



Good clinical practice recommendations in allergen immunotherapy: Position paper of the Brazilian Association of Allergy and Immunology - ASBAI

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ABSTRACT

Background: Allergen Immunotherapy (AIT) represents one of the pillars in the treatment of allergic diseases. AIT is the only therapeutic strategy with curative potential, promoting the reduction of drug use and long-term symptom control even after the end of the treatment. The European Academy of Allergy, Asthma and Immunology (EAACI) guidelines, position papers of World Allergy Organization (WAO), and the US Practice Parameters are the leading official documents that set scientific standard for the use of AIT in the world. The use of AIT in Brazil has specific regional conditions due to the pattern of allergen sensitization, as well as genetic, socioeconomic, and cultural characteristics, climate conditions, and the availability of allergenic extracts. The most prevalent house dust mites are *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* and their allergens have the highest clinical relevance. *Blomia tropicalis* is also very frequent. This position paper has been prepared by the Brazilian Association of Allergy and Clinical Immunology (ASBAI) Task-force on AIT for respiratory allergy and Hymenoptera venom allergy.

Objective: According to the current scientific literature adapted to the Brazilian reality, this position paper aims to establish the main recommendations for the good clinical practice parameters for AIT in Brazil.

Methods: A systematic review using the Pub Med and Cochrane databases was performed, and the websites of major allergy and immunology organizations were consulted. The research was limited to English language literature and was conducted between March 30, 2002, and March 30, 2022. The terms used for the research were: Allergen Immunotherapy, sublingual immunotherapy (SLIT), subcutaneous immunotherapy (SCIT), venom-specific immunotherapy (VIT), and allergen extract.

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Results: The several recommendations that establish the clinical practices for AIT recommended by the main Allergy, Asthma and Immunology world organizations were analyzed and adapted to the Brazilian situation.

Conclusion: This position paper establishes the main recommendations for the effective clinical practice of AIT in Brazil, using current knowledge of evidence-based medicine and precision medicine.

Keywords: HDM, House dust mite, SCIT, Subcutaneous allergen immunotherapy, SLIT, Sublingual allergen immunotherapy, VIT, Venom-specific immunotherapy, Clinical practice

INTRODUCTION

Since 1911, allergen immunotherapy (AIT), a strategy of desensitization and induction of immunological tolerance has been used to treat IgE-mediated allergic diseases.^{1,2} In the last decade, the immunotherapy strategy has also been used to treat certain types of cancer and autoimmune diseases.³ International Allergy and Immunology societies have established a new global nomenclature called allergen immunotherapy to treat allergic diseases with specific allergen extracts.³⁻¹¹

AIT is considered the only therapeutic procedure capable of modifying the natural history of allergic diseases, representing one of the pillars of the professional practice in Allergy and Immunology. AIT is an immunomodulator treatment with curative potential by modifying the allergen-specific immune response. Unlike the use of pharmacotherapy and biologics, this immunomodulatory strategy can promote remission and control of allergic diseases for prolonged periods, even after AIT administration has ceased. In this context, the control of allergic disease remains for at least 7-10 years without medication and may remain for the individual's entire life. Furthermore, when relapsing conditions occur, they are usually less severe.³⁻⁸ In addition, it has preventive potential for the development of asthma in patients with allergic rhinitis (AR).^{6,9,12} Allergic and immunological diseases compromise several organs and systems, such as skin, upper and lower airways, gastrointestinal system, and eyes. The professional training of the specialist in

Allergy and Immunology includes adequate preparation in clinical procedures, diagnostic methods, and therapy, the performance of specific allergy tests, particularly skin prick test (SPT), and the indication and adequate management of AIT.⁶⁻⁹ Thus, the specialist in Allergy and Immunology is the unique professional who has the knowledge and ability to provide accurate etiologic diagnosis and immunomodulation of the allergen-specific responses. Identifying allergen(s) responsible for the disease through complementary exams, particularly allergy tests, and correctly interpreting them is essential to performing AIT. Therefore, AIT represents what we know today as Precision Medicine.¹³⁻¹⁵ There are some differences for AIT management in the various international consensus/guidelines. This position paper has been prepared by the Brazilian Association of Allergy and Clinical Immunology (ASBAI) Taskforce on AIT for respiratory allergy and Hymenoptera venom allergy. The present position paper aims to establish best practice recommendations for using AIT in Brazil, adapting current scientific evidences to the regional reality.

THE QUALIFIED PROFESSIONAL

The AIT should be personalized according to the degree of patient allergic sensitization and the clinical relevance of allergens. The choice of allergenic extracts and their dilution is an essential step, requiring professional expertise. Concerning technical planning, the physician in charge must

analyze the data from the clinical history, physical examination, and complementary exams, and guarantee that there is scientific proof of possible benefit of the AIT for each clinical indication.^{4,6,8,13,14} The indication, orientation, prescription, planning, follow-up, and supervision of the SCIT or SLIT application regimen and technical planning are physicians' private acts.

In Brazil, the resolution of the Federal Council of Medicine (Conselho Federal de Medicina – CFM) number 215/2018 regulates the use of allergenic extracts for diagnostic and therapeutic purposes in allergic diseases.¹⁶ This CFM resolution guides the supervision by the sanitary surveillance organs to control the quality and safety of the population regarding the use of allergenic extracts for diagnostic and therapeutic purposes with AIT administration. A physician must be responsible for the technical responsibility of allergy and immunology services with a specialist qualification record (Registro de Qualificação na Especialidade- RQE) in Allergy and Immunology. In exclusive pediatric patient centers, a physician must exercise technical responsibility with an RQE in Allergy and Immunology or RQE in Pediatric Allergy and Immunology.

Before indicating AIT, the medical specialist in Allergy and Immunology must have confirmed that the patient is sensitive to those specific allergens to which they have contact and that the allergen triggers and/or worsens the symptoms. Adequate training is needed to properly guide the treatment with allergens to a known sensitive person.^{4,6,8,10} The response to AIT is individual, both in terms of treatment efficacy and the incidence of adverse effects. Although there are validated and safe protocols, each prescription is unique and the administration regimen of AIT may vary from one patient to another.^{8,10,11} When prescribing AIT, physicians should take the following into consideration: allergen extracts to be included based on the patient's clinical history and sensitivity, adequate choice of the induction and maintenance doses, potency of the available allergen extracts, cross-reactivity patterns and the possibility of deleterious effects of the mixture of some allergen extracts.

ALLERGEN IMMUNOTHERAPY MODALITIES AVAILABLE IN BRAZIL

The subcutaneous immunotherapy (SCIT) is the longest and most widely used method in Brazil. According to the World Health Organization (WHO), AIT is the only treatment capable of changing the natural history of AR, rhinoconjunctivitis, and asthma.¹⁷ Several studies have pointed out that AIT may also contribute to the treatment of other allergic diseases, such as atopic dermatitis.¹⁸⁻²¹ Recently, a double-blind placebo-controlled clinical trial conducted in Brazil demonstrated the efficacy of SLIT in the treatment of patients with atopic dermatitis sensitized to house dust mites.²¹ Currently in Brazil, SLIT is available only in the form of drops. SLIT in drops has been used in Europe since the 1980s, when the first clinical trials were conducted. The U.S. Food and Drug Administration (FDA) recently approved SLIT in tablet form for use in the United States.^{3,4,22-24}

Although other routes of administration for AIT have been studied around the world, such as epicutaneous, oral, nasal, bronchial, and lymphatic, additional controlled studies are still required for standardization and to guarantee the efficacy and safety of these alternatives.^{7,25}

Subcutaneous immunotherapy (SCIT)

Subcutaneous immunotherapy (SCIT) has proven efficacy and safety in several clinical trials. Classically, it is used to treat patients sensitized to house dust mites (HDM), animal dander and pollens. The SCIT route is the only one with efficacy proven by robust evidence studies for Hymenoptera insect bites/stings immunotherapy.^{4,10,11,26} Currently, several pathways are known about the mechanism of action; we emphasize the participation of allergen-specific IgG4 blocking antibodies and Treg cells. Increased proportions of Treg cells have been described after initiation of treatment with SCIT, which revealed the role of Treg cells, secreting immunomodulatory cytokines, promoting allergen-specific immune tolerance.^{4,5,27-31}

The induction phase involves the administration of increasing doses for the patient to tolerate the maintenance phase. In general, the conventional form of dosing scheme includes a gradual increase

of the allergen doses at 3-, 5-, or 7-days intervals. When the maintenance dose is reached, usually between 3 and 6 months, a constant amount of allergen(s) content is prescribed and will be maintained at longer intervals, eg, 2 and 4 weeks.^{4,6,32,33} The maintenance dose is the effective dose of treatment that will provide clinical improvement with symptom control, reduced use of medications, and improved quality of life.

The clinically noticeable efficacy of SCIT is usually achieved by the sixth month of treatment, whereas in the maintenance phase, the long-term effect after discontinuation is well documented. Standardized allergen extracts, adequate dosage, and follow-up with an allergist and immunologist are essential for treatment success.⁵

The allergenic extract should be injected subcutaneously at variable intervals in the lateral region of the arm, midway between the shoulder and the elbow. The subcutaneous tissue has a limited blood supply and allows slow absorption. The procedure should always be performed in a medical setting with adequate medication and equipment to deal with any potential adverse reaction. Although dose adjustment after a severe reaction is controversial with no evidence-based guidelines, reducing it to the highest previously tolerated dose is possible. A cautious increase in subsequent doses can be made if there is a good response with no systemic reaction. It is crucial to assess the risk/benefit before continuing AIT.^{4,6,8,32-34}

"Accelerated" SCIT schemes are called "Cluster" and "Rush", in which the doses are higher and faster, requiring more than one injection per day. In this way, the maintenance phase is reached more quickly, but adverse effects are more likely to happen.^{29,30,32,33} These regimens are being increasingly used worldwide because they allow rapid clinical control of allergic disease. Although the chance of local and systemic adverse reactions is more expected in these accelerated SCIT regimens, the clinical management is similar to that of conventional ones.

The use of pre-treatment with antihistamines is controversial

Although the use of pre-treatment with antihistamines is controversial, there are studies that demonstrate the applicability of this conduct for

specific immunotherapy for Hymenopteran insect venom (VIT). In several double-blind, placebo-controlled trials, it has been shown that pretreatment with H₁ antihistamines improves the tolerability of VIT.²⁶ We suggest this conduct, particularly for SCIT specific for Hymenoptera venom (VIT), because we believe it contributes to increase the safety of immunotherapy taking into account the characteristics of the Brazilian population and healthcare system. The use of antihistamines 1-2 h prior to the application of the allergen extract is advisable to reduce the possibility of adverse reactions. However, this does not exclude the chances of severe systemic reactions.

The duration of the treatment is 3-5 years defined by the time needed for the effects to be achieved and maintained for a long time even after the end of the AIT.^{4,8,30,32,33} The duration of treatment is counted from the maintenance phase on, corresponding to the effective dose. Assessing the optimal treatment time is necessary to evaluate the diagnosis, disease severity, and clinical response of the patient.

Sublingual immunotherapy (SLIT)

In Brazil, sublingual immunotherapy (SLIT) is available in the form of drops.^{21,35} The administration is applied under the tongue or on the lower lip's buccal mucosa, which allows the allergen to be in contact with the oral mucosa for at least 2 min. We recommend not eating or drinking for at least 10 min before and after application. This recommendation considers the absorption of the allergenic extract in the oral mucosa and the risk of causing lesions in the oral mucosa, such as mucosal lacerations during feeding provoked by certain kind of foods, might allow rapid absorption of allergens that increase the chance of local or even systemic reactions.³⁶ The allergens cross the mucosa in 15-30 min. They are then picked up by the dendritic cells and processed into small peptides, followed by the initiation of a systemic immune response. Treg cells play a key role in the mechanism of action in both SLIT and SCIT. Suppression of allergen-specific Th2 cells is a crucial step in inducing peripheral tolerance and allergic desensitization. A significant decrease in the allergen-specific IgE/IgG4 antibodies ratio occurs after several months.²⁵

Meta-analyses and systematic reviews have postulated that SLIT is safe and effective in children and adults.^{4,6,34,37-39} In this sense, SLIT can be administered at home.^{34,37,38} The Brazilian Association of Allergy and Clinical Immunology Taskforce on AIT suggests that the first dose be administered under the supervision of a physician in a specialized Allergy and Immunology clinic, especially at the beginning of a new concentration.⁵ The majority of adverse reactions are mild (itching of the oral mucosa, swelling of the lips, runny nose, and nausea). Although SLIT has a high safety profile, it can cause systemic reactions, particularly in asthma patients.^{34,35,38,39} Thus, even this type of AIT requires specific indications and clinical management pertinent to a physician with an academic background in Allergy and Immunology.

The studies evaluating the efficacy of SLIT have had great variability in their methodology.^{3-5,31,37} The doses administered individually in each study ranged in the order of 5000-fold. The monthly cumulative dose of SLIT compared with the monthly dose of the subcutaneous route ranged from 0.017 to >500-fold, though all these ranges were effective when comparing daily SLIT allergen doses (<5 µg/day, 5-20 µg/day, and >20 µg/day).³⁷ There is a wide variation in the doses used in the various studies. However, SLIT drops as the SLIT tablet rarely has up dosing. We suggest that the doses to be used take into consideration the manufacturers' guidelines as well as the specificities of the allergenic extracts used.

Real-life studies have also demonstrated excellent therapeutic results for treating atopic diseases with SLIT.^{35,38,39} A recently published Brazilian study³⁵ demonstrated that patients who received SLIT for *Dermatophagoides pteronyssinus* and/or *Blomia tropicalis* showed that the perception of treatment effectiveness was 92%, performance improvement in daily activities was 91%, a satisfactory cost-benefit balance was 84% and general satisfaction was 97%. Therefore, this study showed a high perception of satisfaction in allergic patients undergoing HDM SLIT.

The SLIT regimen usually starts with an induction phase, where increasing doses of the allergen are applied. This induction phase can be slow, as in classical SCIT regimens, but several studies have

shown safety when induction is shortened. There are protocols where the maintenance dose was reached in 30-60 min.⁴

Because there is a discrepancy in dose equivalence among the studies, it is impossible to determine which dosage scheme presents the most remarkable efficacy and the lowest possibility of adverse effects. Some studies have shown that the faster the maintenance dose is reached (weeks, days, or hours), the greater the possibility of local or even systemic reactions. However, other studies have found no such association between higher adverse effect rates when the SLIT induction phase is quicker.⁴⁰⁻⁴⁴

The current accepted practice is to swallow the contents of the SLIT after 1-3 min in the oral cavity since if the content is not swallowed, there is a 30% loss of allergen.^{31,34,37-39} Some studies have shown better results when SLIT was administered daily. Moreover, daily applications seem to contribute to increasing adherence to treatment. Frequent periodic monthly or bimonthly visits improve therapy success, mitigating concerns about clinical efficacy and increasing the possibility of the patient completing their SLIT treatment.^{35,45,46}

A classic study, where patients with AR were followed for 15 years, used a dosing regimen of SLIT administered 3 times a week (mean annual cumulative dose of 390 µg of Der p 1 and Der p 2). Patients whom underwent SLIT were divided into groups where they received treatment for 3, 4, and 5 years. All groups showed improvement in AR symptoms. The longer the treatment lasted, the more the patient's symptoms improved. Patients who completed the treatment in 4 or 5 years, the recurrence of symptoms of the disease can occur at an average of 8 years, while for patients who completed the treatment in 3 years of SLIT had the recurrence of symptoms at an average of 7 years after the end of treatment. It was concluded that the reasonable total time to perform SLIT is 4 years because a large satisfactory period (8 years) was obtained without returning symptoms.³⁴

The maintenance dose of SLIT is usually given daily or up to 3 times a week. SLIT doses should be calculated cumulatively until the recommended monthly dose is reached. Manufacturer's

recommendations should be considered for therapeutic success since allergenic extracts have specific characteristics, such as the amount of major and minor allergens and biological potency. The final dilution to reach the desired maintenance dose, depending on the features of the extract is usually achieved with dilutions of 1:10, 1:5 or 1:1.

The first application of each new bottle of SLIT drops, with increased concentration, should always be done in the doctor's office, after a careful clinical examination. Dose adjustments of any kind (increase or decrease the dilution, number of drops, and/or frequency of application) may be necessary depending on individual clinical progress.^{4,34,37-39,41-43}

SPECIFIC IMMUNOTHERAPY WITH HYMENOPTERA VENOM

Venom-specific immunotherapy (VIT) is the only effective therapy to prevent future anaphylactic reactions in individuals with proven sensitization to the venom of Hymenoptera insects. With the correct prescription and using appropriate extracts, its therapeutic efficacy is about 90%.^{4,8,26}

The indication of treatment with VIT is based on the estimated risk of systemic reactions in future stings, considering the patient's age and severity of previous reactions, in addition to the degree of exposure and the presence or absence of specific IgE sensitization, which should be documented by a positive skin test response and/or by serum detection of specific IgE.^{4,26,47,48} Previous studies have shown that 30-60% of untreated adults with a positive history of systemic reactions and presence of IgE to venom *in vivo* and/or *in vitro* showed a systemic reaction after provocation.²⁶ VIT should be recommended in patients with a clinical history of anaphylaxis after Hymenoptera insect stings. Immunotherapy is generally not recommended in patients who have experienced isolated skin reactions. Large local reactions also do not generally increase the risk of anaphylaxis in subsequent stings; therefore, skin tests and immunotherapy with venoms are not typically indicated, except in occupational exposures with frequent accidents that compromise the patient's

quality of life.²⁶ Once VIT is indicated, the patient or family should be informed about the risks and benefits of treatment and sign an Informed Consent Form.

A maintenance dose of 100 µg/mL should be considered for bee and wasp venoms in both adults and children, although in the latter ones, there is no specific data on optimal dose. A maintenance dose of 100 µg venom is significantly more effective than 50 µg. This dose is equivalent to the dry weight of approximately 2 honeybee stings or 5 wasp stings.²⁶ An individualized maintenance dose is needed in patients who presented reactions during immunotherapy. The recommended starting dose in up dosing protocols lies between 0.001 µg and 0.1 µg, but it has also been shown that a starting dose of 1 µg is usually safe and not associated with a higher rate of side effects in adults or in children.²⁶ The starting concentration of VIT is based on the skin test result (end-pointing). To minimize the risk of reactions during treatment, the starting dose should be 100-fold less one, which turned intradermal test positive and 1000-fold for the skin prick test.

Patients sensitized to ant venom (*Solenopsis invicta*) and have a history of severe systemic reactions and anaphylaxis are also commonly found in Brazil. In this case, immunotherapy is used with *Solenopsis invicta* total body extract. The recommended dilution to start the induction phase is also determined by the prick and intradermal test results.^{4,8,26} Generally, in Brazil, the final maintenance dose allowing symptom control without causing severe adverse reactions corresponds to a dilution of 1/100. Finally, we emphasize that the characteristics of the extracts used by the manufacturers and the choice of doses used for induction and maintenance must be adequately adjusted by the Allergy and Immunology specialist.

There are several dosing schedules and administration intervals. Most protocols suggest a gap between applications of 1 month, though this can be up to 3 months. According to expert consensus, injections are usually given every 4 weeks in the first year of treatment, every 6 weeks in the second year, and in case of a five-year

Absolute contraindications

- Chronic irreversible airway obstruction, including patients with forced expiratory volume in the first second (FEV1) <70% of predicted value, despite adequate treatment
- Severe uncontrolled asthma
- Active autoimmune diseases, malignancies, immunodeficiencies
- Individuals with HIV infection and CD4 count <200 cells/mm³
- Severe psychiatric disorder

Relative contraindications

- Use of β -blockers, angiotensin-converting enzyme inhibitors (ACEI), and monoamine oxidase inhibitors
- Cardiovascular diseases
- Pregnancy - immunotherapy should not be indicated during pregnancy, but the dose may be maintained until the end of pregnancy if the patient becomes pregnant during treatment. Exceptionally, VIT may be initiated during pregnancy in high risk of severe systemic reaction in patients with Hymenoptera hypersensitivity.

Table 1. Absolute and relative contraindications for AIT in patients with allergic rhino conjunctivitis, allergic rhinitis, asthma or venom hypersensitivity

treatment every 8 weeks from year.²⁶ In rush scheme, the induction phase lasts 4-7 days; in an ultra-rush, the maintenance dose is reached in 1-3 days; and the cluster protocol (modified rush), performed with up to 4 daily injections of the allergen in the induction period, with an interval of 15-30 min, and reaching the maintenance dose in approximately 6 weeks. The scheme adopted by a Clinical Immunology and Allergy Service group from a university hospital is the modified rush immunotherapy, using aqueous extract. Four doses are administered per visit during the induction phase. The concentration of the extract increases weekly until the maintenance dose is reached, with applications every 2 weeks (4 times), then every 21 days (4 times), and then monthly until the end of treatment, which should be from 3 to 5 years. **This dosing schedule is based on our own experience considering the safety of patients under venom immunotherapy, once these dose intervals were associated with a less number of local and systemic reactions, according to our clinical observation in Brazilian population.**

AIT - INDICATIONS AND CONTRAINDICATIONS

Allergen immunotherapy (AIT) is used to treat rhinoconjunctivitis, AR, asthma, and Hymenoptera venom allergy in patients with evidence of a

mechanism mediated by specific IgE antibodies to clinically relevant allergens. We also included atopic dermatitis without respiratory allergy associated with sensitization to HDMs in the possible indications for AIT.⁴⁻⁶ Several factors influence whether or not to initiate this treatment,⁴ such as patient preference, adherence to current treatment, drug side effects, and asthma prevention in patients with AR.⁴

While the clinical indications for AIT are well defined, the contraindications remain controversial. Generically, the administration of allergenic extracts should not be performed if it may compromise patient safety. There are differences among the worldwide guidelines published by different Allergy and Immunology medical associations regarding absolute or relative AIT contraindications, the route of administration (subcutaneous or sublingual), and allergens used (aeroallergens or Hymenoptera venoms). Table 1 describes the main contraindications currently described in the literature^{4,6,8,9,49,50,4,6,8,9} and adopted in Brazil.

Conceptually, AIT can be applied in any age group after the above contraindications have been ruled out and provided that the presence of specific IgE against clinically relevant allergens is demonstrated.^{4-6,49,50} However, subcutaneous applications have been avoided in children under 5 years of age because of the difficulty of reporting symptoms of a possible systemic reaction, and because the injections might be traumatic at this

- Adrenaline 1:1000 (1 mg/mL)
- Antihistamines (diphenhydramine) for intramuscular or intravenous application
- Adrenergic agonist
- Glucocorticoid (hydrocortisone, methylprednisolone, prednisolone)
- H2 antihistamine for intravenous application (ranitidine).

Table 2. Drugs that should be available at the clinic for application of AIT

age. A good option would be SLIT. As the sublingual drops must remain under the tongue for 1-2 min before ingestion, it is impractical for children under 2 years of age. Therefore, we consider children over 2 years of age to start AIT.

WHERE TO PERFORM ALLERGEN IMMUNOTHERAPY

Allergen immunotherapy (AIT) is one of the most important therapeutic tools used by allergists and immunologists; however, conventional SCIT may trigger up to 0.025% to 0.4% adverse reactions, including anaphylactic reactions, whereas more accelerated regimens lead up to 4% systemic reactions. Because of this, the allergist and immunologist must have a safe medical facility for dilution and application of allergenic extracts, avoiding risks related to immediate hypersensitivity reactions. Moreover, it is essential to guarantee sterile application and ensure the good quality of extracts that lose potency under inadequate storage.⁵¹⁻⁵³ Aside from specialist's knowledge in Allergy and Immunology, the whole team must be prepared to recognize situations of anaphylaxis and act in a coordinated way to avoid risks to the patient. Thus, periodic training of the staff and checking the entire process are fundamental.¹³ Before starting AIT, the patient should be informed about the risks and sign an informed consent form. The clinical office should have adequate infrastructure to perform SCIT⁵¹⁻⁵⁴ and medication, as shown in [Table 2](#).

The American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI)⁴ advise that the best place to apply SCIT is in the prescriber's clinic. However, if this is not possible, it can be applied under the supervision of another physician as long as the all-safety specifications are guaranteed. Nevertheless, it is strongly recommended that patients with a high risk of

reactions are treated under the supervision of the prescribing physician. The Scientific Department of Immunotherapy of the Brazilian Association of Allergy and Immunology (ASBAI) recommends that the SCIT administration must be under physician supervision. Concerning SLIT, the main side effects are local (pruritus and mild edema of the oropharynx),⁵³⁻⁵⁵ and the patient should be informed about these risks and sign an informed consent form. For this reason, there is no need for SLIT to be done in a clinic, except for the initial doses, and the patient can be oriented to do it at home during the maintenance phase.⁵

HANDLING AND CHOICE OF ALLERGENIC EXTRACTS

The quality of the allergen extract is crucial for both diagnosis and treatment.²⁷⁻²⁹ It is up to the allergist and immunologist to indicate the best extract(s) for their patient. In the case of AIT, the ideal antigenic mixture and dilution must be defined. The best therapeutic results will be obtained when the same allergen extract is used for testing, allowing for customized dilutions according to each individual sensitivity.

In the eventual necessity of performing immunotherapy with compound (or mixed) extracts, some points must be considered: cross-reactivity between the allergens, the ideal dose of each of them, and enzymatic degradation. Standardized extracts can be mixed with non-standardized extracts. Studies have shown that dust mites and cat and dog dander can be mixed. Allergens with high proteolytic enzyme activity, such as those from fungi and cockroaches, should be separated from the other extracts. Mixing allergens from Hymenopteran venoms is not recommended.⁴⁻⁹

Allergen extracts standardized by different laboratories, although labeled with the same potency unit, may contain different amount of major allergens. A customized extract for allergen

immunotherapy should be prepared according to the patient's clinical history and allergy testing.¹⁸ Immunotherapeutic vials must be identified, and the tag should contain the manufacturer, potency unit, manufacturing and expiration date, concentration of individual allergens, and absolute biological unit and/or potency in biological unit determined by serial skin testing.⁵⁶

The vials containing allergen extracts must be stored in a refrigerator (mean temperature in Celsius centigrade) with a maximum and minimum thermometer in a cold room, with no other products (except sterile medications).

The final dilution to reach the desired AIT maintenance dose depends on the characteristics of the extract. The dose used must consider the features of the allergenic extract, taking into account the quantity of major allergens ($\mu\text{g}/\text{ml}$) and the potency (biological units). In Brazil, allergens derived from house dust mites are associated with the development of AR and asthma, and also atopic dermatitis.⁵⁷⁻⁶³ The formulation of the extract used for AIT should be chosen based on the skin prick test result and/or serum level of specific IgE.

BIOMARKERS AND AIT PREDICTION AND EVALUATION RESPONSE

SCIT and SLIT have been used for decades and are effective at reducing symptoms. There are some candidates for biomarkers, like levels of IgG4 blocking antibodies or IL-10 immunomodulator cytokine,^{27,64,65} however, to date, there are no biomarkers that sufficiently predict response to AIT that can be used in routine clinical practice to decide on continuation or cessation of AIT. The main indicator of the efficacy of AIT is the control of signs and symptoms of allergic diseases with reduced or no use of medications, particularly oral or inhaled corticosteroids.^{26,28,66,67}

CONCLUDING REMARKS

AIT characterizes one of the pillars in treating allergic diseases and is the single therapeutic strategy with curative potential. Throughout the world, AIT is successfully used to control the symptoms of allergic diseases, reduce the

consumption of medications, improve the quality of life of atopic patients, and above all, promote long-term control of the allergic process even after the end of treatment.

The prescription of AIT is done according to skin prick test and/or identification of allergen-specific serum IgE. Therefore, the treatment is individualized and personalized. Thus, AIT reaches the principles of precision medicine. The past, present, and indeed the future of AIT require adequate professional training to recognize the etiologic agents associated with the presence of clinical manifestations in each individual. As with the use of biological drugs in the treatment of allergic diseases, AIT also modifies specific pathways in the immunopathological mechanisms of allergic diseases. With biologics, we block specific cytokines and control the clinical manifestations of rhino conjunctivitis, AR, asthma, and atopic dermatitis. Conversely, AIT modifies the production of these cytokines, achieving long-term control of signs and symptoms even after the end of the treatment. When we stop the use of biologics the symptoms usually return. Meanwhile, AIT has the potential to keep the allergic process under control for long periods even after the end of the treatment.

We consider that AIT is an extremely consistent precision medicine strategy. However, AIT is a physician-dependent therapy because adequate academic and professional training is a basic condition for the identification of specific allergens associated with the disease, choice of adequate allergenic extracts, dose administered, clinical management of reactions and personalized guidance in each case.

In this position paper, we provide guidance on good clinical practice for the performance of AIT in Brazil. These conducts were established based on the peculiar characteristics of our country, such as genetic, socioeconomic, educational, cultural and climatic conditions, training of the medical professional, health surveillance legislation, legislation of the medical regulatory bodies in our country, such as the CFM, and current scientific knowledge of evidence-based medicine and precision medicine. Finally, we advocate that this position paper is a work of a guiding character, contributing to the improvement of the use of AIT for treating allergic diseases in Brazil.

KEY POINTS

- The specialist in Allergy and Immunology has a deep and solid knowledge of the immunological mechanisms of allergic diseases.
- Allergen immunotherapy (AIT) is the term currently employed for the allergen-specific immunotherapy used in the treatment of allergic diseases.
- The professional training of the medical allergist and immunologist includes, uniquely, specific hypersensitivity allergy testing and the appropriate indication and implementation of AIT.
- In contrast to pharmacotherapy, AIT aims to manage not only the symptoms of the disease but also the underlying cause.
- Treatment with AIT is capable of promoting remission and control of allergic diseases for prolonged periods, without the use of drugs, even after their administration has ended.
- The technical responsibility of allergy and immunology services must be exercised by a physician with a registered specialist qualification in Allergy and Immunology.
- In pediatric clinics, the technical responsibility should be exercised by a physician specialized in Allergy and Immunology or in Pediatric Allergy and Immunology.
- Good clinical practices for the use of AIT ensure precise indications, safety, and efficacy of the treatment. Related to this work.

Abbreviations

AAAAI, American Academy of Allergy, Asthma, and Immunology; ACAAI, American College of Allergy, Asthma, and Immunology; AIT, allergen immunotherapy; AR, allergic rhinitis; ASBAI, Brazilian Association of Allergy and Clinical Immunology; CFM, Federal Council of Medicine; Der p₁, Peptidase gene Der; FDA, Food and Drug Administration; HDM, house dust mites; Ig G4, Immunoglobulin G4; IgE, Immunoglobulin E; IL-10, Interleukin-10; mL, Milligram per liter; RQE, specialist qualification record; SCIT, subcutaneous immunotherapy; SLIT, Sublingual immunotherapy; SPT, skin prick test; Th2 cells, T helper 2 cells; Treg cells, Regulatory T cells; VIT, Venom-specific immunotherapy; WHO, World Health Organization; µg, microgramme.

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