Review article

Transition between subcutaneous and sublingual allergen immunotherapy: Recommendations of the Brazilian Association of Allergy and Immunology (ASBAI)

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The use of allergen immunotherapy (AIT) in Brazil has specific regional conditions owing to the pattern of allergen sensitization, as well as to genetic, socioeconomic, and cultural characteristics. This review article aims to discuss the clinical practice of AIT by the subcutaneous or sublingual route in Brazil, addressing the possibilities of transition between these forms of administration. A systematic review using the PubMed and Cochrane databases was performed, and the websites of major allergy and immunology organizations were consulted. Knowledge of the mechanism of action of subcutaneous immunotherapy and sublingual immunotherapy, together with Brazilian real-life experience, allowed us to establish recommendations regarding switching routes of AIT administration in selected cases. Careful analysis of each clinical situation is necessary to perform the transition between subcutaneous and sublingual allergen immunotherapy. (J Allergy Clin Immunol Global 2024;3:100281.)

Key words: *SCIT, subcutaneous allergen immunotherapy, SLIT, sublingual allergen immunotherapy, AIT routes*

Abbreviations used

AIT: Allergen immunotherapy
COVID-19: Coronavirus disease 2019
FDA: US Food and Drug Administration
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
Treg: Regulatory T

Allergen immunotherapy (AIT) is a precision medicine strategy that has been used for more than a century for the treatment of allergic diseases such as rhinitis and asthma. More recently, clinical trials have also demonstrated the efficacy of AIT in the treatment of atopic dermatitis. Clinical evaluation with specific selection of patients eligible for treatment and identification of allergic sensitization via the prick test and/or investigation of allergen-specific serum IgE level represent the pillars of this precision medicine strategy, enabling the personalization of AIT treatment. This is the only form of treatment capable of inducing prolonged tolerance against allergens, allowing clinical control with the possibility of remission of the disease for many years even after the end of treatment.[1-6]

The classical form of AIT uses subcutaneous immunotherapy (SCIT). Experimental studies, randomized clinical trials, and reports detailing real-life experience have demonstrated the efficacy and safety profile of SCIT. Approximately 1% of SCIT applications may result in adverse reactions. Reactions usually develop at the application site; however, systemic events such as urticaria and even anaphylaxis may occur.[1,4,7] Therefore, SCIT should always be performed under medical supervision, and the patient should remain under observation for a minimum of 30 minutes. Recent data obtained by the Brazilian Census of Immunotherapy with Allergens, which was conducted with 233 physicians with a specialty qualification in allergy and immunology or area of expertise in pediatric allergy (data not yet published), revealed that 33.14% of the study participants reported systemic adverse reactions, including anaphylaxis, with the consequent need to use intramuscular adrenaline on at least 1 occasion (14.5%).

Because of realization in the 1980s of the possibility of occurrence of serious adverse reactions, studies to develop safer alternative ways of applying AIT were initiated in Europe. Several clinical trials were conducted to investigate the efficacy and safety of AIT sublingually (sublingual immunotherapy [SLIT]). In 1998, the World Health Organization declared that SLIT is a viable alternative to SCIT, with proven efficacy and a superior safety profile. The literature consistently demonstrates that the adverse effects of SLIT, such as itching and swelling at the site of application, are generally local and mild.[1-3,5] Therefore, SLIT can be administered by the patient or guardian at home. However, the

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Department of Immunotherapy of the Brazilian Association of Allergy and Immunology has recommended that the first dose of each vial be applied under medical supervision, preferably in the service of the prescribing physician.[1]

The main objective of this review article is to discuss the clinical practice of AIT by the subcutaneous or sublingual route in Brazil, addressing the possibilities of transition between these forms of administration. Considerations regarding the main differences between the use of AIT in Brazil, the United States, and Europe, taking into account peculiar characteristics of health care systems and professional performance of the specialist in allergy and immunology, were analyzed to better understand the factors that justify the transition between SCIT and SLIT in the Brazilian reality.

METHODS

A systematic review using the PubMed 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, 2000, and March 30, 2022. The terms used for the research were *allergen immunotherapy*, *transition*, *AIT routes*, *SLIT*, *subcutaneous immunotherapy,* and *SCIT*.

WHAT CAN BE LEARNED FROM THE CLINICAL PRACTICE OF SCIT AND SLIT IN THE UNITED STATES AND EUROPE?

Important differences regarding the practice of AIT by US and European medical specialists are observed. SCIT is the main type of treatment performed in the United States. However, since 1990, when SLIT was introduced in Europe with great success, US physicians have become interested in this new form of administration.[8,9] Despite this interest, SLIT was not approved by the US Food and Drug Administration (FDA) for many years and was rarely used in the United States, being used exclusively off-label. As of April 2014, when the FDA approved SLIT in tablet form, US physicians became more comfortable prescribing SLIT. Interestingly, although the FDA approved the tablet-only formulation, some US allergists formulate SLIT in drops in their own clinics, even though it is an off-label procedure. When SLIT drops are prescribed, patients are informed that it is an off-label procedure and given specific advice on possible adverse effects. The extensive experience of US physicians with SCIT despite the fact that health insurance plans do not provide reimbursement to patients for application of SLIT in drops because it represents an off-label use is evidence of the preference for the subcutaneous route of application in the United States. In addition, the use of several allergens in the same formulation for the application of SCIT is the most common prescriptive procedure.[10-13] In Europe, SLIT is considered the preferred form of AIT in some countries, such as Italy and France. When SCIT is used, the applications are carried out in specialized services under medical supervision.

In Brazil, there is a peculiar model of practice of allergy and immunology that illustrates hybrid characteristics regarding the practice of the specialty in the United States and Europe.[1] From the standpoint of preparing allergenic extracts for immunotherapy, supplying vaccines to patients, and applying SLIT, the model is very similar to the US model. In addition, the practice of immunotherapy with allergens in Brazil has a strong private initiative profile, similar to what occurs in the United States. On the other hand, the use of SLIT in drops is similar to that seen in European countries in terms of the characteristics of the allergenic extracts and application protocols. However, dilution of the SLIT extracts and provision of the product are usually performed by allergist/immunologists.

IS IT POSSIBLE TO CHANGE THE ROUTES OF AIT APPLICATION? ARE THERE RATIONAL IMMUNOLOGIC BASES TO SUPPORT THIS APPROACH?

There are few clinical studies regarding switching the route of application from SCIT to SLIT or vice versa. The most robust study, comprising an 18-year follow-up analysis of patients undergoing AIT, was published in 2013. The medical records of 4933 children undergoing treatment with SCIT and 4285 children undergoing treatment with SLIT were analyzed. The possibility of transitioning between the forms of AIT without increasing the incidence of adverse events was confirmed.[14]

Another study with a large number of patients (N = 719) that addressed the transition between SLIT and SCIT was published in 2021. Patients who expressed their intention to discontinue SLIT were switched to SCIT. This study included adults and children of both sexes. The transition from SLIT to SCIT showed an excellent safety profile and considerably increased treatment adherence.[15]

The mechanisms of action of SCIT and SLIT have many similarities and some differences. The main difference is associated with the site and manner of antigen presentation. Oral mucosal dendritic cells are very similar to skin Langerhans cells. Although subcutaneous application suggests the greatest potential for antigen presentation because of the injectability of the allergen, this does not appear to be true. It has been shown that the oral mucosa has a high density of dendritic cells, forming a kind of network and amplifying antigenic presentation. In the mucosa of the sublingual region, in addition to there being such a network of dendritic cells, there is also a high density of blood vessels enabling effective antigen presentation when immunotherapy is applied by the sublingual region.[2,5,16]

One of the hypotheses explaining the better safety profile of SLIT when compared with SCIT is that the dendritic cells of the oral mucosa have a better tolerogenic profile that is associated with lower-intensity stimuli through generally daily applications of SLIT, promoting desensitization to allergens with less chance of immediate adverse reactions.[16,17]

The initial response to both types of AIT application routes occurs from the induction of phenotypic changes in circulating dendritic cells, contributing to suppression of the inflammatory allergic response via the action of allergen-specific regulatory T (Treg) cells, inhibiting type 2 inflammation. AIT reduces the activity of both group 2 innate lymphoid cells of natural immunity and T_H2 cells of acquired immunity. The production of IL-10 and production of TGF-β by Treg cells are key events in the inhibition of type 2 inflammation.[1,16-20]

This Treg cell–promoted immunomodulation is observed between 3 and 6 months after the initiation of SCIT or SLIT. Accelerated SCIT schemes (cluster or rush) may induce immune tolerance earlier. The shift to an allergen-specific T_H1 cell profile response with increased IFN-γ production occurs approximately 12 months after the start of SLIT. In the antibody-mediated

immune response, the effects observed are increases in allergen-specific IgA and IgG4.[16-20]

Regarding these crucial mechanisms of induction of clinical and allergen-specific immunologic tolerance, no important differences regarding the immunomodulation pathways observed in SCIT and SLIT were detected.[16-20] However, Shamji et al[19] found that the serum and nasal fluid antibody responses of patients undergoing SLIT and SCIT with grass pollen extract (*Phleum pratense*) were different, demonstrating that the induction of specific IgA antibody production, especially in the nasal fluid, was greater in SLIT than in SCIT. As expected, the levels of specific IgG and IgG4 antibodies were higher in SCIT than in SLIT.[18] We must consider the possibility that these data show initial evidence, thus requiring further studies to understand more solidly the underlying epigenetic and molecular changes mediated by SCIT and SLIT in the components of innate and adaptive immunity.[19]

Therefore, it is rational to suggest that when we start the induction of allergen-specific peripheral tolerance with one route of immunotherapy administration, there should be no interruption of the process if the switch to another route of application occurs. In addition, the cellular and molecular mechanisms induced by SCIT and SLIT may be complementary, amplifying the immunomodulation responsible for maintaining the state of allergen-specific tolerance.

THE COVID-19 PANDEMIC AND TRANSITION BETWEEN DIFFERENT FORMS OF AIT—WHAT HAS CHANGED?

Recently, with the coronavirus disease 2019 (COVID-19) pandemic, the displacement of patients for the application of SCIT has become a problem for maintaining adherence to treatment. On the other hand, the perception that injectable vaccines have better effects has also been a consequence of the COVID-19 pandemic. Around the world, the possibility of changing AIT application routes has become an issue to be evaluated by doctors and patients themselves.[21-23]

WHAT ARE THE MAIN REASONS WHY PATIENTS WANT TO CHANGE THE ROUTE OF APPLICATION OF AIT?

Extensive local reactions and pain at the site of application are important reasons for abandoning SCIT. SLIT is an excellent option in these cases, both in children and adults. Systemic adverse reactions are much more prevalent with SCIT. For reasons of safety and/or patient desire, switching to SLIT may contribute to better treatment compliance without loss of efficacy.[1,14,24-26]

Although the efficacies of SCIT and SLIT are similar, some studies report that the perception of the beneficial effects of treatment by the patient occurs faster in SCIT, especially when accelerated allergen tolerance induction protocols (cluster or rush) are used.[1-3] Some patients may prefer SCIT because they think that injectable forms are more effective, because of either personal perception or cultural influences.

Adherence to treatment is a major challenge for AIT practice.[27-30] Some patients fail to maintain adherence to treatment with SLIT because they forget to apply the immunotherapy daily or several times a week. In this case, switching to SCIT may be a good option. Difficulty in periodically attending the allergist/immunologist's office to receive SCIT applications is also an important cause of treatment abandonment, indicating the need to switch to SLIT to increase adherence in these specific cases. Children who reach the minimum age of 5 years required to start treatment with SCIT can switch from sublingual to subcutaneous application if their parents prefer this treatment option.[1,27,28]

The costs of treatment with SLIT or SCIT are different. Generally, the sublingual route is more costly for the patient. Therefore, economic reasons may be responsible for the desire to change the form of application of allergen immunotherapy.

WHAT CAN THE BRAZILIAN EXPERIENCE CONTRIBUTE TO THE PRACTICE OF SWITCHING BETWEEN ROUTES OF APPLICATION OF AIT?

The characteristics of AIT practice in Brazil represent a hybrid model of professional performance and AIT management, with the procedures observed in the United States and Europe qualifying the reality of the country as a good scenario to evaluate the transition between the 2 routes of application.

In Brazil, preparation of the dilutions of allergenic extracts and delivery of the product by the specialist physician himself are similar to procedures performed in the United States. Additionally, Brazilian allergist/immunologists perform SLIT in the form of drops, as is done in Europe. Therefore, the Brazilian practice of using SCIT and SLIT has very peculiar characteristics and depends on a personalized choice guided by doctor-patient interactions.

The aforementioned practice allows a favorable environment to make the transition from one form of AIT to another when necessary. In addition, Brazilian allergy and immunology specialists have adequate professional training to perform SCIT and SLIT in drops, as well as easy access to both forms of presentation of allergenic extracts.

WHAT PRECAUTIONS SHOULD BE TAKEN WHEN SWITCHING FROM SCIT TO SLIT?

The safety of SLIT allows for a change in application route with minimal chance of adverse effects. Patients must have controlled allergic disease. Patients and/or caregivers should be counseled on how to properly perform SLIT. As applications will occur daily or several times a week, the need for adherence to treatment to obtain the desired effects should be reinforced.

The Immunotherapy Department of the Brazilian Association of Allergy and Immunology offers the following recommendations: (1) preferably, use extracts from the same supplier; (2) if the patient undergoing SCIT has already completed the induction phase, the switch to SLIT can be performed by using doses recommended for maintenance from the beginning; (3) perform periodic clinical evaluation, initially monthly, so that the effects of the treatment are analyzed; and (4) after clinical evaluation, adjust the dose when necessary to increase effectiveness and/or prevent adverse effects.

WHAT PRECAUTIONS SHOULD BE TAKEN WHEN SWITCHING FROM SLIT TO SCIT?

Adverse reactions, including systemic reactions, are more commonly observed with SCIT. Therefore, greater care is

required when switching from SLIT to SCIT. All patients must have controlled allergic disease.

Patients in the induction phase with SLIT do not yet have the level of allergen-specific tolerance to start SCIT at later stages. Therefore, it is recommended that the switch to SCIT be implemented by restarting the induction phase. In specific cases of patients with controlled allergic rhinitis, it is possible to accelerate the induction phase of the SCIT by using slightly more concentrated extracts than usual from the beginning (eg, 1 dilution = 10×). As adverse reactions in patients with asthma and atopic dermatitis are more common, it is recommended that the induction phase be restarted with SCIT. Measures to prevent adverse reactions, such as the use of second-generation antihistamines 1 to 2 hours before the application of SCIT, can be implemented, especially in the early phases of transition from SLIT to SCIT.

Patients in the maintenance phase of SLIT already have a level of allergen-specific tolerance. However, switching to SCIT may provoke adverse reactions, especially in patients with asthma and atopic dermatitis. Because of the scarcity of studies examining this procedure, it is recommended that the induction phase be moved back, the procedure be started with more concentrated dilutions, or accelerated (cluster) regimens be used. The doses used for this transition should take into account the type of allergic disease of the patients. Patients with asthma and atopic dermatitis require greater caution when choosing the initial dose of SCIT. It is recommended that second-generation antihistamines be administered orally 1 to 2 hours before the application of SCIT until the recommended maintenance phase has been reached, thus making it possible to control symptoms without causing significant adverse effects that may indicate greater risks for presentation of systemic effects.

FINAL CONSIDERATIONS

There are few studies in the literature that focus on the transition between different forms of immunotherapy with allergens. Knowledge of the mechanism of action of SCIT and SLIT, together with real-life experience, allows us to establish basic procedures so that it is possible to switch routes of administration in selected cases. Careful analysis of each clinical situation is necessary to perform this procedure, which should be conducted exclusively by a physician with a specialist qualification in allergy and immunology.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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