MOREIRA JR.

Immunotherapy in allergies

Imunoterapia nas alergias

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Sumário
A imunoterapia alérgeno específica consiste na administração, em pacientes alérgicos com condição IgE mediada, de quantidades gradualmente aumentadas de um determinado alérgeno, no sentido de providenciar proteção contra sintomas alérgicos e reações inflamatórias. A forma de ação da imunoterapia ocorre através da modulação na liberação de mediadores envolvidos na reação alérgica e, consequentemente, inibição do processo inflamatório alérgico. Em 1997 representantes da Organização Mundial da Saúde (OMS) e de várias Sociedades de Alergia, Asma e Imunologia, fizeram uma revisão, buscando estabelecer normas de utilização e indicação da imunoterapia. Atualmente várias publicações a respeito da eficácia, assim como diversos guidelines sobre a utilização da imunoterapia no tratamento das doenças alérgicas estão disponíveis. Este artigo tem como objetivo focar as mais atuais evidências sobre a imunoterapia nas doenças alérgicas em relação ao seu mecanismo de ação, efetividade, assim como considerações práticas.

Sumary
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.

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.

The allergen-specific Immunotherapy (SIT) has proven to be an effective treatment for IgE-mediated allergy, which is characterized by administration of gradually augmented doses of a specific allergen in the allergic patients. The aim of this treatment should propose the

protection against the allergic symptoms developed by the inflammatory responses from the patients exposed to the same allergen.

Immunotherapy is already well established for use in respiratory allergies and insect bites, which does not occur in relation to hives, food allergies and atopic dermatitis. The main purpose of the treatment of respiratory allergy is the prevention of the allergic crisis and allows an improvement of health quality of these patients. Than the respiratory allergy therapeutics would involve the following possibilities: an improved environment controls, a medical therapy and when possible, if necessary, the SIT.

The two main manifestations of respiratory allergies would be rhinitis and asthma but symptoms involving conjunctiva, nasopharynge or paranasal sinuses can be presents too. At this point the SIT allows the therapeutic direction for the cause of the problem and the result includes all the possible manifestations such as asthma, rhinitis, conjunctivitis or any another manifestation that patient could have. Also other differential aspect in favor of the immunotherapy is the modulation of the immune system and thus modifying the natural development of the disease(2).

Although there are other routes for the immunotherapy not well established as nasal, oral and bronchial this article focuses on SIT in the subcutaneous and sublingual routes and their main aspects such as mechanism of action, effectiveness and questions for its use.

The effectiveness and safety of SIT

In 1997, physicians and researchers from many countries, together with the representatives of the World Health Organization (WHO) and several World Associations of Allergy, Asthma and Immunology considered the credibility of effectiveness of the immunotherapy(3). Although these researchers established standards of use and the immunotherapy indications, the effectiveness of the SIT was, in that moment, not fully established.

The best evidences of efficacy of any treatment can be obtained through randomized controlled clinical trials (preferring double blind) or throughout systematic reviews with meta-analysis, where the results of many studies can be analyzed simultaneously(4). Abramson et al.(5,6) in the systematic reviews with meta-analysis, evaluated, the allergen-specific sub cutaneous immunotherapy (SCIT) for asthma whose efficacy has been proven by reducing the symptoms, less need for medications and improves bronchial hyper reactivity. But the authors pointed out the possibility of adverse effects, including anaphylaxis. With sublingual immunotherapy (SLIT), Durham et al.(7,8), carried out a meta-analysis which supports the evidence of efficacy and safety of this treatment in rhinitis. In the asthma, Calamita et al.(9) investigated the effectiveness and security of SLIT. This meta-analysis found that SLIT is beneficial for asthma treatment albeit the magnitude of effect it is not very large but it is a safe alternative to the subcutaneous route; however the authors concluded that further studies are needed. Also there are two important points in favor of SIT this is it should be the prevention of new allergen sensitization, so far observed by some authors(10,11) and the maintenance of SIT efficacy in the long-term after the pause of the immunotherapy(12,13). Recently, many guidelines in extended reviews and studies(14-19), with the most critical world researchers, support the theory and functional apply of SIT as treatment in the respiratory allergies.

Unfortunately there is the possibility of local or systemic reactions for both SCIT and SLIT(3,5-9,14-19) mainly in the induction phase. Although not common the systemic reaction occurs more frequently in SCIT and rarely in SLIT. There are many types of local and systemic reactions. In the case of SCIT may be observed a local reaction and an edema at the point of vaccination application. This reaction can occur in the first 60 minutes after the application or in the long-term; but it is well tolerated and does not require specific therapy. For SLIT, the local reaction develops oral symptoms such as pruritus, edema and eritema in oral cavity usually in the first 60 minutes and tends to solve spontaneously.

The systemic reactions are characterized by general symptoms, distant from the site of the application. These reactions, in most of the cases, occur in the first 60 minutes after the application and present a diversity of symptoms such as rhinitis, asthma, angioedema, urticaria and anaphylaxis. A great attention should be given in the case of immunotherapy for allergies to insect bites at high risk of serious systemic reactions.

The allergic inflammation and mechanisms of SIT action

Before we discuss the possible mechanism of action of the immunotherapy(20-24) would be interesting to elucidate how the allergen-inflammation occurs: in previously sensitized individuals, the exposure of inhaled allergen stimulate the local dendritic cells (DC) which uptake and process the antigen, working as professional antigen-presenting cells (APC) which then stimulate the TCD4 helper lymphocytes (Th)(25,26). The Th lymphocytes differentiate into two subsets, known as Th1 and Th2(27). The Th1 cells are responsible for the production of interleukin-2 (IL-2) and IFN-g cytokines acting mainly in tumor and infection diseases of immune response(28). On the other hand, the Th2 cells provide IL-4 and contact-mediated signals that promote differentiation of B lymphocytes specific for production and secretion of immunoglobulin E (IgE), identified as humoral immune response, the main course in the development of asthma(29). The IgE molecule bound to receptors on airways mast cells, which in contact with sensitizing allergen, trigger these mast cells activation and release of preformed mediators of their granules, such as histamine and leukotrienes(29,30). These mediators are vasoactive amines and drive the vasodilation, mucosal edema, increase mucus secretion and bronchoconstriction; thus, amplifying the airway inflammation.

Beside this immediate hypersensitivity describe above, also occurs a late phase reaction which is initiated by the action of IL-5 and other chemotactic factors which increase the cell recruitment and maintain the chronic inflammatory infiltrate. The main cells presented in this inflammatory infiltrate are the eosinophils which release additional inflammatory mediators such as major basic proteins, eosinophil cationic protein and leukotrienes, just mentioned(32). A wide variety of allergens in environmental conditions inside and outdoor home could develop the allergic reactions. Furthermore the constant exposure to the allergens results in immediate hypersensitivity together with the delayed allergy reactions resulting in chronic airway inflammation.

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. Also, the presence of suppressive cytokines as IL-10 and transforming growth factor b (TGF-b) appear to be important for controlling the allergic inflammatory response(33,34). Besides Th1 cells and cytokines orchestrate the suppression of allergic inflammation, a third subset of T lymphocyte, referred as regulatory T cell (Treg), plays a role for the development of a balanced Th2/Th1 profile with down-regulatory tone in allergic reaction(35-38). These Treg cells constitutively express the IL-2 receptor a-chain, a cell-surface marker CD25+(39), and the specific intracellular marker molecule, as forkhead family transcription factor 3 (Foxp3)(40). In addition, Treg cells function as critical regulators of the effectors T cells activity and then preventing the autoimmune diseases and allergy(41,42). Moreover, there is the existence of two subsets of Treg, natural and adaptive, differing in terms of their development, specificity, mechanism of action and dependence on T-cell receptor and co-stimulatory signaling(43). The natural Treg cells develop in the thymus, typically express high levels of IL-2 receptor a-chain (CD25), commonly called TCD4+CD25+. The adaptive Treg cells are generated from mature T-cell populations under certain conditions of antigen stimulation in periphery promoting suppression through the production of IL-10 and TGF-b cytokines. In addition to adaptive Treg cells, also other types of T cells with regulatory function including TGF-b-producing Th3 cells(44) , IL-10-producing Tr1(45) cells, CD8+CD28-T cells(46), gd T cells(47), and NKT cells(48) have been described previously.

In addiction to the previously describe mechanism which apply to both SCIT and SLIT, currently another studied question triggers the specific local mechanism of the SLIT action. The oral mucosa is well-known to have its peculiarities which induce allergen tolerance. Because of the high mucosal permeability, it contributes to the absorption of the extracts used during the immunotherapy. As a result, decreased local inflammatory infiltrate could reduce the adverse reactions. Furthermore, the presence of professional antigen-presenting cells (APC), as dendritic cells (DC) which could orchestrate the immune response stimulating the activity of regulatory T cells. It seems without a doubt that oral DC could have an essential role in the induction of tolerance and local homeostasis. Accordingly, the major oral mucosa DC population is characterized by oral Langerhans cells (LC), unlike that cutaneous LC, due to the constitutive presence of the high affinity IgE receptor (FceRI)(22,49). During the SLIT, the LC recognizes the allergen that is being processed and presented by these LC to the T lymphocytes. Then the Treg may elicit an induction of tolerance with production of suppressive IL-10 and TGF-b cytokines(50). The immunotherapy can also induce B lymphocytes switching to IgG4 isotype which is called "block antibody"; as a result, it occurs a favored balance between IgG4/IgE, as well as an increase of IgA synthesis(22). It is worth to note that both IgG4 and IgA isotypes are immunoglobulins which do not participate in inflammatory response and in the activation of classical pathway of the complement system. Finally, high levels of both isotypes correspond with the increased synthesis of IL-10 and TGF-b cytokines in the control of the allergic response.

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 rhinits, allergic conjunctivits, 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 rhinits, 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 allergy. The contraindication of skin test is for patients who have highly sensitive skin (dermogram) 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 previously the skin test. For example, the antiH1 antihistamines should be discontinued a week before the skin test and the antiH2 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 patients. The supposed allergen of a particular 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 risck, 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/volume or PNU), may present different biological potencies. 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 mainly in allergen-specific IgE "in vivo" and "in vitro" detection. The skin tests permit the extract standardization into Biological Unit (BU) or Bioequivalent Allergy Unit (BAU). In Europe the skin prick testing is most frequently used, comparing the reaction produced by the allergen, in a population group, with the histamine production (10 mg/mL) and BU is used as unit. In contrast, in the USA, the extract potency is determined through the intradermic skin tests and BAU as unit. The characterization of the main allergen and its laboratorial measurement technology are important to inform about the content and the quantified presentation in terms of the main allergens mass (mcg/mL). The natural allergens can suffer physical or chemical modifications. In general the physical modification occurs after the addition of some elements, such as aluminum which allow the gradual release of the allergen; these vaccines are widely used in the treatment of respiratory allergies unlike aqueous vaccines generally used in allergies to insect stings. The chemical modifications of vaccines (known as allergoids) reduce its allergenicity with less risk of adverse reaction but without changing its immunogenicity. Currently the molecular biology research, with the recombinant DNA technology, may offer safety and efficacy of recombinant vaccines(51).

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 prescription of SIT should be the choice of the route used whether subcutaneous or sublingual. Unfortunately, there are no sufficient studies to compare the efficacy for both routes. Thus, the choice will depend on each particular situation, because for both routes there are already promising proves. So the decision will be based on other aspects. For instance regarding the collateral effects, the SLIT presented itself safer than SCIT; because of the ease of manipulating, due to the first doses, the physician supervision is recommended and then the permanent treatment can be completed at home. On the other hand, the SCIT doses should be taken with medical 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 recommends the daily frequency, whereas for SCIT the frequency is once or twice a week, during from 3 to 6 months. In addition, for SLIT 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 oropharynges infections, odontology 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 times lower than the further maintenance dose. Also, the 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 allergen) 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 SLIT recommended doses and it is believed that the allergen used in SLIT doses must be higher than SCIT doses.

The interruption of the immunotherapy, before the previous conclusion date, can occur in the following situations: no therapeutic responsibility by the patient, some contraindication symptoms, persistent and regular serious collateral effects, absence of the clinical response after 2 years of treatment. Because of the possible adverse reactions, it is indispensable that SIT is made in a safe place, with medicament and medical emergency equipment, and by a competent professional. It is also recommended a period of at least 60 minutes for patient observation after the used dose. A possible anaphylactic reaction must be treated immediately, and the most 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 uncontrolled variables as emotional stress or irritable substances (e.g. cigarette smoke)(52,53). Therefore the immunotherapy should be continuously accompanied with others 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 acceptable as an excellent alternative therapy to allergic asthma since recommended with criterion form and well-applied.

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