, it was demonstrated that there was a significant reduction of symptoms and medication scores in studies enrolling children and adults. All studies of this review there was no side-effects. Mild local effects consisting

by pruritus and mild oral mucosal edema were described in several studies, but with no clinical significance. This feature was discussed in this study as a great advantage of the sublingual immunotherapy compared to subcutaneous immunotherapy, which in some patients may lead to severe systemic reactions.
Another meta-analysis study on sublingual immunotherapy in children concluded that sublingual immunotherapy was effective. An additional DBPC study involving 88 children, ranging from 5 to 15 years, with allergic rhinoconjunctivitis caused by betula pollen, the specific sublingual immunotherapy was well-tolerated and resulted in significant reduction on symptom and medication scores.

Conclusion

Allergen-specific immunotherapy has demonstrated to be highly effective in some patients with disease mediated by IgE antibodies, particularly in respiratory allergy, when appropriately implemented. In recent years, the sublingual immunotherapy has shown favorable results, especially with pollen and dust mite allergens, demonsrating that immunotherapy has a role in the future and can be used with great efficacy, security and easy administration, particularly in children.

Recomended readings

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