

CME Article

Specific immunotherapy with allergens: an important tool in the treatment of the allergic diseases

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Specific immunotherapy (SIT) is a treatment in which specific allergens are administered to individuals who are allergic to these allergens. The goal of SIT is to reach a maintenance dose that modulates the immunological system and allows the allergen to be tolerated.

Tolerance that is produced by SIT is caused by the increase in CD4+ CD25+ regulatory T cells.

The success of SIT depends on the use of standardized extracts for which the potency and the relevant allergenic compounds are known.

Summary

Immunotherapy was introduced 100 years ago and still is the only treatment that modifies the course of allergic diseases. The success of its use depends on correct indications, use of standardized extracts and monitoring the therapeutic response.

Introduction

Specific immunotherapy (SIT) is a treatment in which specific allergens are administered to individuals who are allergic to these allergens. The goal of SIT is to reach a maintenance dose that modulates the immunological system and allows the allergen to be tolerated [1–4]. SIT is the only treatment that can modify the natural course of allergic diseases [1, 4–9]. The most frequent application forms are: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT).

Actions mechanism

The initial immunological tolerance that is produced by SIT is caused by the increase in CD4+ CD25+ regulatory T cells, or inducible Tregs (formerly called suppressor T cells), which secrete anti-inflammatory cytokines, such as Interleukin 10 (IL-10) and transforming growth factor- β (TGF- β). These cytokines suppress effector cells (mastocytes, eosinophils, basophils) and reduce the release of proinflammatory cytokines [5]. In contrast to T cells, there is no evidence suggesting the induction of immunological tolerance of B cells during the course of SIT [4].

In the initial phase of this treatment, there is an increase in specific IgE release that is followed by a gradual reduction during the maintenance phase. Immunoglobulin A (IgA) and G (IgG 1 and 4) levels also increase, but the levels do not correlate with clinical improvement or the duration of SIT effectiveness [4, 5, 10, 11].

Standardization of the extracts

Allergen extracts may be obtained from various sources, such as pollen, fungi, or animals; they correspond to those fractions of proteins or glycoproteins that induce the allergic response. Such extracts may be used to diagnose and specifically treat allergic diseases [1].

The success of SIT depends on the use of standardized extracts for which the potency and the relevant allergenic compounds are known. The potency may be continually degraded by the storage temperature (which is why the extract should be stored at 4 °C), contamination (which accelerates the degradation of the extract), the effect of dilution (loss of potency is proportional to the extract's dilution), the type

There is no universally accepted standard for measuring allergen content. Many laboratories use in-house reference materials.

SIT is indicated for IgE-mediated diseases, such as moderate-severe allergic rhinitis, rhinoconjunctivitis, and controlled allergic asthma.

Contraindications to SIT: malignancies, a forced expiratory volume in 1 second (FEV1) of less than 70 % of the predicted value, uncontrolled asthma, and acute infections, such as a cold with a fever.

The use of beta-blockers should be substituted because they decrease the appropriate response to adrenaline in the case of a systemic reaction.

SIT should be prescribed by a physician experienced in this treatment.

The following allergens have been successfully used: birch, hazel, olive, ash, grass, cypress, cat dander, *Parietaria*, mugwort, ragweed, *Dermatophagoides pteronyssinus*, *D. farinae*.

of allergen (the concentration and presence of enzymes), the diluents used, and the preservatives added. Currently, lyophilization is the technique that best preserves the extract's potency [1, 12]. There is no universally accepted standard for measuring allergen content. Many laboratories use in-house reference materials and their own units to assess the potency of each extract [13].

Once the lyophilisates are reconstituted, stabilizing substances, such as glycerin (50 %) and human serum albumin (0.03 %) must be added to maintain the vaccine's potency. The latter impedes the adsorption of the allergen into the bottle's inner surface, while the former inhibits the proteolytic activity of enzymes that are present in some extracts, although it may cause discomfort during subcutaneous application. Phenol is a preservative (similar to glycerin) that is added to prevent the growth of microorganisms because this substance can denature proteins in the extracts. The deleterious effects of this substance are mitigated by the presence of human serum albumin [5].

The extracts may undergo physical and chemical modification. Physical modification includes the adsorption of allergens to aluminium to promote slow, continuous antigen release (depot vaccines). Although this modification may provide an immunological advantage, it may cause discomfort when applied [1].

A chemical modification process involving denaturing chemicals such as formaldehyde or glutaraldehyde changes the tertiary structure and can decrease the amount of reactive immunoglobulin E binding protein, thus decreasing the incidence of adverse systemic reactions. However these denatured proteins can still activate the production of specific IgG, and regulatory T-cells needed for the therapeutic success. These SIT extracts are called allergoids [1, 14].

Indications

SIT is indicated for IgE-mediated diseases, such as moderate-severe allergic rhinitis, rhinoconjunctivitis, and controlled allergic asthma [2, 5]. Few studies have tested the use of subcutaneous SIT to treat food allergies, although the effectiveness of this treatment form is being further evaluated with sublingual use of extracts and oral use of whole food. For example, protocols exist for milk. In addition, no evidence supports the use of this treatment for chronic urticaria or angioedema [5]. Insect venom SIT is indicated for patients with a history of anaphylaxis after exposure, with positive cutaneous tests, and positive tests for the presence of specific IgE [5]. SIT is indicated for adults and children; there are no age limitations. Care must be taken to ensure the correct indication, the lack of significant comorbidities, and the cooperation of the patients [5].

Contraindications

The following are contraindications to SIT: malignancies, a forced expiratory volume in 1 second (FEV1) of less than 70 % of the predicted value, uncontrolled asthma, and acute infections, such as a cold with a fever. SIT may be continued during pregnancy, but it should not be initiated during pregnancy. The use of beta-blockers should be substituted because they decrease the appropriate response to adrenaline in the case of a systemic reaction [2]. SIT may be carefully considered also among patients with autoimmune and immunodeficiency diseases because no evidence suggests that the use of this treatment may worsen the disease [5]. However many manufacturers still list autoimmune disease as contraindication. This is not based on evidence but on the fear that alterations of immune functions in SIT which are not yet known might aggravate autoimmune reactions.

Prescription

SIT should be prescribed by a physician experienced in this treatment. The appropriate allergens should be selected according to the patient's clinical history (duration and severity of the symptoms throughout a year), the impact over the patient's quality of life, the difficulty of environmental control, and the presence of allergen-specific IgE, which does not indicate clinical sensitivity [2, 5].

The following allergens have been successfully used: birch, hazel, olive, ash, grass, cypress, cat dander, *Parietaria*, mugwort, ragweed, *Dermatophagoides pteronyssinus*, *D. farinae*, hymenoptera venom (bees, wasps, and yellow jackets), and to some extent

fungi and cockroach [2]. Some factors impede the use of fungi in SIT, including the existence of hundreds of different fungal species; the frequent lack of correlation between symptoms and exposure; the lack of fungal extract standardization; the high mutation rates; the presence of enzymes (making it impossible to mix fungi with pollens or mites); and the failure of many genera to grow in artificial media, which makes many clinically important fungi unavailable for therapeutic use [5, 15].

Allergies to the most common species of cockroaches, *Blattella germanica* (Blat g 2, 4, 5) and *Periplaneta americana* (Per a 1), constitute a common risk factor for the development of bronchial asthma [16]; however, the data on the effectiveness of this SIT are still limited [5].

SIT with latex proteins has shown good results with regard to improving respiratory and cutaneous symptoms, but is not widely available for clinical practice [17]. In general, vaccines may be prepared with a single allergen or with a mixture of allergens; data are available regarding the stability and clinical effectiveness of mixtures. However, the GA²LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma [2] does not recommend the use of mixtures of unrelated allergens since this leads to dilution, and instead suggests using two treatments in parallel.

SIT consists of two phases: the induction phase and the maintenance phase. With subcutaneous administration, the induction phase is characterized by the progressive administration of the allergen one to three times per week for 8 to 28 weeks. The duration depends on the frequency of administration. The allergen should always be administered in the presence of a physician [13].

The interval of the applications in the maintenance phase is in most cases 2–6 weeks for inhalants and 4–8 weeks for hymenoptera. The dosage is always the same (approximately 5–20 µg of the major allergen, which possesses a known concentration. For hymenoptera, 100 µg, which corresponds to two wasp stings), although it may be altered in the presence of adverse reactions as well as increased in some highly endangered patients (such as with mastocytosis) to 200 µg to ensure better protection [5].

Rush SIT refers to the administration of multiple doses during each visit (two or more in the beginning), once or twice a week, to more rapidly reach the maintenance phase (after approximately 4 weeks). Once the maintenance dose is reached, it should be administered monthly. Rush SIT is associated with a greater risk of a systemic reaction among some patients. The use of pre-medication (antihistamines) decreases the risk of this reaction. Each application is administered over a 30-minute interval [1, 5].

Each bottle should contain the patient's name and date of birth, the allergens contained in the mixture, the manufacturing and expiration date, and the route of administration. The bottles should ideally be labeled in different colors that correspond to the concentration [5].

The patient should receive written information on the vaccine, the expected symptoms, and the possible complications and be asked for informed consent [5]. The observation period after the subcutaneous application of the vaccine is generally 30 minutes but may be longer depending on the individual risk [1, 5].

Among asthmatic individuals, the patient's peak expiratory flow should be measured before the application; the SIT should be suspended when the value is below the predicted value [5]. While they are undergoing SIT, the patients should be continuously reevaluated to observe the treatment's effectiveness, adverse reactions, patient adherence to the treatment, and the need to suspend or adjust the dosage or the allergen content [5]. No prospective or retrospective studies have been performed on the modification of IT doses when gaps exist during the induction phase. In this case, it is possible to decrease one dose for each week lost [5].

If effective, the SIT for inhalant allergens should continue for 3 years [18]. The decision to suspend treatment should be individualized, considering the disease severity before treatment, the inconvenience to the patient, and the effects of a relapse in the patient [5].

Subcutaneous SIT may only be applied in the presence of a physician and readily available equipment for treating anaphylaxis, including adrenaline and oxygen [5].

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SIT effectiveness in the individual patient however depends on the correct indications.

The standardization of the extracts, and the dosage are crucial.

Local reactions occur at the application site in 26–82 % of patients.

Subcutaneous nodules may form at the location of SCIT application, especially when aluminum-adsorbed vaccines are used. These nodules may persist and disappear after a few weeks. There is no need to adjust the SIT dosage, but one should consider to switch to a vaccine that does not contain aluminum.

The prevalence of systemic reactions to conventional SCIT is less than 1 % especially when allergoids are used but may reach 34 % in patients receiving rush SIT.

The severity of the reaction is related to the speed at which the symptoms appear following the application.

Factors influencing SIT effectiveness

In large studies SIT has been proven effective both with subcutaneous and sublingual administration in adults of all ages and children alike. SIT effectiveness in the individual patient however depends on the correct indications. Patients must not only have cutaneous tests that are positive for allergens but also a history indicating that the SIT allergen is relevant for the clinical symptoms. This is especially important in polysensitized patients. The standardization of the extracts, and the dosage are also crucial, since low doses are ineffective and very high doses may lead to adverse reactions [1, 5, 18].

Clinical parameters (the symptom score and the type and duration of the rescue medication) may be useful in measuring SIT effectiveness [5]. Nasal, conjunctival, and pulmonary provocation and spirometry may also be used as parameters to measure SIT effectiveness [8].

With subcutaneous SIT, a positive treatment response depends on the volume of the injection, the dose of the allergen, the modifications in the preparation of the allergen, and the nature and concentration of the adjuvant. The success of sublingual SIT is related to the preparation (liquid or solid), the solution volume, the adjuvant, and the contact time with the mucosa [13].

The relationship among the treatment duration, the administration frequency, and the effectiveness has not been established [19]; however, the treatment appears to be more effective after 3 years of application and with adherence to the treatment [1]. Some factors may lead to a lack of an SIT response in some patients, such as erroneous allergen selection, insufficient allergen concentration in the extract, lack of adhesion, continued exposure to the allergen at home (such as cat dander), or exposure to aggravating factors, such as tobacco. If no improvement is recorded after 1 year of maintenance, the causes underlying the lack of effectiveness should be investigated [20]. If no cause is identified, the suspension of SIT should be considered, and other treatments should be proposed [19].

Adverse reactions

The reactions may be local or systemic.

Local reactions

Local reactions occur at the application site in 26–82 % of patients [5] and are observed both in SLIT and SCIT. According to the time of their appearance they can be classified as immediate, which occurs 20–30 minutes after the application, and late, which occurs at least 30 minutes following the application.

Immediate reactions can involve local swelling, erythema, and itching. There is no relationship between late reaction symptoms and the risk of developing severe systemic reactions during the next application [1, 14].

Subcutaneous nodules may form at the location of SCIT application, especially when aluminum-adsorbed vaccines are used. These nodules may persist and disappear after a few weeks. There is no need to adjust the SIT dosage, but one should consider to switch to a vaccine that does not contain aluminum [1]. The presence of more than 50 % glycerin is not related to an increase in local reactions but does lead to increased pain during injection [5].

When a local reaction occurs, cold compresses or oral antihistamines may be used. In the event of the recurrence of a local reaction, the patient should be pre-medicated with antihistamines [5, 21].

Systemic reactions

The prevalence of systemic reactions to conventional SCIT is less than 1 % especially when allergoids are used but may reach 34 % in patients receiving rush SIT [5]. These reactions frequently begin just a few minutes after administration of the allergen. They are characterized by the appearance of symptoms such as rhinitis, asthma, urticaria, angioedema, aphonia, dizziness, nausea, vomiting, tinnitus, abdominal pain, or sphincter relaxation. In these cases, the patient should be observed for at least 1 hour [1, 5].

The severity of the reaction is related to the speed at which the symptoms appear following the application. The occurrence of itching or erythema on the soles, palms

and scalp is often a first warning sign. If urticaria, rhinitis and asthma appear within a few minutes after SIT, this often progresses rapidly to severe anaphylaxis. In this situation, immediate treatment is necessary [14].

The following are considered to be risk factors for systemic reactions: uncontrolled bronchial asthma and a FEV1 that is ≤ 70 % of the predicted value; the use of beta-blockers; high doses of potent, standardized vaccines for inhalable allergens; rush SIT with insect venom or inhalable allergens; the incorrect application technique; a dosage error; and administration of allergen during a period of exacerbated symptoms [1, 22].

The procedure for these severe cases is to administer intramuscular 1 : 1,000 adrenaline in an aqueous solution and provide oxygen. Additional measures may include parenteral antihistamines, intravenous corticosteroids, and possibly bronchodilators according to the guidelines for treatment of anaphylaxis. Although these treatments are not effective in the immediate phase of anaphylaxis, they are effective in the late phase [1, 5].

Pre-medication, such as antihistamines, may be used, although some authors believe that this method may mask a minor reaction that could alert the physician to the development of a systemic reaction. In addition, some patients may exhibit an anaphylactic reaction even with medication. Currently, no studies have demonstrated the effectiveness of leukotriene antagonists in preventing systemic reactions. Pre-medication is not routine in SIT for hymenoptera [5].

Pre-treatment with omalizumab, which is an anti-IgE monoclonal antibody, has been demonstrated to increase the safety of rush SIT among patients with moderate persistent asthma and allergic rhinitis. This treatment prevents free IgE from binding to mast cells, basophils, and dendritic cells, which decreases the release of allergic reaction mediators, including histamines, cytokines, and leukotrienes. Omalizumab amplifies the SIT response [23].

Experimental routes of SIT administration

Due to the frequent applications, their discomfort, and the possibility of adverse reactions, alternate SIT administration routes have been evaluated. When alternate administration routes are chosen which allow self-administration, additional care should be taken.

Intralymphatic: A course of three injections administered every 4 weeks was as effective as subcutaneous SIT for 3 years in an uncontrolled study. The allergen concentration was 1,000 times lower, and the risk of a systemic reaction was also lower [5].

Epicutaneous: This route offers the possibility of SIT without needles and may be self-administered by the patient. A patch that contains the allergen is applied for 48 hours once a week for 12 weeks. Scarification is performed beforehand with adhesive tape. Adjuvants, such as cholera toxin and heat-labile enterotoxin, have been used with this route of SIT to target infectious diseases in humans. The primary reaction was eczema at the application site. However, the immunological mechanisms of this route are unknown [24].

Nasal: The vaccine in the form of powder or an aqueous solution is administered through a spray mechanism. This treatment was generally used for pollen rhinitis [14], but has been substituted with SLIT [1, 5, 18].

Bronchial: This medium may also be a powder or an aqueous solution, and it is applied in the lungs using an appropriate device. The effectiveness of this treatment is controversial but surely the risks are high [1, 18].

Future outlook

The future of SIT involves the use of purer and standardized extracts; component-resolved, recombinant allergens, peptides, chimeras, and adjuvants; combinations of viral and biological vaccines; and naked DNA vaccines [3, 11]. With a better understanding of the regulatory T cells and the diversity of the immune response in different groups of individuals, in the longer future it is likely that patient-targeted therapies will also be available for SIT. <<<

Conflict of interest

None.

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Pre-medication, such as antihistamines, may be used.

Pre-treatment with omalizumab has been demonstrated to increase the safety of rush SIT.

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