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REVIEW ARTICLE

Allergen-specific Immunotherapy for Inhalants Allergens in Children

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Abstract: Allergen-specific immunotherapy (AIT) for aeroallergens consists of the administration of standardized allergen extracts to patients with respiratory IgE-mediated diseases to the same allergen in order to achieve immune tolerance to the allergen and prevent the onset of symptoms. AIT is usually delivered by sublingual (SLIT), subcutaneous (SCIT) route. AIT with one or multiple allergens currently represents the only causal treatment able to change the natural history of allergic airway diseases. Significant progresses have been made in terms of AIT efficacy and safety.

In this paper, mechanisms of action, indication and side effects of allergen immunotherapy are reviewed.

SLIT and SCIT have been found to be effective in the treatment of asthma and rhinoconjunctivitis due to inhalant allergens. The route of AIT administration should be selected on availability, cost (dependent from the local health system), tolerability (better for SLIT), patient's preference (injections are less accepted in young children), and adherence (higher for SCIT beyond pediatric age). However, it should be taken into account that metanalyses on AIT do not consider that effectiveness and safety depend upon the product chosen for treatment. Each product should be separately assessed to avoid generalization on administration routes or age group that may affect the decision.

Keywords: Asthma, children, immunotherapy, allergic rhinitis.

1. INTRODUCTION

Allergen-specific immunotherapy (AIT) for aeroallergens consists of the administration of standardized allergen extracts to patients with respiratory IgE-mediated diseases to the same allergen in order to achieve immune tolerance to the allergen and prevent the onset of symptoms. AIT is usually delivered by sublingual, subcutaneous route. Both Sublingual Immunotherapy (SLIT) and Subcutaneous Immunotherapy (SCIT) are given at increasing doses in the build-up phase and then at maintenance dose. The allergen dose is regularly administered throughout the year or pre/co-seasonally, depending on the causal allergen and the type of allergen extract. AIT with one or multiple allergens currently represents the only causal treatment able to change the natural history of allergic airways diseases [1]. Significant progresses have been made in terms of AIT efficacy and safety since the first report of the treatment of hay-fever by SCIT using pollen extracts, described by Noon and Freeman in 1911 [2, 3]. The first randomized study on SLIT dates back to 1986 [4]. Several placebo-controlled studies on AIT in the subsequent years have allowed systematic reviews suggesting evidence for improvement of symptoms and reduction of medication use for both allergic rhinitis (AR) and asthma [5]. However, AIT remains underused since the interpretation of evidence remains challenging for heterogeneity among studied populations, selection of potential responders, outcomes, regimens and products for AIT. Moreover, the use of AIT is hampered by fluctuating availability of AIT products, different educational levels of physicians and lack of consciousness of AIT in the general population [6].

2. MECHANISM OF ACTION OF AIT

AIT implies the administration (by subcutaneous or sublingual route) of a defined amount of the patient's relevant allergens, gradually increasing the delivered dose until attaining immunologic tolerance to the allergen [7]. This therapy [8] has been applied in clinical practice for decades to treat patients with allergic rhinitis, allergic asthma, and stinging insect anaphylaxis.

Among all the possible therapeutic options displayed for immunoglobulin E (IgE)-mediated allergic disease, AIT is actually to be considered the only disease-modifying therapy. Even if many mechanisms of action beside allergen immunotherapy are not completely understood, this effect could probably be linked to very early desensitization of mast cells and basophils, regulation of migration of inflammatory cells to tissues, decreased activity of basophils

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in circulation, and reduction in numbers and activity of effector cells in mucosal of target organs, such as mast cells, basophils and eosinophils.

Even dendritic cells (DCs) are involved in the disease modifying process: under stimulation of AIT, DCs release IL-12, IL-27, and IL-10, bringing to the activation and production of natural (nTreg) and inducible regulatory T (iTreg) cells, both different phenotypes of T-regulatory (Tregs) that suppress allergic response.

A very important role is the switch from an allergic T helper (Th)2 response to a Th1-type one, secondary to an upregulation of specific Tregs and B-regulatory cells. These cells reach this purpose releasing cytokines, such as interleukin-10 (IL-10) [9] and transforming growth factor- β (TGF-β), suppressing the activation of allergen-specific Th2 lymphocytes (and suppressing in this way Th2-dependent inflammation), reducing allergen-specific IgE synthesis, directly inducing tolerogenic DCs subsets, downregulating the expression of FCεRI receptors on mast cells [10] and generating a change from Th2 to Th1 responses [11].

Another important mechanism of action of AIT through Treg cells stands in changes in antibodies isotypes. AIT, including SLIT, enhances serum allergen-specific immunoglobulin G4 (sIgG4) and reduces allergen-specific IgE (sIgE) [9]. Furthermore, there is an increased production of immunoglobulin A (IgA) and IgG4, promoted by B-cell. The latter antibody mediates a sort of "immunologic blockade" inhibiting mast cell and basophil degranulation, binding in a competitive way to the same site epitopes recognized by IgE. Another possible role of IgG4 stands in co-stimulating the inhibitory IgG receptor FcγRIIb, which can negatively regulate FcεRI signaling and in turn inhibit effector cell activation.

The modulating effect of AIT, with special regards to the sublingual route of administration, could even be reached by a local interaction between the allergen administrated and the mucosal immune system.

A possible mechanism of sublingual immunotherapy could be secondary to oro-mucosal contact with allergen, with a consequentdevelopment of tolerance through an interaction of dendritic cells, Langherans cells, and T-cells within the mucosa or in the regional lymph nodes [11-13].

The major cellular and humoral changes induced by AIT are shown in Table **1** and Fig. (**1**).

Due to the advances in understanding the mechanisms of action of AIT there have been proposed/conducted studies focused on the understanding of the possible role of cytokines and interleukins as markers of pathology, with the purpose to find out possible markers that predict thosepatients which do not respond to AIT treatment [10].

Table 1. Main immunological changes produced by allergen-specific immunotherapy.

↑ Increasing Factors	↓ Decreasing Factors
↑ nTreg e iTreg	↓ activity of basophils in circulation and allergen-specific Th2 lymphocytes
↑ IL-10, TGF- β, production of IgA and IgG4	↓ in numbers and activity of mast cells, basophils and eosinophils in mucosal of target organs
↑ inhibitory IgG receptor FcγRIIb	↓ IgE production

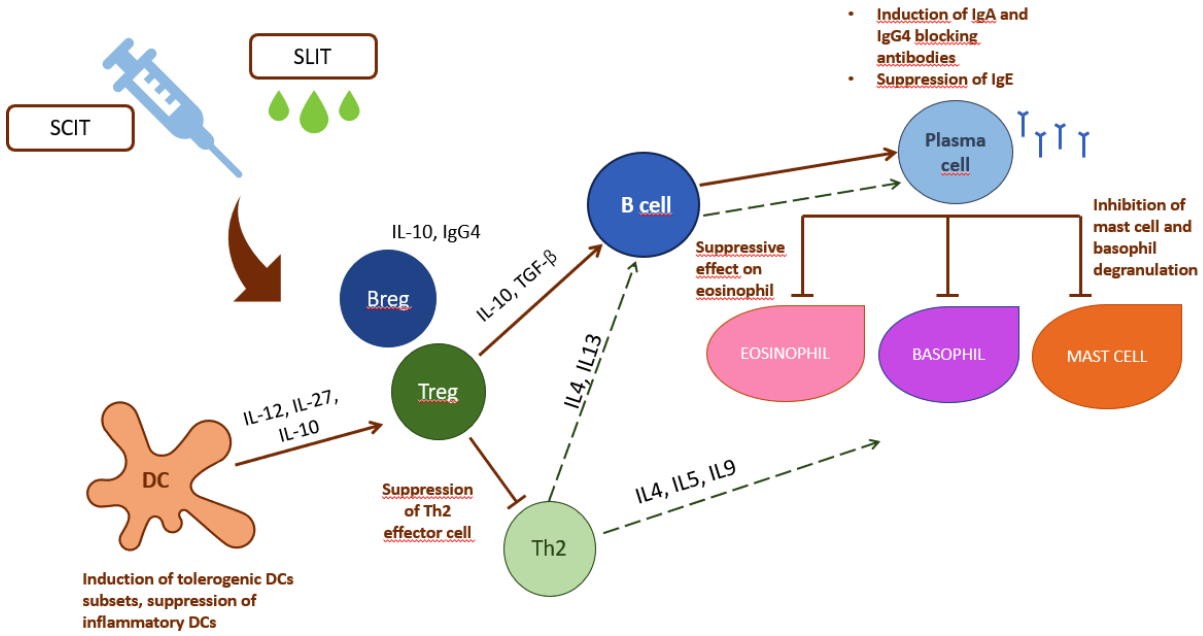

Fig. (1). Mechanisms of action of SLIT and SCIT for respiratory allergic diseases.

Many biomarkers, both cellular and humoral, used in clinical trials involving AR patients with or without asthma have been investigated and then reviewed by The EAACI Taskforce, for example: IgE- both total IgE, specific IgE (sIgE) and sIgE/Total IgE ratio-; specific IgG (sIgG)subclasses (sIgG1, sIgG4 including sIgE/IgG4 ratio); serum inhibitory activity for IgE-facilitated antigen binding (FAB) and IgE-binding factors); basophil activation; interleukins, cytokines and chemokines [14-16]. Among the cellular markers: Tregs, B regulatory cells, DCs and in vivo biomarkers (*e.g*. provocation tests) have been studied [15].

Actually, studies specifically performed on AIT biomarkers are limited, although several studies have assessed biomarkers as the secondary outcomes. Despite data discrepancy, IgE specific activity (ratio specific IgE/ total IgE) and serum IgE-FAB are considered promising biomarkers which are helpful to select patients eligible for AIT. These biomarkers could even be used to assess compliance, response and efficacy to that therapy [10, 15].

More data and studies are needed to better corroborate and interpret the possible link between biomarkers, clinical response and maintenance of clinical efficacy after discontinuation of AIT [10].

3. SLIT EFFICACY

SLIT represents nowadays the dominant approach in several European countries [17]. SLIT can be taken at home, and consists of exposure to the allergen *via* an aqueous solution as drops or tablet formulation placed under the tongue for 2 minutes and then swallowed. SLIT has the advantage over SCIT because of improved safety and suitable administration, thus avoiding the discomfort of injections and the inconvenience of office visits required for allergy shots, in particular in pediatrics [18]. A harmonized and international regulation of AIT products is lacking. SLIT products are most commonly available as "named patient products" (NPP), prepared simply in compliance with Good Manufacturing Practice [19]. SLIT tablets for grass pollen and house dust mite (HDM) have obtained a marketing authorization and they have been recently registered for use in children, adolescents, and adults [20]. There is clear evidence that in children with allergic rhinoconjunctivitis, SLIT is effective in significantly reducing nasal and ocular symptoms, medication use and symptom-medication score [1, 5, 21, 22]. In children, SLIT efficacy has been shown for perennial and seasonal allergens, pre/costagional and continuous schedule [21]. SLIT prevents the progression of AR to asthma, and may potentially reduce new sensitizations [21, 23-27]. Recently a double-blind, placebo-controlled trial in 812 children aged from 5 to 12 with seasonal allergic rhinitis reported a positive clinical effect on rhinoconjunctivits and a reduced risk of experiencing asthma symptoms and using asthma medication [28]. Moreover, these benefits seem to be maintained after discontinuation of therapy [25, 29-31]. SLIT in patients with AR is cost-effective over symptomatic treatment [21, 32]. SLIT improves allergic asthma symptoms, which reduces medication use based on studies of HDM, dog, cat, tree pollen, and grass [33-36]. SLIT may also reduce the need for quick-relief medication [33]. Future research should include specific tools for evaluating asthma symptoms, including exacerbation, health care utilization, airway hyperresponsiveness and quality of life. It is also warranted to assess concerns regarding safety [37]. Preliminary studies have shown that SLIT to HDM is also effective in allergic diseases that do not involve airways such as atopic eczema [38]. Some clinical trials (patients aged from 6 to 46) have shown that the combination of omalizumab and AIT clinically improves its effectiveness, with the reduction in systemic adverse reaction risk [39]. The combination of AIT with probiotics may potentially decrease the allergen specific immune response [16, 40].

4. SCIT EFFICACY

SCIT has been the first route of administration of AIT. The allergen extracts may be delivered as either aqueous, physically-adsorbed (depot) or depot formulations as chemically modified allergens (allergoids). It provides an injection of repetitive doses of an allergen extract and it is available for allergens like grass, tree pollen and house dust mite [41].

Over the years, SCIT was modified, in particular with enhancements in composition and formulations of the specific allergen, in order to improve its safety profile, its standardization, its efficacy, long-term duration of treatment and costs. This topic has been treated in a review published in 2015 by Akdis *et al*. [42] with the aim of evaluating the efficacy and safety of depigmented polymerized grass pollen immunotherapy. In a prospective, double-blind, placebo-controlled trial [43], 195 grass pollen allergic patients were enrolled showing immunogenicity and clinical efficacy of the depigmented polymerized SCIT. With referral to pediatric population, Pfaar *et al.* [44] in 2015 published a retrospective study of 2927 children and adolescents having pollen- and/or mite-induced RA with/or without allergic asthma. That study revealed significant reductions in the recourse to rescue medication, and in the frequency referred to nasal symptoms over the course of treatment.

With referral to the duration of treatment, there could be a continuous, pre- (defined as starting AIT at least 2, preferably 4 months before the pollen season) and pre−/co-seasonal administration. The European Academy of Allergy and Clinical Immunology (EAACI) actually suggests at least a 3-year therapy course [45] (a shorter duration treatment could be associated with a reduction in efficacy).

One of the most historically and validated field of application of SCIT has been in patients affected by Hymenoptera venom allergy, proving to be effective in preventing systemic reaction to stings. Its efficacy has been shown in many trials, and even in a systematic review [46] of randomized controlled trials, involving 6 randomized controlled trials and 1 quasi-randomized controlled trial (n=392 participants).

Nowadays, SCIT is even routinely used in patients with AR and/or allergic asthma due to sensitization to aeroallergen, such as pollens and HDM, as sanctioned even by guidelines on allergen Immunotherapy for allergic rhinoconjunctivitis [9, 47].

For these applications, the strength of evidence is high in adult patients but there is a lack of data regarding pediatric patients, for whom even other review documented moderate evidence [14, 21, 47]. Recently, a systematic review of Di

Bona *et al*. [48] assessed the efficacy and safety of AIT for the treatment of respiratory allergies to moulds evaluating 9 studies and a total of 168 children and 99 adults, showing low strength evidence of efficacy of AIT for the treatment of respiratory allergies, although advocating the necessity of higher-quality studies with an adequate sample size.

The efficacy of this route of administration is also used to globally evaluate any single case, balancing with other aspects, such as frequent administration requiring hospital admission and potentially severe systemic adverse reactions.

Evaluating the efficacy of the AIT, we have to distinguish between a "short-term efficacy" and a "long-term one", defining the latter as evidence of clinical improvement for at least 1 year after stopping of the AIT course.

Concerning AIT indication of treatment in AR, there is actually evidence of efficacy in the short-term course for both seasonal and perennial AR. In 2017, Dhami *et al*. [21] published a systematic review and meta-analysis based on 160 studies showing AIT efficacy in improving the symptom, rescue medication, combined symptom and medication scores in patients with allergic rhinoconjunctivitis while on treatment. Even some evidence suggesting maintenance of benefits after discontinuation of therapy was encountered.

Long-term efficacy is instead actually limited to continuous grass pollen performed for a minimum of 3 years in seasonal AR due to grass pollen, as stated by Guidelines on allergic rhinoconjunctivitis [47] published in 2017.

Also, the role of SCIT in asthma control has been investigated, demonstrating its effectiveness in reducing symptoms and medication use. This has been evidenced even by meta-analyses of randomized clinical trials, such as the one published by Dhami *et al*. [33] in 2017. It evaluated 98 studies on adults and children, showing reductions in short-term symptoms and medication scores in allergic asthma without conclusive data on longer-term effectiveness and cost-effectiveness.

Even if these data were obtained mostly involving the adult population, studies conducted in children showed similar results [49, 50]. With this aim, a randomized, double-blind, placebo-controlled study was performed by Roberts *et al*. [49] and published in 2006, involving 35 children aged 3-16 years, with a history of seasonal allergic asthma sensitized to grass pollen (P. pratense) and in therapy with inhaled corticosteroids (ICS). The study showed the efficacy of AIT in that population of patients, bringing a significant reduction in asthma symptom-medication score, and in cutaneous, conjunctival and bronchial reactivity to an allergen after AIT compared with the placebo group.

In order to evaluate the possible role of SCIT in having a positive long-term impact on childhood asthma, a retrospective study was published in 2000, in which asthmatics children allergic to either HDM or grass pollen (n=34), were treated with SCIT and compared with a control group (n=42) of asthmatic people who underwent appropriate anthiasthmatic drugs during childhood. The 2 groups were then assessed about 9 years after the discontinuation, demonstrating a reduction of three-time of recurrence of asthma symptoms compared with controls. No difference in lung function or medication use was found [10, 51].

The long-term efficacy of SCIT has even been evaluated in a prospective study using HDM SCIT performed by Stelmach *et al* in 2012. This study compared 30 patients treated for 3 years with HDM AIT, 30 patients treated with a 5 years course of HDM AIT and other 30 who refused HDM AIT, showing that asthma remission was significantly higher in both treated groups compared with controls after 3 years of discontinuation therapy, without clinical benefits in continuing therapy for other 2 years [52].

Another aspect of AIT that has been investigated was its steroid-sparing effect. [10] With this purpose, a randomized controlled trial has been performed by Zielen *et al*. [50], enrolling 65 children aged 6-17 years old with controlled asthma who received HDM-SCIT with fluticasone propionate or ICS alone for 2 years. During the 2 subsequent 5-months winter period, the variations in ICS dosages and the lowest fluticasone propionate dose effective to maintain asthma control were evaluated. The study showed that children who received HDM-SCIT plus ICS needed a statistically significantly lower dose of CSI compared with patients treated with ICS alone. A significant improvement of the morning peak expiratory flow (PEF) and increased levels of IgG1 and IgG4 were also recorded.

Studies comparing the effect of the two main routes of administration of AIT, SCIT and SLIT, were performed with conflicting results.

Nelson *et al*. in 2016 published a meta-analysis reporting superiority of SCIT to SLIT [53].

Table **2** showed some peculiar characteristics that distinguish SCIT and SLIT.

5. SIDE EFFECTS

Both SCIT and SLIT increase the risk of adverse events [21, 33]. One fatality/7.770.000 injections after SCIT has been reported [54]. Adverse reactions to SCIT range from local site reactions, from skin pruritus to systemic reactions, such as anaphylaxis and have been previously classified in a

Table 2. Main features that clinically distinguish SCIT from SLIT.

SCIT	SLIT
Higher adherence for SCIT beyond pediatric age	Improved safety
Greater experience on its use (historically the first and most used route of administration)	Reduced burden to the patient, avoiding the discomfort of injections
Some evidence of greater efficacy, yet to be confirmed	Avoids the inconvenience of office visits

grading system [55]. Local reactions are frequent, in 26-86% of SCIT injections, but are often well-tolerated [56]. Systemic reactions occur in 8.7 cases every 10.000 SCIT injections [53]. Recently, Lee *et al*. [57] found that 24% of patients experienced adverse reactions to SCIT and only 1 case of anaphylaxis developed. So, SCIT requires that injections should be performed by trained personnel in clinical settings equipped to manage any possible systemic adverse reactions or anaphylaxis. Although systemic reactions are rare when AIT is performed according to proper safety recommendations, a systematic review reported severe anaphylactic reactions requiring adrenaline in 3.4% of cases among 13 trials [58].

SLIT has an impressive safety profile in clinical trials [59, 60] and post-marketing surveillance of large cohorts [61]. Although there have been case reports of severe allergic reactions, including anaphylaxis, no fatalities have been reported [62]. SLIT is rarely associated with systemic reactions [63] or life-threatening adverse events [34]. The rates of anaphylaxis with SLIT were compared however, no treatment was determined (no cases reported in the randomized controlled trials due to insufficient evidence). Three case reports suggested that, anaphylaxis rarely occur with SLIT treatment [64, 65]. Two of 3 reports of anaphylaxis secondary to SLIT were of patients who received multiple-allergen therapy [64, 65], perhaps signaling that multiple allergen SLIT poses higher risk for systemic adverse effects, as recently suggested [66] In the US, the package for SLIT tablets was approved by the Food and Drug Administration which recommends that an epinephrine autoinjector device should be prescribed for patients taking SLIT tablets [67]. Randomized controlled trials showed that local adverse reactions to SLIT are common (up to 80% of patients). SLIT is frequently associated with local itching at the oral cavity and throat and swelling of the mouth which can occasionally be inconvenient and persist for weeks [68, 69]. Gastrointestinal symptoms may occur but not irritable bowel disease or constipation [70]. SLIT should be interrupted in case of fever, asthmatic exacerbation [71], wound at mouth to minimize the adverse events.

6. ALLERGEN CHOICE: THE ROLE OF MOLECULAR DIAGNOSIS

AIT is efficacious when the inhalant allergens triggering all or most respiratory symptoms have been properly identified in the individual patient [72], defined as "relevant allergens" by the European Medicines Agency (EMA) [73, 74]. Allergens should be accurately quantified in preparations used for AIT with an allergen amount from 5 to 20 mcg of the major or prevalent allergen for SCIT and 15-187 mcg for SLIT [75]. Currently, although the allergen quantity is still flexible, several preparations with high concentration, good safety and tolerance, are comprised in the official pharmacopoeia. In order to increase the efficacy and patient's adherence, reduce side effects and treatment duration, novel approaches have been developed. The natural extract can be reconstituted with a mixture of multiple recombinant allergens. Allergens might be coupled with adjuvants that stimulate various aspects of innate immunity or chemically modified with molecules binding allergens (formaldehyde, glutaraldehyde, alginate) or with functional substitutes (potassium cyanate), in so-called "allergoids", creating a product with reduced IgE affinity and a partial resistance to the proteolytic enzymes in the digestive system [76].

Nowadays, many patients with pollen allergy are sensitized to different pollen sources with overlapping seasonality. Moreover, many patients are sensitized to profilin or other highly cross-reacting molecules shared by many unrelated pollen sources and their extracts (panallergens) [77]. For instance, sensitization profiles to pollens in children are highly heterogeneous and polysensitization increases with age [78]. Thus, the identification of the disease-eliciting pollen sources by means of extract-based skin prick tests (SPTs) in patients sensitized to multiple pollens with overlapping seasonality is often difficult.

Component-resolved diagnosis (CRD) can now be used in routine clinical practice to detect sensitization to major allergens and to determine cross-reactivity due to panallergens sensitization. CRD, then, can be a useful tool in polysensitized patients to define the right composition of AIT expected to improve outcomes [79].

In a clinic-based population of 651 Italian children with pollen-related AR, the measurement of serum specific IgE levels to the major allergenic molecules of pollens was able to modify very frequently the prescription of AIT based on the same clinical history integrated with SPT responses with pollen extracts [80]. So, molecularly designed AIT preparations tailored to patients' goes to the standpoint of a "precision medicine" and needs an appropriate selection of patients and allergen extracts, matching clinical history and environmental exposure, confirmed by diagnostic tests. This concept needs further studies on the influence of CRD in the efficacy of AIT. Several factors associated with AIT in polysensitized patients should be considered, such as the clinical response and the real efficacy in case of prompt prescription of AIT; the guaranty of the extracts' quality; its use in polysensitized patients even when pollination periods overlap [81].

Other approaches have been used for selecting AIT (*e.g.*: nasal provocation tests), however, these procedures are not usually performed in routine clinical practice, because they are not standardized and time-consuming.

7. INDICATIONS FOR AIT

AIT is indicated for the treatment of children with allergic respiratory disease when symptoms persist despite measures for avoiding triggering allergens. Eligible children for AIT are those positive skin prick test/IgE towards one or more allergens, whose exposure is associated with moderate/severe symptoms of allergic rhinitis with or without conjunctivitis interfering with usual daily activities or sleep and/or allergic asthma [5]. AIT should be considered when pharmacotherapy controls symptoms but patients prefer avoiding long-term treatment and in patients with frequent and serious adverse events elicited by drugs. The willingness of the patient should also be considered [82] (Table **3**). Standardized allergen extracts are available for pollens, HDM, mold and animal dander.

AIT is contraindicated in patients with conditions that increase the risk of treatment-related severe SRs, such as severe or poorly controlled asthma or significant cardiovas-

Table 3. Indication of AIT in children.

Indication AIT	Contraindication AIT
Persistent symptoms	Uncontrolled asthma
Positive skin prick test/IgE towards one or more allergen associated with moderate/severe allergic rhinitis with or without conjunctivitis	Cardiovascular disease
Adverse events elicited by drugs	Caution to patients receiving b-blockers or angiotensin-converting enzyme inhibitors

cular diseases (*e.g*., unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension) and should be administered with caution to patients receiving b-blockers or angiotensin-converting enzyme inhibitors. Chronic nasal inflammatory responses and nasal polyps are not a contraindication for AIT. Severe or uncontrolled asthma or forced expiratory volume in the 1st second (FEV1) < 80% are the major independent risk factor for both nonfatal and fatal adverse reactions and thus a major contraindication for both SLIT and SCIT. All patients undergoing AIT should be observed typically for at least 30 minutes after injection to ensure proper management of systemic reactions.

Recent guidelines on AIT for AR recommend that a minimum of 3 years of therapy should be used to achieve long-term efficacy [1].

Adherence to treatment has also been raised as a potential issue. Regular follow-up for educating patients and families prescriptions has been shown to be effective in improving adherence. Pharmacotherapy should be continued during AIT. Among skin tests, prick tests [83] but no patch test is useful for the diagnosis of IgE-mediated diseases [84].

8. OTHER ROUTE OF AIT

AIT could even be administered by other route, such as epicutaneus and intra-lymphatic.

Epicutaneous immunotherapy (EPIT) [85] implies the application of a patch. There are two different delivery systems developed to ease allergen skin penetration: adhesive stripping and the hydration/occlusive system. Studies actually set up to evaluate the efficacy of EPIT involved basically adult people. The first monocentric, placebo-controlled, double-blind trial on patients aged from 18 to 65 years, performed with the attempt to evaluate the efficacy and safety of EPIT was conducted by Senti *et al*. [86]. The study enrolled thirty-seven adult patients randomized and allocated to receive patches with allergen (Phelum (Phl) p 5) or placebo that were applied weekly for 12 weeks and left for 48 hours on the skin. Changes in the nasal provocation test (NPT), symptoms scored using the visual analog scale (VAS), and the use of rescue medications were evaluated, showing a statistically significant evidence only for the symptoms evaluated by the VAS scale.

Senti *et al*. [87] performed even another monocentric, placebo-controlled, double blind dose escalation study involving 132 patients with grass pollen-induced rhinoconjunctivitis. Patients were randomly allocated to receive, before and during the pollen season 2008, a 6-weekly patches of placebo or 3 different doses of allergen and were then followed up for 4 to 5 months later (n=110) and during the subsequent pollen season treatment-free. The study showed EPIT efficacy in a dose-dependent manner after 6 patches only, with a reduction of hay fever symptoms during the pollen season of more than 30% in 2008 and 24% in 2009 in the high-dose group vs placebo group, with a correlation between the alleviation of symptoms in the follow-up year and the treatment dose. The conjunctival provocation test (CPT) and medication scores were also evaluated but didn't show a statistical difference.

These studies show EPIT efficacy in patients with grass rhinoconjunctivitis but they are developed on an adult population and performed with methods not directly comparable, for this reason, more studies are needed to give strength to these data.

Intra-lymphatic immunotherapy (ILIT) implies allergen application directly into the lymph node. This application has some advantages, such as low allergen dose required and short duration of therapy: the treatment course contemplates 3 ultrasound- guided injections into inguinal lymph nodes with a 1-month time interval [88]. Recently, an up-to-date review [89] stated that even if clinical results for ILIT are encouraging, the number of patients included in randomized controlled trials is scarce, so more clinical trials are needed.

Two other novel routes of AIT under investigation are the intradermal, and the local intranasal one, for which the actual data are discordant [90, 91].

9. AIT AS PREVENTION

There have been concerns about the preventive role of AIT on subsequent development of asthma and other allergic sensitizations. According to the concept of "atopic march" [14], AR often precedes the onset of asthma and, therefore, it can be considered a risk factor for the development of the allergic asthmatic disease.

The natural course of allergic disease could be modified by AIT, both preventing the onset of new sensitizations and the clinical disease progression (from rhinitis to asthma).

Another possible focus of investigation could be the possible role of AIT in avoiding the development of allergy symptoms in patients asymptomatic but sensitized or at high risk of developing atopy. The "primary immune-prophylaxis" deals with the prevention of the development of first allergic disease in not-sensitized children, the "secondary immune-prophylaxis" consists of prevention in healthy

children with specific IgE antibodies and the "tertiary immune-prophylaxis of atopy" that is the prevention of allergic sensitization in patients with other allergic conditions.

The importance of preventing new sensitization is also linked to the concept of "molecular spreading" [92], according to which in most children the IgE response to a specific allergen undergo an evolution and rising complexity over time. This "spreading" concerns a gradual increase of the serum concentration of IgE antibodies, due to both an increase in sensitizing molecules, and to a growing concentration of IgE antibodies directed against any specific allergenic molecule.

The "Prevention allergy treatment study" (PAT study) could be considered as one of the first biggest study planned to evaluate the preventing role of AIT, in particular in which the terms SCIT could reduce the outcome of asthma in children with allergic rhinoconjunctivitis sensitized to birch and/or timothy pollen. This was a European multi-center study dated 1999, which enrolled 210 children aged from 5 to 13 years, randomized into two groups: the treatment group who received immunotherapy for 3 years with standardized allergen extracts of grass and/or birch and control group who received optimal pharmacotherapy. After 3 years of AIT or symptomatic treatment in the control group, it was shown that the actively treated children had significantly fewer asthma symptoms evaluated by clinical diagnosis (odds ratio, 2.52; P <.05). The active group even showed improved results in methacholine bronchial provocation test (P <.05). According to this data, immunotherapy could reduce the development of asthma in children with seasonal rhinoconjunctivitis [93]. The 5-year follow up - 2 years after termination of immunotherapy- investigated 183 patients aged 6-14 years showing long-term clinical effect and preventive effect on the development of asthma in children with seasonal rhinoconjunctivitis actively treated with immunotherapy (odds ratio 2.68 (95%CI 1,3-5,7) [94]. The 10-year follow up (n: 147 patients, aged 16-25 years) showed persistence of improvements in rhinoconjunctivitis and conjunctival sensitivity and the potential of preventing the development of asthma in children with allergic rhinoconjunctivitis up to 7 years after treatment. The odds ratio for no-asthma was 4.6 (95% CI 1.5-13.7) in favor of AIT [23].

Even the preventive role of SLIT on asthma has been investigated, in particular with the "grass tablet asthma prevention" (GAP) study [95]. This was the first randomized, double blind, placebo-controlled trial involving 812 children aged 5-12 years with grass pollen rhinoconjuctivitis without asthma. Patients have been divided into two groups, the treated group who received Standardized Quality (SQ) grass-SLIT tablet, and the control group who received placebo. After a 3-year course of therapy, the patients were followed up for another 2 years. The overall 5-year follow up showed a reduction of the risk of presentation of asthma symptoms or need for asthma medication. Even an improvement in AR symptoms was documented [28].

The preventive effect of SLIT on asthma symptoms has been shown even by another open randomized study involving 113 children, in which a higher risk (3,8 times higher) of developing asthma in patients who were not submitted to AIT has been documented [27].

According to the results of these studies, there is some evidence of the efficacy of AIT in preventing the development of asthma in children with rhinoconjunctivitis, as already shown in a systematic review of Kristiansen *et al*. [96]. A 3-year-long course of subcutaneous or sublingual AIT can be recommended for patients with moderate to severe AR due to grass or birch pollen in order to prevent the onset of allergic asthma for up to 2 years post-AIT cessation. However, there is a lack of evidence for AR triggered by house dust mites or other allergens different from grass/ birch.

With the aim of investigating the role of single-allergen AIT in reducing the risk of new sensitization in monosensitized children, Inal *et al*. [97] published in 2007 the results of an open group study involving 147 children with AR and/or asthma, showing that after a 5-year follow up 75.3% of children in the AIT group did not show new sensitization versus 46,7% of children in the control group (p=0.002).

A systematic review of 18 studies involving 1049 children and 10 057 adults performed by Di Bona *et al*. [98] showed low-grade level of evidence in favor of AIT role in preventing new allergen sensitizations.

Therefore, even if some evidence of the preventive potential role of AIT has been found, data achieved a lack of consistency, so AIT can't actually be recommended for the prevention of new sensitizations. Therefore, in order to corroborate this possible role, high-quality studies should be performed [14, 27, 98, 99].

With regard to administrating AIT as "primary immune-prophylaxis" in children at risk or in infants with atopic manifestations, such as atopic eczema and food allergy, it could not be made any recommendation in favor or against due to of lack of data. However, it has been shown that SLIT to HDM can inhibit molecular spreading [100].

CONCLUSION

SLIT and SCIT have been found to be effective in the treatment of asthma and rhinoconjunctivitis due to inhalant allergens. Furthermore, they prevent the development of asthma in children with seasonal rhinoconjunctivitis. Regarding the route of administration, SLIT and SCIT have not been demonstrated to have different efficacy. Therefore, the choice should be based on availability, cost (dependent from the local health system), tolerability (better for SLIT), patient preference (injections are less accepted in young children), adherence (higher for SCIT beyond pediatric age). However, it should be taken into account that metanalyses on AIT do not consider that effectiveness and safety depending on the product used for treatment. Each product should be separately assessed to avoid generalization on administration routes or age groups that may affect the decision.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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