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Brazilian guidelines for allergen immunotherapy in the treatment of allergic rhinitis

Fernando Monteiro Aarestrup[1], Geórgia Véras de Araújo Gueiros Lira[1], Ernesto Akio Taketomi[1], Elaine Gagete[1], Nelson Augusto Rosário Filho[2], Maria Cândida Rizzo[3], Dirceu Solé[4], Norma de Paula Motta Rubini[5], Emanuel Savio Cavalcanti Sarinho[5], Wanderley Marques Bernardo[6]*

INTRODUCTION

Epidemiological studies show that allergic rhinitis (AR) is observed in 10–40% of the world's population. This disease significantly compromises the quality of life, impairing development in children and professional activities in adults. AR is also frequently associated with allergic asthma (AA)[1,2]. It has been observed that 15–38% of patients with AR develop concomitant AA. This relationship between AR and AA is based on robust pathophysiological mechanisms, which are consistent with the united airways theory. This model states that environmental exposure to allergenic molecules in genetically predisposed individuals directs the production of specific cytokines responsible for the development of the allergic inflammatory process in the nasal mucosa and lungs[1,3].

The association between AR and AA or atopic dermatitis (AD) is very common, usually developing since childhood, representing a phenomenon called the atopic march. Therefore, patients with AR should be evaluated in a broad and systemic way due to the implications and interactions of this disease that is part of a broad allergic process that can affect the upper airways, lower airways, skin, and mucous membranes. These diseases, classified as atopic diseases, are characterized by the presence of a specific, genetically directed immune response after exposure to allergens[1,2,4,5]. In Brazil, the components derived from the house dust mites *Dermatophagoides farinae* (Df), *Dermatophagoides pteronyssinus* (Dp), and *Blomia tropicalis* (Bt) are the main allergens associated with the etiology of AR. Particularly in southern Brazil and in rural areas, pollens are also allergens associated with the etiology of AR[6].

Knowledge of the pathophysiology of AR is important for understanding the diagnostic strategies and therapeutic possibilities. Sensitization in the nasal mucosa starts with the presentation of allergens by antigen-presenting cells, such as dendritic cells, macrophages, and Langerhans cells, to naive $CD4^+$ T lymphocytes, which at the level of innate immunity may present themselves as dysfunctional, and individuals with genetic predisposition in the presence of allergens have a tendency to differentiate naive $CD4^+$ T cells into Th2 cells, which are characterized by producing interleukin (IL)-4, IL-5, and IL-13. In addition, other important cytokines in this allergen-specific response or even in nonspecific triggers (irritants, pollutants, virus infection, etc.) are IL-25, IL-33, and thymic stromal lymphopoietin produced by respiratory mucosal epithelial cells. These cytokines (alarmins) can contribute to induce immunoglobulin E (IgE) production and the recruitment of eosinophils to the site of the inflammatory allergic process by stimulating, respectively, IL-4- and IL-5-producing Th2 and ILC2 cells. This entire process is currently referred to as type 2 inflammation, characterizing the pathophysiological mechanisms of AR and AA[5,6].

[1]Brazilian Association of Allergy and Immunology biennium 2021-2022, Department of Immunotherapy – Brazil.
[2]Brazilian Association of Allergy and Immunology biennium 2021-2022, International Relations – Brazil.
[3]Brazilian Association of Allergy and Immunology biennium 2021-2022, Department of Rhinitis – Brazil.
[4]Brazilian Association of Allergy and Immunology biennium 2021-2022, Research – Brazil.
[5]Brazilian Association of Allergy and Immunology biennium 2021-2022 – Brazil.
[6]Brazilian Medical Association, Guidelines Program – Brazil.
*Corresponding author: wmbernardo@usp.br
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The Allergic Rhinitis and its Impact on Asthma (ARIA) guideline was an initiative during a World Health Organization workshop in 1999 that established guidelines for the treatment of AR based on allergy testing and therapeutic approach using evidence-based medicine strategies (Grading of Recommendations, Assessment, Development and Evaluation [GRADE] Approach). The ARIA recommendations state that allergen immunotherapy (AIT) represents one of the cornerstones in the treatment of AR with a level of evidence of A. The guidelines of the European Academy of Allergy and Clinical Immunology (EAACI), World Allergy Organization (WAO), and the American Academy of Allergy, Asthma and Immunology (AAAAI) until 2022 represented the main official documents establishing guidelines for the use of AIT. Recently, the "position paper" of the Brazilian Association of Allergy and Immunology (ASBAI)[6] was published, establishing recommendations for good AIT practices in Brazil. Most of the consensus in the field considers AIT to be the unique treatment capable of modifying the allergen-specific immune response by promoting desensitization and a state of tolerance. The control of AR symptoms remains satisfactory in the long term even after the end of the AIT, reducing or even abolishing the use of drugs. Therefore, we can consider this therapy potentially able to promote total remission of the disease[1,5,6,7,8,9].

The present study aimed to contribute to the Guidelines Project, an initiative of the Brazilian Medical Association. Through evidence-based medicine strategies, we conducted a systematic review in order to guide and standardize management and procedures on the use of AIT in the treatment of AR. Clinical issues on the selection of patients eligible for treatment with AIT through clinical history, allergy testing and/or serum-specific IgE, information on safety and efficacy, indications and contraindications, monitoring treatment, routes of application, and considerations on adequate professional preparation were addressed and discussed.

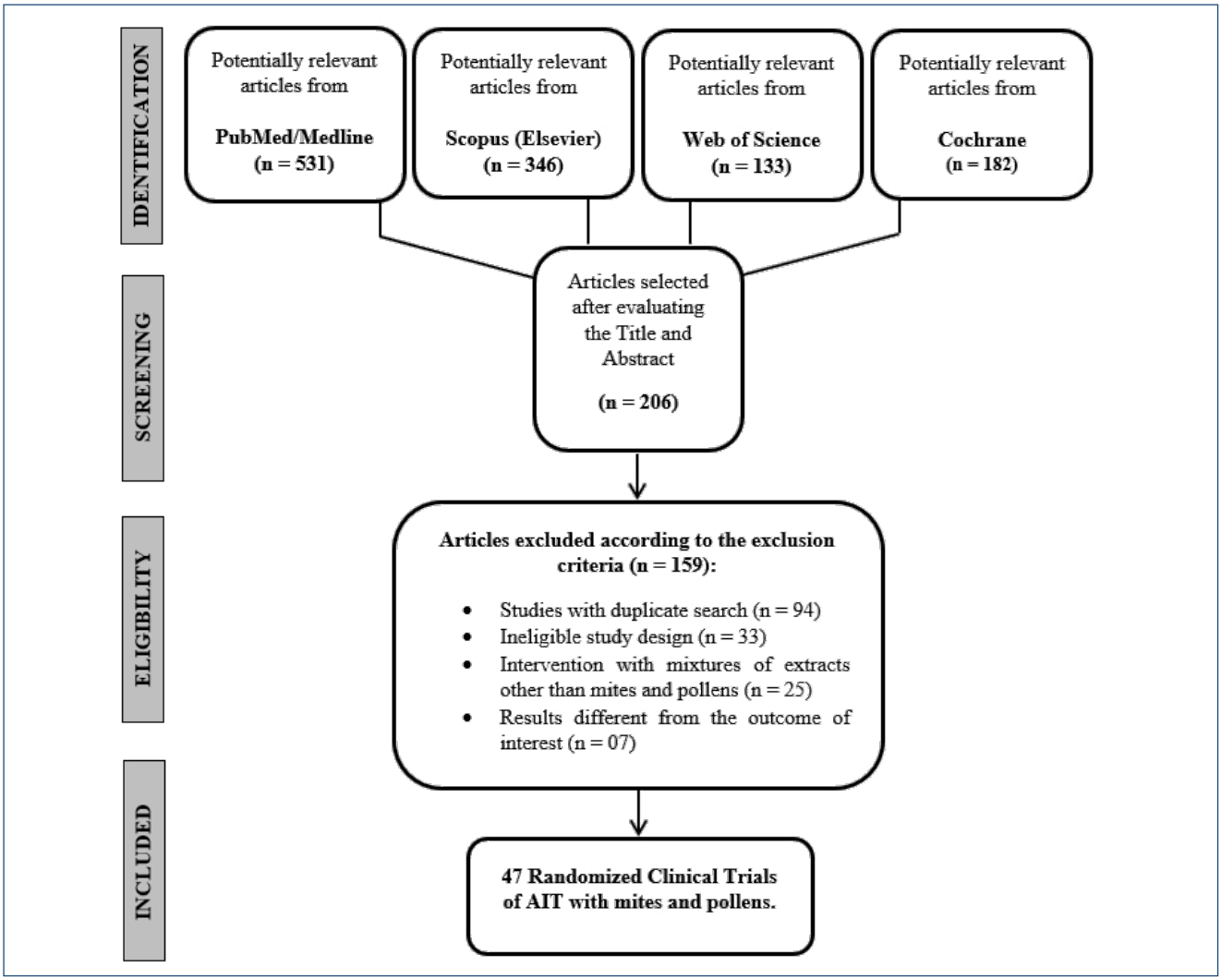

Figure 1. Flow diagram of the randomized clinical trial selection process by Preferred Reporting Items for Systematic Reviews and Meta-Analyses

METHODS

Members of the Scientific Department of Immunotherapy of the ASBAI conducted a systematic review of randomized clinical trials (RCTs) for the construction of medical guidelines on the use of sublingual and subcutaneous immunotherapy with dust mites and pollens in AR. Figure 1 shows flow diagram of the RCT selection process by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

The research methods and criteria are available in the International Prospective Register of Systematic Reviews (PROSPERO) protocol with registration number CRD42022383864; the data from the studies were qualitatively evaluated following the PRISMA guidelines.

ELIGIBILITY CRITERIA

Inclusion criteria were defined following the P.I.C.O.S. framework. Studies that met these criteria were eligible.

1. Population: patients diagnosed with persistent and/or moderate-to-severe AR (ARIA criteria) aged >2 years.
2. Intervention: standard treatment (ARIA) with AIT with dust mites or pollens or standard treatment without AIT.
3. Comparator: standard treatment with AIT and without AIT.
4. Outcomes: for the primary endpoint, we evaluated symptom reduction with clinical improvement of rhinitis.
5. Study type: RCTs published in the past 30 years until November 2022, in English, Portuguese, and Spanish languages.

SEARCH STRATEGY AND STUDY SELECTION

Searches were performed in MEDLINE/PubMed, Web of Science, Scopus, and Cochrane Library databases for articles published until November 30, 2022, using the following descriptors, through the Medical Subject Headings tool, in the same search protocol: for subcutaneous immunotherapy with dust mites: "allergic rhinitis" AND "allergen immunotherapy" AND "house dust mite extracts" AND "subcutaneous"; for sublingual immunotherapy with dust mites: "allergic rhinitis" AND "allergen immunotherapy" AND "house dust mite extracts" AND "sublingual"; for subcutaneous immunotherapy with pollens: "allergic rhinitis" AND "allergen immunotherapy" AND "pollens extracts" AND "subcutaneous"; and for sublingual immunotherapy with pollens: "allergic rhinitis" AND "allergen immunotherapy" AND "pollens extracts" AND "sublingual."

DATA EXTRACTION AND SYNTHESIS

Quality assessment was obtained using the GRADE approach to assign levels of evidence and rate the strength of recommendation of the results. The quality of evidence was classified into four levels: high, moderate, low, and very low. The following factors were considered to determine the level of evidence: study design, methodological limitations (risk of bias), inconsistency, imprecision, and magnitude of effect. After this analysis, the strength of the recommendation was identified as weak or strong, and an evaluation of the clinical trials was performed together.

For risk of bias assessment, the revised Cochrane Risk of Bias (RoB2) tool was used for selected randomized trials. RoB2 was judged as low, moderate, high, or unclear for each domain: randomization process, deviations from intended interventions, lack of outcome data, outcome measurement, selection of reported outcomes, and overall bias. The domains included in this tool were divided according to the phase of the intervention: pre-intervention (bias due to confounding, bias in selection of participants for the study), intervention (bias in classification of interventions), and post-intervention (bias due to deviations from intended interventions, bias due to lack of data, bias in measurement of outcomes, and bias in selection of reported outcomes).

CLINICAL QUESTIONS: EVIDENCE ANALYSIS

Tables 1, 2, and 3 present the data analysis of the risk of bias and grading of the value of evidence by the GRADE approach. In each clinical question answered below, these analyses were taken into account to establish the conclusions and recommendations. The GRADE analysis was performed using the set of articles analyzed specifically for house dust mites and pollens.

Question 1: Is subcutaneous allergen immunotherapy effective in allergic rhinitis in children and adults?

The clinical picture of AR may present in seasonal or perennial clinical form, caused respectively by pollen/fungi and house dust containing predominantly components derived from house dust mites, animal epithelia, and fungi[2,6,7,10-17].

In cases of moderate-to-severe persistent AR, AIT, administered by sublingual (SLIT) or subcutaneous (SCIT) route, is a therapeutic modality considered one of the pillars of the professional practice of the specialist in allergy and immunology. AIT has shown to be effective, contributing significantly to clinical improvement by reducing symptom scores

Table 1. RoB2 analysis to house dust mite allergen immunotherapy.

Intention-to-treat	Unique ID	Study ID	D1	D2	D3	D4	D5	Overall
	1	Bahçeciler - 2001	+	+	+	-	!	
	2	Bergmann - 2014	+	+	+	+	-	
	3	Bernstein - 2018	+	+	+	+	+	
	4	Bozek - 2013	+	+	+	+	+	
	5	Chen - 2020	+	!	+	+	+	
	6	De Bot - 2012	+	!	+	+	!	
	7	Demoly - 2021	+	+	+	+	+	
	8	Di Gioacchino - 2012	+	+	+	+	!	
	9	Didier - 2015	!	+	+	+	!	
	10	Dokic - 2005	+	+	!	+	!	
	11	Guez - 2000	+	!	+	-	+	
	12	Karakoc-Aydiner - 2015	+	!	+	+	+	
	13	Masuyama - 2019	+	!	+	+	!	
	14	Mosbech - 2015	+	+	+	+	+	
	15	Okamoto - 2017	+	+	+	+	!	
	16	Okamoto - 2019	+	+	+	!	!	
	17	Riechelmann - 2010	+	!	+	+	+	
	18	Tonnel - 2004	+	!	+	+	!	
	19	Tseng - 2008	+	!	+	!	+	
	20	Valero - 2022	!	+	+	+	!	
	21	Varney - 2003	+	+	+	+	!	
	22	Vesna - 2016	+	+	+	+	+	
	23	Xian - 2019	+	+	+	+	+	
	24	Yu Guo - 2017	+	+	+	+	+	
	25	Yukselen - 2013	+	+	+	+	!	

+	Low risk
!	Some concerns
-	High risk

D1	Randomisation process
D2	Deviations from the intended interventions
D3	Missing outcome data
D4	Measurement of the outcome
D5	Selection of the reported result

and medication use, whose effects may persist for several years after discontinuation (termination). Thus, the etiologic diagnosis of AR responsible for IgE antibody-mediated sensitization, determining its clinical relevance, is crucial for the allergist with RQE (specialty qualification record) doctor in allergy and immunology and/or pediatric allergy practice area to carry out the selection (formulation) of allergenic extract components and their use in different dilutions in an appropriate manner for the proper choice of route of administration, whether subcutaneous or sublingual, and its application scheme (protocol). Also, it is of fundamental importance to know the properties of the allergens so that the specialist can

Table 2. RoB2 analysis to pollens allergen immunotherapy.

Intention-to-treat	Unique ID	Study ID	D1	D2	D3	D4	D5	Overall
	1	Ahmadiafshar - 2012	+	!	+	+	!	
	2	Bowen - 2004	+	!	+	+	!	
	3	Bozek - 2020	+	+	+	+	!	
	4	Bufe - 2004	+	+	+	+	!	
	5	Clavel - 1998	+	!	+	-	+	
	6	Couroux - 2019	+	+	+	+	+	
	7	De Blay - 2007	+	!	+	+	!	
	8	Durham - 2012	+	+	+	+	+	
	9	Gotoh - 2019	+	+	+	+	+	
	10	Lou - 2020	+	+	+	+	+	
	11	Nolte - 2020	+	+	+	+	+	
	12	Nolte - 2021	+	+	+	+	!	
	13	Okamoto - 2015	+	!	+	+	!	
	14	Pfaar - 2008	+	!	+	+	-	
	15	Pfaar - 2010	+	+	+	+	!	
	16	Pfaar - 2019	+	+	+	+	+	
	17	Sharif - 2019	+	+	+	+	!	
	18	Ünal - 2020	-	+	+	+	+	
	19	Wahn - 2012	+	+	+	!	+	
	20	Worm - 2019	+	+	+	+	!	
	21	Yang - 2022	+	+	+	+	+	
	22	Yonekura - 2021	+	+	+	+	+	

+	Low risk
!	Some concerns
-	High risk

D1	Randomisation process
D2	Deviations from the intended interventions
D3	Missing outcome data
D4	Measurement of the outcome
D5	Selection of the reported result

choose whether or not to mix certain allergens in cases of polysensitized patients[6,18-26].

This systematic review included 25 double-blind, placebo-controlled (DBPC) RCTs with a total of 4,518 patients with perennial AR with or without asthma who underwent immunotherapy with house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, in a 1:1 ratio) and 3,887 placebo-treated control patients, and when analyzed by the GRADE approach (Table 3; classification of recommendations, assessment, development, and evaluation) showed a level of CERTAINTY considered HIGH, with no seriousness detected in the parameters of risk of bias, inconsistency, indirect evidence, and imprecision, as shown in Table 3 (GRADE for RCTs involving AIT with dust mites). Among the total of these 25 RCTs, 3 studies involved three comparative groups: SCIT, SLIT, and placebo/control (pharmacotherapy only, in the study conducted by Karakoc-Aydiner)[15], and the rest employed only one active treatment modality. Thus, in all seven trials (four trials with SCIT active group and placebo; three trials with SCIT and SLIT active groups versus control) that employed ITSC, they demonstrated clinical efficacy in the treatment of AR by reducing symptom and/or medication scores compared to the placebo group, as shown in Table 1 (RoB2, AIT with dust mite allergens).

Table 3. GRADE analysis.

Question: Dp and Df mite extracts compared to Placebo with the same organoleptic characteristics for persistent and/or moderate-to-severe allergic rhinitis (ARIA criteria)									
Context: To evaluate the reduction of symptoms with clinical improvement in allergic rhinitis.									
Certainty assessment							Number of patients		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Dp and Df mite extracts	Placebo with the same organoleptic characteristics	
25	Randomized clinical trials	Nonsevere	Nonsevere	Nonsevere	Nonsevere	None	4.518	3.887	⊕⊕⊕⊕ High

Question: Grass pollen extract compared to placebo for perennial or seasonal allergic rhinitis									
Context: To evaluate the reduction of symptoms with clinical improvement in allergic rhinitis.									
Certainty assessment							Number of patients		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Grass pollen extracts	Placebo with the same organoleptic characteristics	
22	Randomized clinical trials	Severe	Nonsevere	Nonsevere	Nonsevere	None	2.945	2.248	⊕⊕⊕◯ Moderate

For AIT with grass or tree pollen allergens, 22 DBPC RCTs were included, with a total sample size of 2,945 patients with seasonal AR receiving grass or tree pollen immunotherapy and 2,248 patients in the placebo group. Analyzing these trials, because they are the most heterogeneous trials, the joint analysis of these trials by GRADE (Table 3) showed a level of CERTAINTY considered MODERATE, although it was not detected any severity in the parameters of inconsistency, indirect evidence, and imprecision, but showed serious risk of bias, as can be seen in Table 3 (GRADE of RCTs with pollens). Of the total of these 22 RCTs, 5 employed SCIT, and 17 SLIT, as shown in Table 2 (RoB2, AIT with pollen allergens).

Conclusions

1. SCIT with house dust mites is effective in AR in children and adults (GRADE: high; GRADE OF RECOMMENDATION: strong).
2. SCIT with pollens is effective in AR in children and adults (GRADE: moderate; RECOMMENDATION: strong).

Question 2: Is subcutaneous immunotherapy safe in allergic rhinitis in children and adults?

Despite the evidence of beneficial clinical effect of SCIT, this therapeutic modality presents risks of developing adverse effects, either in children or adults, especially local reactions such as discomfort, erythema, edema, pain, and pruritus at the application site, usually of mild intensity. Local treatment can be given for these local reactions with cold/iced compresses and/or topical corticosteroids or oral antihistamines. However, patients with frequent and extensive local reactions should be treated with caution, as they may be at greater risk of systemic reactions. In this context, systemic adverse effects may occur, mostly mild, including sneezing, pruritus, nasal congestion, and/or urticaria, which are easily controlled and are not troublesome for the continuation of immunotherapy. In patients with AR and concomitant asthma, it is always recommended to evaluate the acute exacerbation of asthma and measure the peak flow before the application of SCIT, and it should be suspended in the presence of acute asthmatic symptoms. In addition, the greatest concern should be directed toward the serious systemic adverse effects, which, although rare, can occasionally present anaphylaxis and even death has been reported in the literature. Thus, for SCIT, applications require a location with appropriate infrastructure[18], according to the Annex of Resolution CFM 2.215/2018 (Federal Medical Council), and immediate medical care. In cases of anaphylaxis, the treatment of choice is intramuscular application of millesimal epinephrine/adrenaline. Antihistamines and systemic corticosteroids are considered secondary medications. It is recommended that the site of the SCIT should be at the prescribing physician's facility[2,6,9,14].

In addition, Purkey et al.[21] in their evidence-based review recommended the use of SCIT for patients with AR, whether seasonal or perennial, especially for those who are not responsive to usual pharmacological therapy and whose symptoms

significantly impact their quality of life. These authors stated that SCIT is safe when administered carefully to specific patients and applied in settings capable of providing appropriate medical care in the event of systemic adverse reactions.

Conclusions

1. SCIT with house dust mites is safe in AR in children and adults (GRADE: high; GRADE OF RECOMMENDATION: strong).
2. SCIT with pollens is safe in AR in children and adults (GRADE: moderate; GRADE OF RECOMMENDATION: strong).
3. It is recommended that SCIT should be performed at the prescribing physician's facility. The application must always be performed under medical supervision in a place with adequate infrastructure to attend eventual systemic adverse reactions[2,6].

Question 3: Is sublingual immunotherapy effective in allergic rhinitis in children and adults?

Due to its clinical efficacy and high safety, SLIT, initially approved by European health surveillance agencies, particularly in Italy, has spread its use all over the world, including countries in the East, such as Japan, China, and Australia; North America, such as the United States and Canada; and several countries in South America, especially Brazil.

Among the 25 RCTs employing AIT with dust mite allergens used in this systematic review shown in Table 1 (RoB2, AIT with dust mite allergens), 21 clinical trials used SLIT containing a proportional mixture of the dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, all of which showed clinical efficacy by reducing symptom and/or medication scores when compared to the placebo group, except in a study by Karokoc-Aydiner[15] which was found to have reduced symptoms in both the intervention group and the placebo group. Interestingly, 12 trials employed SLIT in the form of sublingual drops, and 9 studies used SLIT in the form of tablets. Thus, the data from most well-controlled clinical trials have demonstrated that SLIT is indeed effective in treating AR in both children and adults, not only in its short-term use (12 months), but also in its long-term use (up to 3 years in the active group). Therefore, it has been well documented through controlled double-blind trials that SLIT is capable of inducing modifying effects on the natural course of the disease, particularly when SLIT is employed with grass pollens, since the duration of its effects lasts for at least 2 years after a 3-year treatment period[24]. Its preventive effect should also be taken into consideration, since children and adolescents with AR treated with SLIT are found to have less chance of developing asthma later, that is, this intervention has altered the atopic march. Due to its beneficial effects, SLIT with house dust mites has been registered and authorized as a drug/medication by health surveillance agencies[25].

Among the 22 RCTs using grass or tree pollens presented in Table 2, 17 trials used SLIT, 10 of which were in the form of sublingual drops, 6 in tablet form, and 1 in spray form. Also, SLIT with grass and tree pollens has been shown to be effective, whether employing a continuous or noncontinuous regimen. In the latter type, the period of SLIT administration can be on a pre-seasonal, pre-co-seasonal, or seasonal regimen. Meta-analysis studies, where a set of patients are analyzed by different investigators, have shown that SLIT with grass extract in pre-co-seasonal regimens has progressively reduced the combined symptom and medication scores over the course of treatment, a reduction from 29% in the 1st year to 45% in the 3rd year of treatment. It has also been noted that the clinical efficacy of using SLIT with pollens can be seen from the first month of treatment[25].

Conclusions

1. SLIT with house dust mites is effective in AR in children and adults (GRADE: high; GRADE OF RECOMMENDATION: strong).
2. SLIT with pollens is effective for AR in children and adults (GRADE: moderate; RECOMMENDATION: strong).

Question 4: Is sublingual immunotherapy safe in allergic rhinitis in children and adults?

SLIT is generally well tolerated, even at high doses, with good clinical safety[27-45]. In the vast majority of patients undergoing SLIT, the predominant adverse effects are mild or moderate oral reactions, such as itching, and mouth and throat irritation. Many of these effects are observed early in the course of treatment (in the induction phase). Tingling sensation (oral paresthesia), lip edema, tongue edema, glossodynia, dysgeusia, abdominal pain, diarrhea, and headache have also been reported. Coughing and dyspnea are likely to occur in patients who have AR concomitant with asthma[26,36,40,42]. It is important to know that mild adverse effects are relatively frequent, with studies showing that 46–69% of the patients treated with SLIT with grasses have reported that the adverse effects were directly linked to the treatment. In this regard, 5% of patients have discontinued treatment due to adverse effects secondary to SLIT.

Radulovic et al.[3] performed a meta-analysis of 60 clinical trials of SLIT in patients with AR with or without asthma, and the overall interpretation was that SLIT was shown to be quite safe, showing predominantly mild-to-moderate local reactions with no need for treatment in numerous studies, but there were no serious adverse reactions, and no patients required the use of adrenaline. Thus, the authors considered that analyses of adverse events were crucial, giving the advantage of SLIT as an alternative to SCIT for its low incidence of systemic adverse effects. Local reactions are common in SLIT with seasonal or perennial allergens compared to the placebo group, and these effects are unavoidable but are generally seen as an inconvenience that cause little distress and have no lasting effect, although some effects may be distressing enough to abandon treatment. Systemic reactions are largely confined to the upper respiratory tract and associated organs (rhinitis, conjunctivitis, or rhinoconjunctivitis), with these occurring more frequently in the SLIT group than in the placebo group. Gastrointestinal effects occur predominantly in pediatric patients, but no reactions were considered serious. Importantly, no serious systemic reaction, anaphylaxis, or death was observed in this meta-analysis.

Di Bona et al.[27], in their systematic review and meta-analysis, found the occurrence of adverse events in 1,384 (61.3%) of 2,259 adult and child patients who received SLIT with grass pollen allergens and in 477 (20.9%) of 2,279 patients in the placebo group. In addition, seven patients in the SLIT group were reported to have had adverse events related to immunotherapy that required the application of epinephrine. The authors concluded that the findings showed little benefit of SLIT with grass pollen tablets for reducing symptom and medication (antihistamines and corticosteroids) scores in patients with seasonal allergic rhinoconjunctivitis, and thus, due to the small benefit, these authors opined that convenience and ease in its administration do not seem to be sufficient reasons for choosing this route.

It should be noted that the EAACI guidelines recommend both routes of administration, subcutaneous or sublingual, for the treatment of AR or allergic rhinoconjunctivitis, perennial, or seasonal, in children or adults. The allergic disease should necessarily be mediated by IgE antibodies to clinically relevant allergens in one or more allergen groups, especially in patients with moderate or severe allergy, whose symptoms affect the quality of life or nighttime sleep[27-29]. It is crucial to know and keep in mind that the recommendations for good clinical practice in AIT from the ASBAI are in agreement with these EAACI guidelines[6,9]. However, the data needed to determine which route of administration is more effective, subcutaneous or sublingual, are currently insufficient[29]. Therefore, each specialist in Allergy and Immunology should carefully analyze each case individually, using their technical and scientific knowledge, and, together with the patient or caregiver, choose and decide on the best route of administration of AIT.

Conclusions

1. SLIT with house dust mites is safe for AR in children and adults (GRADE: high; RECOMMENDATION GRADE: strong).
2. SLIT with pollens is safe for AR in children and adults (GRADE: moderate; RECOMMENDATION: strong).

Question 5: What are the criteria for indicating allergen immunotherapy in allergic rhinitis?

AR can be classified in terms of frequency into intermittent and persistent, and in terms of intensity into mild and moderate-to-severe, according to the ARIA guidelines[1]. The so-called seasonal form, whose main characteristic is intermittence, is caused by a mechanism of immediate hypersensitivity to allergens that are predominantly external to the home (mainly pollens and fungi); on the contrary, persistent (perennial) rhinitis is characterized by sensitization to in-home allergens, such as dust mites, fungi, cockroaches, and animals.

The main criterion for AIT indication is that the rhinitis should be moderate-to-severe, caused by an identified allergen responsible for the induction of specific IgE antibodies, either perennial or seasonal, that is related to the patient's symptoms, and whose drug therapy, together with specific environmental control measures, has not been sufficient for symptom control. This criterion was used in all DBPC RCT studies analyzed in this current systematic review. A few comments will follow.

All these studies referred to *Dermatophagoides pteronyssinus* and *D. farinae*, as shown in Table 1 (RoB2 AIT with mites)[15,19,30-52] or regional pollens, according to Table 2 (RoB2 AIT with pollens)[12,16,24,26,53-70], requiring more consistent studies on other common mites in our environment, such as *Blomia tropicalis*, and even controlled studies with other aeroallergens, such as fungi and epithelium from domestic animals. Nevertheless, Aria[1] as well as guidelines from AAAAI[2], EAACI[5], and ASBAI[6] recognized the AIT as valid when performed with other extracts, as long as they are of good quality, preferably standardized, and with the correct mixture of allergens/antigens, since some allergens may have proteolytic enzymes that inactivate other components of the mixture.

Besides the diagnosis of allergic sensitization, the correlation between allergic sensitization and the onset of symptoms is essential for the indication of AIT. In this context, several

authors have performed nasal provocation tests[15,19,33,42,45,47,66] and ocular provocation tests[44,64,67] to better characterize this association.

Regarding age, DBPC studies in young children are scarce. The minimum age reported was 4 years for SLIT[34,67] and 5 years for SCIT[15]. Considering that SLIT is safe and easily accepted by children, the Brazilian consensus suggests an age of 2 years as the lower limit of indication for this treatment[6]. There is no maximum age beyond which AIT cannot be used, and the contraindications are much more due to comorbidities in this age group than the age itself. Gotoh et al.[59] used SLIT in a large number of patients between 5 and 64 years of age. Bozek et al.[33,55] studied elderly patients up to 75 years old, attesting to the efficacy and safety of AIT, since these contraindications are respected.

Most studies and consensus suggest the age of 65 years as the limit for AIT indication, since the immune response decreases and the risks increase with senescence[2,5,6,24,49,65].

Conclusions

The indications for AIT in patients with AR or allergic Rhinoconjunctivitis are as follows:

1. Moderate-to-severe disease not controlled despite environmental and medication measures or when the patient desires control without the use of medications.
2. Accurate diagnosis of IgE-mediated allergic sensitization through allergy testing (prick test) and/or serum-specific IgE.
3. Correlation between allergic sensitization and triggering of symptoms. In practice, this correlation is clinical and, if possible, nasal and/or ocular provocation tests can be added; however, these procedures are more often reserved for studies.
4. Patients with minimum and maximum age and clinical condition compatible with the chosen treatment (SLIT or SCIT), namely from 2 to 4 years for sublingual treatment and above 5 years for subcutaneous treatment, up to approximately 65 years old for both therapies.

Question 6: What are the absolute and relative contraindications of allergen immunotherapy in allergic rhinitis?

SLIT has a higher safety profile than SCIT since the latter can develop systemic reactions and even anaphylaxis, which is extremely rare in the sublingual route[46-48]. Therefore, contraindications are less restrictive in SLIT. However, in general, the diseases listed below constitute relative or absolute impediments to indicating both.

Severe and poorly controlled asthma

This is an absolute contraindication in all studies and consensus statements[2,4-6,8,9,12,14-17,19,20,24,26,29-70].

AR is often associated with asthma, and it is mandatory that asthma be controlled before AIT can be indicated. Individuals with FEV1 whose value is less than 70–80% of baseline are not included in research protocols[15,30,32,33,38]. However, mild or moderate asthma, since it is controlled, is not an absolute contraindication but a relative one because the risks versus benefits of the procedure have to be controlled, particularly in AIT-SC[15,16], although the sublingual route is more indicated for these patients[15,26,30,33,44,45,52,56,57,64-67].

Underlying diseases

Diseases cited as contraindications to AIT are severe diseases of the immune system, such as autoimmunities; active infectious diseases, such as tuberculosis; heart disease, especially coronary heart disease; and any other disease that contraindicates the use of adrenaline: severe hypertension, even if controlled; severe kidney disease; systemic use of corticosteroids; use of beta-blockers and angiotensin-converting enzyme (ACE) inhibitors; use of immunosuppressants; severe AD; neoplasms; psychiatric diseases that prevent the individual from being fully conscious; lack of adherence to treatment; and drug abuse[26,37,44,47,49,51,54,64,67].

However, according to the main consensus[1,2,6,29], the stage of the disease and its severity must be considered, since controlled immunological diseases, use of ACE inhibitors, beta-blockers, and diseases in general, where the risk of AIT is lower than its benefits, are relative contraindications.

Some studies report anatomical alterations of the upper airways and/or previous otorhinolaryngological surgery as exclusion factors for AIT[35,46], but these are not absolute contraindications, and the cost/benefit ratio and the correct diagnosis of rhinitis should always be considered in these cases.

Nolte et al.[61] excluded patients with eosinophilic esophagitis for using SLIT.

Pregnancy and lactation

There is consensus among researchers that for pregnant and nursing women, AIT should not be prescribed[19,24,26,32,37-39,41,45,47-49,51,54,57,63-66]. In this context, Guo et al.[51] have even required that patients be on contraceptives to enter in their research protocol. However, if the patient becomes pregnant during treatment, the consensuses recommend that treatment does not need to be discontinued, but that the allergen concentration should not be increased if the AIT is still in induction phase[1,2,4-6,29]. This is in agreement with Mosbech et al.[41] who reported pregnancy

during the course of the study without mentioning that such patients were excluded from the study.

Conclusions

1. Poorly controlled asthma and severe active diseases (especially immunological, infectious, and neoplastic) are absolute contraindications for using AIT.
2. Eosinophilic esophagitis is an absolute contraindication for the use of SLIT.
3. Controlled cardiovascular diseases, use of ACE inhibitors, beta-blockers, chronic diseases under control, and mild psychiatric diseases are relative contraindications where risk versus benefit must be evaluated individually.
4. Pregnancy and lactation are conditions that absolutely contraindicate the beginning of treatment, but not in its continuity, when increasing the AIT concentration is contraindicated if it is in the induction phase.
5. Lack of compliance should be considered as a factor to contraindicate the initiation or continuation of the AIT.

Question 7: What are the criteria for monitoring the effectiveness of allergen immunotherapy in allergic rhinitis?

There are simple questionnaires, where a score is assigned according to the intensity of symptoms and need for medication, in diaries requested to the patient or caregivers, and at regular intervals these scores are analyzed[15,19,24,26,30-32,35,39,40-46,48,49,51-54,56,57,63-67]. Several authors use the visual analog scale (VAS) standardized by ARIA[15,33,35,37,47], in which rhinitis symptoms, such as obstruction, itching, sneezing, rhinorrhea, and ocular symptoms, as well as the general perception of such symptoms in the quality of life, are jointly measured on a ruler with figures, and the patient is asked to mark his or her situation along this ruler, which ranges from 0 (totally asymptomatic) to 10 (very bad symptoms, totally uncontrolled)[71,72]. Some authors use their own VAS, with different scores for symptoms[42,44,51,64].

In addition, some researchers ask for an overall score for the AIT to be given at each year of treatment where zero is where there was worsening of rhinitis after 1 year with therapy and the maximum score where there was marked improvement[31,49,51]. Studies also emphasize the need to have questionnaires for specific scoring regarding adverse effects[32,35,37,38,40]. Quality of life questionnaires have been added in several trials[16,35,40,41].

Currently, studies with immunological biomarkers such as IgG4 and specific IgE still show conflicting results, and they are not used in clinical practice for monitoring efficacy or even for treatment discontinuation, remaining restricted to the research field. It is also important to note that the decrease in papule size in skin tests is controversial, with some authors reporting a decrease[19,30,53], but others not[39,47,53]. Therefore, this is not a good parameter for monitoring or for the efficacy of the AIT.

Conclusions

1. Currently, the criteria for monitoring AIT are clinical, evaluating the symptom and medication scores, preferably through the various scales provided in the consensuses. This evaluation can be complemented with quality of life questionnaires.
2. Assessment of side effects should also be monitored.
3. There are currently no clinically available immunological biomarkers for monitoring AIT.
4. Skin testing should not be performed as a means of monitoring the efficacy or duration of the AIT.

Question 8: What are the recommendations for discontinuation of allergen immunotherapy in allergic rhinitis?

All consensus statements[1,2,4-6,29] suggest a minimum of 3 years of duration of AIT, at least for perennial allergens, which is necessary to have a sustained response to treatment. In fact, Durham et al.[24] continued to evaluate patients treated or not treated (control group) after the end of SLIT during 3 years for pollens and found a significant improvement in the active group regarding clinical scores even 2 years after the end of treatment. Chen et al.[34] observed children for three more years after 3 years of treatment with SLIT for dust mites and likewise found sustained efficacy in the group that received active treatment. Gotoh et al.[59] likewise obtained positive results even after 2 years of the termination of SLIT for pollen, maintained for 3 years in the pollen seasons.

Conclusions

1. The optimal duration time for AIT is 3–5 years after the beginning of the maintenance phase. AIT should be maintained for at least 3 years to achieve lasting efficacy.
2. In case of pollinosis, AIT can be performed only for a few months before and during the pollen season (pre-co-seasonal regimen), although in most Brazilian regional, allergens are perennial and not seasonal, except in the southern states.
3. As previously mentioned, the skin test is not a good parameter for discontinuation of AIT, and at present, there are no laboratorial biomarkers to guide the duration of the treatment.

4. Clinical evaluation is always the best parameter to assess the efficacy of AIT. In case of lack of clinical results after reaching the maintenance dose, AIT can be discontinued.

CONCLUDING REMARKS

The main purpose of this systematic review was to establish best practice guidelines for the use of AIT in the treatment of AR. Evidence-based medicine strategies were used to answer relevant clinical questions. The primary endpoints investigated in each study included in this systematic review showed a high degree of evidence for the efficacy and safety of AIT in the treatment of AR in patients sensitized to house dust mites, which correspond to the major allergens associated with the etiopathogenesis of AR in Brazil. We emphasize that recognition of allergic sensitization through appropriate allergy testing and careful clinical evaluation of patients is critical to recognize patients with indications for allergy treatment. Since AR is one of the diseases that is part of the atopic march, a systematic evaluation of patients should be performed, taking into consideration the diagnosis and treatment of other atopic diseases such as AA and AD.

The appropriate choice and management of allergenic extracts to be used in the personalized vaccine used in the AIT is a fundamental condition for achieving the expected results in clinical practice. In Brazil, CFM Resolution No. 2215/2018 regulates the use of allergenic extracts for diagnostic and therapeutic purposes in allergic diseases[18]. The technical responsibility of allergy and immunology services must be exercised by a physician with a RQE in Allergy and Immunology, in the CRM of their jurisdiction, according to Chapter III, article 9, paragraph 1 of the Annex of CFM Resolution No. 2147/2016. In services with exclusive care of pediatric patients, the technical responsibility must be exercised by a physician with an RQE in Allergy and Immunology or RQE of qualification in Pediatric Allergy and Immunology.

Taken together, the data presented here allow us to make a strong recommendation for the use of AIT, either subcutaneously (SCIT) or sublingually (SLIT) in the treatment of AR.

AIT induces changes in the immune response and promotes symptom control in AR through immunomodulation of the allergen-specific response. In this way, AIT allows for clinical remission of AR for prolonged periods without the use of drugs, even after administration has ceased. This therapeutic strategy is currently the only known way to modify the natural history of allergic diseases. Due to the immunomodulation promoted by AIT, patients with AR, besides benefiting from the control of symptoms through this allergen-specific treatment, can also be preventively protected against the development of other atopic diseases such as AA and AD.

AUTHORS' CONTRIBUTIONS

FMA: Investigation, Project administration, Methodology, Writing – original draft, Writing – review & editing. GVAGL: Investigation, Methodology, Writing – original draft, Writing – review & editing. EAT: Writing – original draft, Writing – review & editing. EG: Writing – original draft, Writing – review & editing. NARF: Investigation, Methodology. MCR: Project administration. DS: Investigation, Project administration, Methodology, Writing – review & editing. NPMR: Investigation, Project administration, Methodology, Writing – review & editing. ESCS: Project administration, Writing – review & editing. WMB: Project administration, Writing – review & editing.

REFERENCES

1. Brożek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol. 2017;140(4):950-8. https://doi.org/10.1016/j.jaci.2017.03.050
2. Dykewicz MS, Wallace DV, Amrol DJ, Baroody FM, Bernstein JA, Craig TJ, et al. Rhinitis 2020: a practice parameter update. J Allergy Clin Immunol. 2020;146(4):721-67. https://doi.org/10.1016/j.jaci.2020.07.007
3. Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. Cochrane Database Syst Rev. 2010;2010(12):CD002893. https://doi.org/10.1002/14651858.CD002893.pub2
4. Canonica GW, Cox L, Pawankar R, Baena-Cagnani CE, Blaiss M, Bonini S, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organ J. 2014;7(1):6. https://doi.org/10.1186/1939-4551-7-6
5. Alvaro-Lozano M, Akdis CA, Akdis M, Alviani C, Angier E, Arasi S, et al. EAACI Allergen immunotherapy user's guide. Pediatr Allergy Immunol. 2020;31 Suppl 25(Suppl 25):1-01. https://doi.org/10.1111/pai.13189
6. Aarestrup FM, Taketomi EA, Santos Galvão CE, Gagete E, Nóbrega Machado Arruda AC, Alves GB, et al. Good clinical practice recommendations in allergen immunotherapy: Position paper of the Brazilian Association of Allergy and Immunology - ASBAI. World Allergy Organ J. 2022;15(10):100697. https://doi.org/10.1016/j.waojou.2022.100697
7. Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. Allergy. 2005;60(1):4-12. https://doi.org/10.1111/j.1398-9995.2005.00699.x

8. Bozek A, Cudak A, Walter Canonica G. Long-term efficacy of injected allergen immunotherapy for treatment of grass pollen allergy in elderly patients with allergic rhinitis. Allergy Asthma Proc. 2020;41(4):271-7. https://doi.org/10.2500/aap.2020.41.200035
9. Aarestrup FM, Taketomi EA, Gagete E, Galvão CE, Sarinho ESC, editors. Imunoterapia com Alérgenos. Rio de Janeiro: Atheneu; 2022. p. 1-104.
10. Noon L. Prophylactic inoculation against hay fever. Int Arch Allergy Appl Immunol. 1953;4(4):285-8. https://doi.org/10.1159/000228032
11. Taketomi EA, Miranda JS, Cunha-Júnior JP, Silva DAO. Allergen-specific immunotherapy follow-up by measuring allergen-specific IgG as an objective parameter. In: Metodiev K, editor. Immunotherapy - myths, reality, ideas, future. Rijeka, Croatia: InTech; 2017. Ch. 17, p. 381-401.
12. Sharif H, Singh I, Kouser L, Mösges R, Bonny MA, Karamani A, et al. Immunologic mechanisms of a short-course of ***Lolium perenne*** peptide immunotherapy: a randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol. 2019;144(3):738-49. https://doi.org/10.1016/j.jaci.2019.02.023
13. Celebi Sözener Z, Mungan D, Cevhertas L, Ogulur I, Akdis M, Akdis C. Tolerance mechanisms in allergen immunotherapy. Curr Opin Allergy Clin Immunol. 2020;20(6):591-601. https://doi.org/10.1097/ACI.0000000000000693
14. Zuberbier T, Bachert C, Bousquet PJ, Passalacqua G, Walter Canonica G, Merk H, et al. GA² LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma. Allergy. 2010;65(12):1525-30. https://doi.org/10.1111/j.1398-9995.2010.02474.x
15. Karakoc-Aydiner E, Eifan AO, Baris S, Gunay E, Akturk E, Akkoc T, et al. Long-term effect of sublingual and subcutaneous immunotherapy in dust mite-allergic children with asthma/rhinitis: a 3-year prospective randomized controlled trial. J Investig Allergol Clin Immunol. 2015;25(5):334-42. PMID: 26727762
16. Ünal D. Effects of perennial allergen immunotherapy in allergic rhinitis in patients with/without asthma: a-randomized controlled real-life study. Int Arch Allergy Immunol. 2020;181(2):141-8. https://doi.org/10.1159/000504916
17. Clavel R, Bousquet J, André C. Clinical efficacy of sublingual-swallow immunotherapy: a double-blind, placebo-controlled trial of a standardized five-grass-pollen extract in rhinitis. Allergy. 1998;53(5):493-8. https://doi.org/10.1111/j.1398-9995.1998.tb04086.x
18. Conselho Federal de Medicina (CFM). Resolução CFM n. 2.215, 27 de setembro de 2018. Estabelece as normas mínimas para a utilização de extratos alergênicospara fins diagnósticos e terapêuticos nas doenças alérgicas [Internet]. DiárioOficial da União. Brasília, p. 231, 3 de dezembro de 2018.
19. Dokic D, Schnitker J, Narkus A, Cromwell O, Frank E. Clinical effects of specific immunotherapy: a two-year double-blind, placebo-controlled study with a one year follow-up. Prilozi. 2005;26(2):113-29. PMID: 16400234
20. Bozek A, Cudak A, Walter Canonica G. Long-term efficacy of injected allergen immunotherapy for treatment of grass pollen allergy in elderly patients with allergic rhinitis. Allergy Asthma Proc. 2020;41(4):271-7. https://doi.org/10.2500/aap.2020.41.200035
21. Purkey MT, Smith TL, Ferguson BJ, Luong A, Reisacher WR, Pillsbury HC, et al. Subcutaneous immunotherapy for allergic rhinitis: an evidence based review of the recent literature with recommendations. Int Forum Allergy Rhinol. 2013;3(7):519-31. https://doi.org/10.1002/alr.21141
22. Larenas-Linnemann D, Blaiss M, Bever HP, Compalati E, Baena-Cagnani CE. Pediatric sublingual immunotherapy efficacy: evidence analysis, 2009-2012. Ann Allergy Asthma Immunol. 2013;110(6):402-15.e9. https://doi.org/10.1016/j.anai.2013.02.017
23. Compalati E, Passalacqua G, Bonini M, Canonica GW. The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: results of a GA2LEN meta-analysis. Allergy. 2009;64(11):1570-9. https://doi.org/10.1111/j.1398-9995.2009.02129.x
24. Durham SR, Emminger W, Kapp A, Monchy JG, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. J Allergy Clin Immunol. 2012;129(3):717-25.e5. https://doi.org/10.1016/j.jaci.2011.12.973
25. Blanco C, Bazire R, Argiz L, Hernández-Peña J. Sublingual allergen immunotherapy for respiratory allergy: a systematic review. Drugs Context. 2018;7:212552. https://doi.org/10.7573/dic.212552
26. Blay F, Barnig C, Kanny G, Purohit A, Leynadier F, Tunon Lara JM, et al. Sublingual-swallow immunotherapy with standardized 3-grass pollen extract: a double-blind, placebo-controlled study. Ann Allergy Asthma Immunol. 2007;99(5):453-61. https://doi.org/10.1016/s1081-1206(10)60571-6
27. Di Bona D, Plaia A, Leto-Barone MS, Piana S, Di Lorenzo G. Efficacy of grass pollen allergen sublingual immunotherapy tablets for seasonal allergic rhinoconjunctivitis: a systematic review and meta-analysis. JAMA Intern Med. 2015;175(8):1301-9. https://doi.org/10.1001/jamainternmed.2015.2840
28. Birk AO, Andersen JS, Villesen HH, Steffensen MA, Calderon MA. Tolerability of the SQ Tree SLIT Tablet in Adults. Clin Ther. 2017;39(9):1858-67. https://doi.org/10.1016/j.clinthera.2017.08.003
29. Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth Wijk R, et al. EAACI Guidelines on allergen immunotherapy: allergic rhinoconjunctivitis. Allergy. 2018;73(4):765-98. https://doi.org/10.1111/all.13317
30. Bahçeciler NN, Işik U, Barlan IB, Başaran MM. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. Pediatr Pulmonol. 2001;32(1):49-55. https://doi.org/10.1002/ppul.1088
31. Bergmann KC, Demoly P, Worm M, Fokkens WJ, Carrillo T, Tabar AI, et al. Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis. J Allergy Clin Immunol. 2014;133(6):1608-14.e6. https://doi.org/10.1016/j.jaci.2013.11.012
32. Bernstein DI, Kleine-Tebbe J, Nelson HS, Bardelas JA, Sussman GL, Lu S, et al. SQ house dust mite sublingual immunotherapy tablet subgroup efficacy and local application site reaction duration. Ann Allergy Asthma Immunol. 2018;121(1):105-10. https://doi.org/10.1016/j.anai.2018.04.007
33. Bozek A, Ignasiak B, Filipowska B, Jarzab J. House dust mite sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with allergic rhinitis. Clin Exp Allergy. 2013;43(2):242-8. https://doi.org/10.1111/cea.12039
34. Chen WB, Shen XF, Li Q, Zhou WC, Cheng L. Efficacy of a 3-year course of sublingual immunotherapy for mite-induced allergic rhinitis with a 3-year follow-up. Immunotherapy. 2020;12(12):891-901. https://doi.org/10.2217/imt-2020-0006
35. Bot CM, Moed H, Berger MY, Röder E, Groot H, Jongste JC, et al. Randomized double-blind placebo-controlled trial of sublingual immunotherapy in children with house dust mite allergy in primary care: study design and recruitment. BMC Fam Pract. 2008;9:59. https://doi.org/10.1186/1471-2296-9-59
36. Demoly P, Corren J, Creticos P, Blay F, Gevaert P, Hellings P, et al. A 300 IR sublingual tablet is an effective, safe treatment for house dust mite-induced allergic rhinitis: an international, double-blind,

placebo-controlled, randomized phase III clinical trial. J Allergy Clin Immunol. 2021;147(3):1020-30.e10. https://doi.org/10.1016/j.jaci.2020.07.036

37. Di Gioacchino M, Cavallucci E, Ballone E, Cervone M, Di Rocco P, Piunti E, et al. Dose-dependent clinical and immunological efficacy of sublingual immunotherapy with mite monomeric allergoid. Int J Immunopathol Pharmacol. 2012;25(3):671-9. https://doi.org/10.1177/039463201202500313

38. Didier A, Campo P, Moreno F, Durand-Perdriel F, Marin A, Chartier A. Dose-dependent immunological responses after a 6-month course of sublingual house dust mite immunotherapy in patients with allergic rhinitis. Int Arch Allergy Immunol. 2015;168(3):182-92. https://doi.org/10.1159/000442467

39. Guez S, Vatrinet C, Fadel R, André C. House-dust-mite sublingual-swallow immunotherapy (SLIT) in perennial rhinitis: a double-blind, placebo-controlled study. Allergy. 2000;55(4):369-75. https://doi.org/10.1034/j.1398-9995.2000.00413.x

40. Masuyama K, Okamoto Y, Okamiya K, Azuma R, Fujinami T, Riis B, et al. Efficacy and safety of SQ house dust mite sublingual immunotherapy-tablet in Japanese children. Allergy. 2018;73(12):2352-63. https://doi.org/10.1111/all.13544

41. Mosbech H, Canonica GW, Backer V, Blay F, Klimek L, Broge L, et al. SQ house dust mite sublingually administered immunotherapy tablet (ALK) improves allergic rhinitis in patients with house dust mite allergic asthma and rhinitis symptoms. Ann Allergy Asthma Immunol. 2015;114(2):134-40. https://doi.org/10.1016/j.anai.2014.11.015

42. Okamoto Y, Fujieda S, Okano M, Yoshida Y, Kakudo S, Masuyama K. House dust mite sublingual tablet is effective and safe in patients with allergic rhinitis. Allergy. 2017;72(3):435-43. https://doi.org/10.1111/all.12996

43. Okamoto Y, Fujieda S, Okano M, Hida H, Kakudo S, Masuyama K. Efficacy of house dust mite sublingual tablet in the treatment of allergic rhinoconjunctivitis: a randomized trial in a pediatric population. Pediatr Allergy Immunol. 2019;30(1):66-73. https://doi.org/10.1111/pai.12984

44. Riechelmann H, Schmutzhard J, Werf JF, Distler A, Kleinjans HA. Efficacy and safety of a glutaraldehyde-modified house dust mite extract in allergic rhinitis. Am J Rhinol Allergy. 2010;24(5):e104-9. https://doi.org/10.2500/ajra.2010.24.3508

45. Tonnel AB, Scherpereel A, Douay B, Mellin B, Leprince D, Goldstein N, et al. Allergic rhinitis due to house dust mites: evaluation of the efficacy of specific sublingual immunotherapy. Allergy. 2004;59(5):491-7. https://doi.org/10.1111/j.1398-9995.2004.00456.x

46. Tseng SH, Fu LS, Nong BR, Weng JD, Shyur SD. Changes in serum specific IgG4 and IgG4/ IgE ratio in mite-sensitized Taiwanese children with allergic rhinitis receiving short-term sublingual-swallow immunotherapy: a multicenter, randomized, placebo-controlled trial. Asian Pac J Allergy Immunol. 2008;26(2-3):105-12. PMID: 19054928

47. Valero A, Ibáñez-Echevarría E, Vidal C, Raducan I, Castelló Carrascosa JV, Sánchez-López J. Efficacy of subcutaneous house dust mite immunotherapy in patients with moderate to severe allergic rhinitis. Immunotherapy. 2022;14(9):683-94. https://doi.org/10.2217/imt-2021-0353

48. Varney VA, Tabbah K, Mavroleon G, Frew AJ. Usefulness of specific immunotherapy in patients with severe perennial allergic rhinitis induced by house dust mite: a double-blind, randomized, placebo-controlled trial. Clin Exp Allergy. 2003;33(8):1076-82. https://doi.org/10.1046/j.1365-2222.2003.01735.x

49. Vesna TS, Denisa D, Slavenka J, Lidija B, Aleksandra B, Jasna B, et al. Efficacy of sublingual immunotherapy with dermatophagoides pteronyssinus: a real-life study. Iran J Allergy Asthma Immunol. 2016;15(2):112-21. PMID: 27090364

50. Xian M, Feng M, Dong Y, Wei N, Su Q, Li J. Changes in CD4+CD25+FoxP3+ regulatory T cells and serum cytokines in sublingual and subcutaneous immunotherapy in allergic rhinitis with or without asthma. Int Arch Allergy Immunol. 2020;181(1):71-80. https://doi.org/10.1159/000503143

51. Guo Y, Li Y, Wang D, Liu Q, Liu Z, Hu L. A randomized, double-blind, placebo controlled trial of sublingual immunotherapy with house-dust mite extract for allergic rhinitis. Am J Rhinol Allergy. 2017;31(4):42-7. https://doi.org/10.2500/ajra.2017.31.4447

52. Yukselen A, Kendirli SG, Yilmaz M, Altintas DU, Karakoc GB. Two year follow-up of clinical and inflammation parameters in children monosensitized to mites undergoing subcutaneous and sublingual immunotherapy. Asian Pac J Allergy Immunol. 2013;31(3):233-41. https://doi.org/10.12932/AP0276.31.3.2013

53. Ahmadiafshar A, Maarefvand M, Taymourzade B, Mazloomzadeh S, Torabi Z. Efficacy of sublingual swallow immunotherapy in children with rye grass pollen allergic rhinitis: a double-blind placebo-controlled study. Iran J Allergy Asthma Immunol. 2012;11(2):175-81. PMID: 22761191

54. Bowen T, Greenbaum J, Charbonneau Y, Hebert J, Filderman R, Sussman G, et al. Canadian trial of sublingual swallow immunotherapy for ragweed rhinoconjunctivitis. Ann Allergy Asthma Immunol. 2004;93(5):425-30. https://doi.org/10.1016/S1081-1206(10)61408-1

55. Bozek A, Cudak A, Walter Canonica G. Long-term efficacy of injected allergen immunotherapy for treatment of grass pollen allergy in elderly patients with allergic rhinitis. Allergy Asthma Proc. 2020;41(4):271-7. https://doi.org/10.2500/aap.2020.41.200035

56. Bufe A, Ziegler-Kirbach E, Stoeckmann E, Heidemann P, Gehlhar K, Holland-Letz T, et al. Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. Allergy. 2004;59(5):498-504. https://doi.org/10.1111/j.1398-9995.2004.00457.x

57. Clavel R, Bousquet J, André C. Clinical efficacy of sublingual-swallow immunotherapy: a double-blind, placebo-controlled trial of a standardized five-grass-pollen extract in rhinitis. Allergy. 1998;53(5):493-8. https://doi.org/10.1111/j.1398-9995.1998.tb04086.x

58. Couroux P, Ipsen H, Stage BS, Damkjaer JT, Steffensen MA, Salapatek AM, et al. A birch sublingual allergy immunotherapy tablet reduces rhinoconjunctivitis symptoms when exposed to birch and oak and induces IgG4 to allergens from all trees in the birch homologous group. Allergy. 2019;74(2):361-9. https://doi.org/10.1111/all.13606

59. Gotoh M, Yonekura S, Imai T, Kaneko S, Horikawa E, Konno A, et al. Long-term efficacy and dose-finding trial of japanese cedar pollen sublingual immunotherapy tablet. J Allergy Clin Immunol Pract. 2019;7(4):1287-97.e8. https://doi.org/10.1016/j.jaip.2018.11.044

60. Lou H, Huang Y, Ouyang Y, Zhang Y, Xi L, Chu X, et al. Artemisia annua-sublingual immunotherapy for seasonal allergic rhinitis: a randomized controlled trial. Allergy. 2020;75(8):2026-36. https://doi.org/10.1111/all.14218

61. Nolte H, Bernstein DI, Nelson HS, Ellis AK, Kleine-Tebbe J, Lu S. Efficacy and safety of ragweed SLIT-tablet in children with Allergic rhinoconjunctivitis in a randomized, placebo-controlled trial. J Allergy Clin Immunol Pract. 2020;8(7):2322-31.e5. https://doi.org/10.1016/j.jaip.2020.03.041

62. Nolte H, Waserman S, Ellis AK, Biedermann T, Würtzen PA. Treatment effect of the tree pollen SLIT-tablet on allergic rhinoconjunctivitis during oak pollen season. J Allergy Clin Immunol Pract. 2021;9(5):1871-8. https://doi.org/10.1016/j.jaip.2021.01.035

63. Okamoto Y, Okubo K, Yonekura S, Hashiguchi K, Goto M, Otsuka T, et al. Efficacy and safety of sublingual immunotherapy for two seasons in patients with Japanese cedar pollinosis. Int Arch Allergy Immunol. 2015;166(3):177-88. https://doi.org/10.1159/000381059

64. Pfaar O, Klimek L. Efficacy and safety of specific immunotherapy with a high-dose sublingual grass pollen preparation: a double-blind, placebo-controlled trial. Ann Allergy Asthma Immunol. 2008;100(3):256-63. https://doi.org/10.1016/s1081-1206(10)60451-6

65. Pfaar O, Robinson DS, Sager A, Emuzyte R. Immunotherapy with depigmented-polymerized mixed tree pollen extract: a clinical trial and responder analysis. Allergy. 2010;65(12):1614-21. https://doi.org/10.1111/j.1398-9995.2010.02413.x

66. Pfaar O, Bachert C, Kuna P, Panzner P, Džupinová M, Klimek L, et al. Sublingual allergen immunotherapy with a liquid birch pollen product in patients with seasonal allergic rhinoconjunctivitis with or without asthma. J Allergy Clin Immunol. 2019;143(3):970-7. https://doi.org/10.1016/j.jaci.2018.11.018

67. Wahn U, Klimek L, Ploszczuk A, Adelt T, Sandner B, Trebas-Pietras E, et al. High-dose sublingual immunotherapy with single-dose aqueous grass pollen extract in children is effective and safe: a double-blind, placebo-controlled study. J Allergy Clin Immunol. 2012;130(4):886-93.e5.https://doi.org/10.1016/j.jaci.2012.06.047

68. Worm M, Rak S, Samoliński B, Antila J, Höiby AS, Kruse B, et al. Efficacy and safety of birch pollen allergoid subcutaneous immunotherapy: a 2-year double-blind, placebo-controlled, randomized trial plus 1-year open-label extension. Clin Exp Allergy. 2019;49(4):516-25. https://doi.org/10.1111/cea.13331

69. Yang J, Shen Z, Liu L, Kang W, Shao Y, Zhang P, et al. Clinical efficacy and safety of artesimia annua-sublingual immunotherapy in seasonal allergic rhinitis patients based on different intervention time. Int Arch Allergy Immunol. 2022;183(8):852-9. https://doi.org/10.1159/000524108

70. Yonekura S, Gotoh M, Kaneko S, Maekawa Y, Okubo K, Okamoto Y. Disease-modifying effect of japanese cedar pollen sublingual immunotherapy tablets. J Allergy Clin Immunol Pract. 2021;9(11):4103-16.e14. https://doi.org/10.1016/j.jaip.2021.06.060

71. Bousquet PJ, Combescure C, Neukirch F, Klossek JM, Méchin H, Daures JP, et al. Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. Allergy. 2007;62(4):367-72. https://doi.org/10.1111/j.1398-9995.2006.01276.x

72. Ciprandi G, Mora F, Cassano M, Gallina AM, Mora R. Visual analog scale (VAS) and nasal obstruction in persistent allergic rhinitis. Otolaryngol Head Neck Surg. 2009;141(4):527-9. https://doi.org/10.1016/j.otohns.2009.06.083