Immunotherapy in allergies

Imunoterapia nas alergias

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Summary

The allergen specific immunotherapy is the administration, in IgE-mediated allergic patients, of a specific allergen in a gradually increased number to provide protection against allergic symptoms and inflammatory reaction. The current immunotherapeutic approaches occur by modulating the release of inflammatory mediators involved in allergic reaction and consequently the inhibition of allergic inflammatory process. Since 1997 several World Associations of Allergy, Asthma and Immunology have reviewed this issue, seeking to establish standards for its use. Also many publications about the immunotherapy’s efficacy, as well as, several guidelines on the use of immunotherapy in the treatment of allergic are available. This article will focus on the most current evidence about the immunotherapy in allergies regarding its mechanism of action, effectiveness and practical considerations.

Introduction

Early studies in the field of immunotherapy were performed by Noon and Cantab in 1911[1]. In this work, these authors observed that grass pollen allergic patients had reduced symptoms after the repetitive exposition of this same pollen extract.
Th1 cells and cytokines orchestrate the suppression of allergic inflammation, a third subset of T lymphocyte, referred as regulatory T cells, activity and then preventing the autoimmune diseases and allergy(41,42). Moreover, there is the existence of two subsets of Treg, Th1 pattern, with diminished levels of IL-4 and IL-5 and enhanced synthesis of IFN-g. Also, the presence of suppressive cytokines as IL-10 and TGF-b, which promote Treg cell differentiation, is of great importance for the prevention of allergic diseases. In addition to adaptive immunity, the innate immune response also plays a role in the control of allergic inflammation. Natural killer T cells (NKT cells) and plasmacytoid dendritic cells (pDC) play a crucial role in the regulation of allergic inflammation through the production of IL-10 and TGF-b. These cytokines act on other immune cells, such as Treg, to promote their differentiation and suppressive activity.

The mechanism of action of immunotherapy may occur by changing the predominant phenotype of antigen-specific T cells from Th2 to Th1 pattern, with diminished levels of IL-4 and IL-5 and enhanced synthesis of IFN-g. This change in Th1 profile is achieved through the administration of allergens at low doses, resulting in the activation of Treg cells and the suppression of Th2-related cytokines. The immunotherapy induces the differentiation of T cells into Th1 cells, which secrete IL-2 and IFN-g, and the suppression of Th2 cells, which secrete IL-4 and IL-5. This shift in cytokine production helps to modulate the immune response and reduce the symptoms of allergic diseases.

In addition to the suppression of allergic inflammation, immunotherapy also has a role in the modulation of the immune system. It promotes the development of regulatory T cells and the production of suppressive cytokines, which help to maintain tolerance to self-antigens and prevent autoimmune diseases. Moreover, immunotherapy may also help to alter the gut microbiota, which plays a crucial role in the regulation of immune responses. The gut microbiota can influence the development of regulatory T cells and the production of Treg cells, which are important for the maintenance of immune tolerance.

In conclusion, the immunotherapy has a dual role in the treatment of allergic diseases. It acts as an immunosuppressive agent, reducing the immune response and preventing tissue damage, and it also has a role in the modulation of the immune system, promoting the development of regulatory T cells and the production of suppressive cytokines. These effects help to control the allergic inflammation and prevent the development of chronic allergic diseases.
SIT: indications, contraindications and extract quality

Indication of immunotherapy does not cover all types of allergy. There is no consensus about his statement on food allergies, urticaria or atopic dermatitis. Immunotherapy is effective for the treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma and stinging insect hypersensitivity (14-19).

The SIT is indicated in moderate allergic asthma with FEV1 over 70%, moderate to severe allergic rhinitis (intermittent or persistent) and the allergic conjunctivitis mainly in non-responsive medical therapy cases, or with the environmental care. In general, the SIT is restricted to children over 5 years old and rarely used to patients over 60 years old.

The following will discuss some aspects of immunotherapy in allergic asthma and rhinitis, leaving considerations in relation to other forms of allergy for another opportunity.

Before the indication of SIT it is necessary to prove the correlation between the clinical symptoms and the suspected allergen. For this the skin tests or the “in vitro test” for specific serum IgE levels can complete the investigation. The skin tests (“in vivo”) and more specifically the skin-prick test are routinely used. The skin-prick test uses extracts of suspected purified allergen which seems to be the cause of the allergy. The contraindication of allergen test is for patients who have highly sensitive skin and as consequence could provide false positive results. In addition, individuals who take medication (antihistamine, antidepressants with antihistamines effects, corticoids etc.) could interfere in cutaneous reactivity resulting false negative outcomes. As a result, these drugs may be avoided or replaced before the skin test. For example the AA1 antihistamines, the skin test and the anti-IgE antihistamines a day before the test, whereas the tricyclic antidepressant at least two weeks before the skin test. The corticoids depend on their dosage, the long-term and the precise administration route. The dosage of prednisone, at least 30 mg/daily, oral route for no more than a week do not alter the skin test. Besides for contraindications of skin tests, there are “in vitro” alternative tests, with blood tests, which measure specific serum IgE levels in the allergic patient's serum. The supposed allergen of a particular patient area may be included in the test. Habitually, these allergens, as extracts in the test, could be: house dust mites, pollen, cockroach, epithelium of animals etc.

The absolute contraindications for the beginning of the immunotherapy are the severe immune diseases (autoimmune, primary immunodeficiency, AIDS etc.), malign diseases, severe cardiovascular disease, chronic infections, severe asthma with FEV1 under 70%, patients with continuous beta-blockers treatment, patients with critical mental disorders and acute infections. The relative contraindications include the severe atopic eczema and the beginning of SIT during pregnancy, not because of the teratogenic risk, but due to the anaphylactic reaction in the induction phase. The patient, who is already pregnant and has been using the immunotherapy, mainly in the maintenance phase, can continue the treatment with her consent.

The extract quality for the “in vivo” diagnosis, such as skin test, and for the SIT, is crucial for success in both procedures. The allergen source materials should be well selected and its industrialization based on stabilized rules according to the European and American Societies as well as the World Health Organization. The source of allergen extract comes from the nature where the allergen is responsible for the allergy development such dust mite, pollen, fungi etc. Most of the times these allergens are made of protein or glycoprotein which each one may have numerous of identified antigens that develop the allergic process.

The extracts can be classified as standardized and non-standardized. The non-standardized extracts are identified in weight/volume (w/vol), with the weight in grams and the volume in milliliter, or then in Protein Nitrogen Units (PNU) which 1 PNU corresponds to 0.01 g of nitrogen protein. Indeed, the non-standardized extracts may have a wide potency discrepancy, and the identical label extracts, in terms of concentration (weight/vol or PNU), may present less potent biological properties. The standardized extracts may be commercially available for the majority of antigens previously known as allergy-sources. In addition, it is worth to note the safety of standardized extracts in biological potency; thus causing minimal risk from adverse reaction. The procedures of standardization are based in a specific method and are called “in vitro” or “in vivo” standardization. The skin tests permit establishing the “in vitro” or “in vivo” tests. In the immunotherapy, the skin test is a method to confirm the diagnosis and to titrate the therapy. The extracts must be used under the supervision because of the risk of systemic collateral effects.

The immunotherapy involves two phases: firstly, described as induction phase, gradually increased concentrations of antigen are taken until achieving the maximal dose. Secondly, initiate the maintenance phase which the maximal dose obtained before will be the maintenance dose taking regularly for 3 to 5 years. The frequency of application, in the induction phase, depends on the route used. The SLIT mainly in allergic patients, the frequency is once or twice a week from 0 to 0.5 mg/month. In addition, for SLIT it is necessary caution to the commercial recommendations such as drop medication therapy which should be used under the tongue during 1 to 3 minutes and then swallowing. Besides, it has a preference to take the medication when the patient requires fasting and usually daily at the same time. In some specific cases, the SLIT must be delayed when the patient develops ophthalmic infections, otology surgery, gastroenteritis, exacerbated asthma or with simultaneous administration of viral vaccines.

The recommendation for SCIT treatment requires constant medical supervising and the initial doses (induction phase) should be 1000 to 10,000 mcg/dose lower than the subcutaneous injection dose. Allergy subcutaneous injection must be made carefully and slowly in the superior external arm, avoiding the inverse vascular aspiration. Then, when the maintenance dose will be reached, following the commercial recommendations (around 5 mcg and 20 mcg of the higher allergens) and the individual tolerance, the SCIT applications will be made monthly (maintenance phase). In the case of SLIT, there is a wide variability for the SCIT recommended doses and it is believed that the allergen used in SLIT doses must be higher than SCIT doses.

Practical considerations for use of the SIT in respiratory allergies

First, before proposing to immunotherapy as treatment, the medical recommendation should be detailed to the patient such as the expected results, the duration of the treatment, the period for manipulating vaccine, the probable collateral effects and finally, the financial costs. Then, after a clarified consent from the patient, the therapy may initiate. An issue to be considered of as the expected results, the duration of the treatment, the period for manipulating vaccine, the probable collateral effects and finally, the financial costs.

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The interruption of the immunotherapy, before the previous conclusion date, can occur in the following situations: no therapeutic response of the patient, of the absence of compliance, skin test positive reactions, persistent and regular serious symptoms, persistence by absence of symptoms, lack of therapeutic response by 2 years of treatment. Because of the possible adverse reactions, it is indispensable that SIT is made in a safe place, with medication and medical emergency equipment, and by a competent professional. It is also recommended a period of at least 60 minutes of observation for patient after administration of the dose. A possible anaphylactic reaction must be treated immediately with 0.1% epinephrine; if the dose used is the adrenaline (1 mg/mL); for children, doses of 0.01 mg/kg (until maximum 0.3 mg per dose) without dilution and for adults, initial doses of 0.3 to 0.5 mg which can be repeated in a short time according to the requirement.

Finally it is noteworthy that in clinical practice, therapeutic non-response to immunotherapy may be due to other uncontrollable variables such as emotional stress or irritable substances (e.g. cigarette smoke) (52, 53). Therefore the immunotherapy should be continuously accompanied with other therapeutic appliances such as medical orientation, environmental control, emotional support and many
times, the use of medication, mainly in the initial phase (induction phase).

Concluding remarks

With regard to the implications for research even though further studies are needed to fully understand the various aspects of SIT, such as the complete knowledge of its action mechanism as well as the whole understanding of its efficacy magnitude; even so, the SIT has been accepted as an excellent alternative therapy to allergic asthma since recommended with criterion form and well-applied.

Bibliografia