ORIGINAL ARTICLE

SLIT: indications, follow-up, and management

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Abstract

Specific sublingual immunotherapy (SLIT) has been proved to be a safe and effective approach in respiratory allergy. However, further research is required on aspects such as patient selection, use of optimal dosing, effects on asthma, long-term effects, and management of adverse reactions. In addition, the widely heterogeneous nature of studies on SLIT performed to date and the application of the criteria for subcutaneous immunotherapy make it difficult for the prescribing clinician to draw accurate and useful conclusions. Therefore, the QUASAR Group (QUality in the Administration of SLIT in Allergic Rhinitis), which comprises allergologists with broad clinical experience in SLIT, investigated the latest research findings and available data on this approach. Working parties were formed in 3 different categories: selection of candidates for SLIT, treatment efficacy, and adverse reactions. We performed a PubMed search for articles that were representative of each category and found 850. From these, we finally selected 266 articles, which were reviewed to retrieve data on SLIT. Evidence for each clinical question was graded according to the Oxford classification. The resulting text was evaluated on 3 occasions by all the members of the group until the final version was agreed upon. In this version, we review available evidence on SLIT, particularly with pollens, which is the subject of most articles. In areas where evidence is insufficient, an alternative agreed upon by the members of the QUASAR group is presented. Finally, we propose algorithms for selecting candidates for SLIT and for management of adverse events.

Key words: SLIT. Adverse reactions. Evidence. Adherence. Efficacy of SLIT. Patient selection. Allergic rhinitis.

Resumen

La inmunoterapia específica sublingual (SLIT) ha demostrado ser un tratamiento seguro y eficaz para la alergia respiratoria. Sin embargo, aspectos como la selección del paciente, el empleo de dosis óptimas, sus efectos en el asma y a largo plazo, o el manejo de las reacciones adversas necesitan una mayor investigación. Además, la gran heterogeneidad de estudios realizados con SLIT y la aplicación de los mismos criterios que los que se aplican a la inmunoterapia subcutánea dificultan la obtención de conclusiones precisas y útiles al clínico que prescribe este tratamiento. Por ello, el grupo Quasar (QUality in the Administration of SLIT in Allergic Rhinitis), grupo de alergólogos con amplia experiencia clínica con SLIT, se propuso recoger el estado de la investigación actual y los datos reales disponibles con SLIT. Para ello, se establecieron grupos de trabajo en tres categorías distintas: selección del paciente candidato a recibir SLIT, eficacia del tratamiento y reacciones adversas. Se realizó una búsqueda de artículos representativos para cada tema, localizándose inicialmente en PubMed 850, de los que se seleccionaron y analizaron 314 para extraer la evidencia disponible con SLIT, incorporando finalmente 266 al documento. Se realizó la gradación de la evidencia para cada pregunta clínica según la clasificación de Oxford. El texto resultante fue evaluado hasta en tres ocasiones por todos los miembros del grupo hasta consensuar el documento final que revisa el cuerpo de la evidencia existente hasta el momento sobre SLIT, particularmente con pólenes, sobre los que existe un mayor número de artículos, y, para aquellos aspectos en los que se ha demostrado evidencia insuficiente, propone una alternativa consensuada entre los miembros del grupo Quasar. Finalmente, se proponen algoritmos de selección del paciente candidato para SLIT y de manejo de reacciones adversas.

Palabras clave: SLIT. Inmunoterapia sublingual. Reacciones adversas. Evidencia. Cumplimiento. Eficacia de SLIT. Selección de paciente. Rinitis alérgica.

1. Introduction

1.1. Historical background

Allergen immunotherapy (AIT) is currently based on the administration of increasing quantities of allergen (although not in all cases) to relieve the symptoms that develop during natural exposure to the allergen. The history of immunotherapy began in the early years of the 20th century and was based on the notion of pollen as a toxin and the need for immunization against infectious agents [1]. Although the theoretical basis of this approach was incorrect, immunotherapy proved to be effective for alleviating symptoms; therefore, it became widely used, with subcutaneous immunotherapy (SCIT) remaining the most common application in practice.

Several attempts at nonparenteral administration of immunotherapy had been made (e.g., oral administration in 1928 [2]); however, the first attempts to administer extracts without injection began at the end of the 20th century [2, 3]. The oral route in particular was investigated in several clinical trials during the 1980s [4-7], but the results were controversial, and severe gastrointestinal adverse effects were reported in some cases.

In 1986, the British Committee for the Safety of Medicines [8] reported deaths caused by SCIT, thus casting doubt on the risk-benefit ratio of immunotherapy, especially given that more effective drugs were available at the time for treatment of the symptoms of respiratory allergy (e.g., antihistamines and corticosteroids). In this context, interest in other routes of administering immunotherapy began to grow, and, in 1986, the findings of the first controlled randomized clinical trial with sublingual immunotherapy (SLIT) were reported [9]. From that moment on, the number of studies on SLIT increased, thus demonstrating, at least from a clinical perspective, that SLIT was effective and safe both in tablet form and as drops [10, 11]. The safety and efficacy profile of SLIT has been demonstrated in large-scale, double-blind, placebo-controlled, randomized clinical trials, with the result that the approach is now widely accepted (reviewed in [12, 13]). Furthermore, several review articles in both adult and pediatric populations have highlighted the efficacy and safety of SLIT for the treatment of rhinitis, rhinoconjunctivitis, and asthma [14, 15]. It is also important to bear in mind that these reviews compare routes of administration and not specific products, although the levels of evidence are not the same for all of the products.

1.2. Rationale and objectives

Despite the large number of clinical trials carried out to date, many aspects of SLIT require further investigation and confirmation. These include patient selection, optimal dosing, long-term effects and monitoring, management of adverse reactions, preventive effect of the technique, and the exact mechanism of action. This relative lack of information is not surprising if we consider that SLIT has only been used for 20 years and that most studies were performed to demonstrate its efficacy and safety.

In most studies, the criteria used are those that were classically applied for SCIT, although it seems clear that this approach cannot be maintained; for example, SLIT has proven effective at a wide range of doses (5- to 300-fold more than SCIT) [16].

Therefore, the members of the QUASAR Group (QUality in the Administration of SLIT in Allergic Rhinitis), comprising 16 Spanish allergologists with broad clinical experience in the management of SLIT, drew up this consensus document, which reviews all currently available data on SLIT. Nevertheless, it must be stressed that studies on SLIT with pollen, particularly grass pollen, are clearly more numerous that those on SLIT with other allergens. Given this premise, the document draws upon current evidence. For those aspects for which the existing evidence is insufficient, the document proposes an alternative agreed upon by the members of the QUASAR Group. Finally, 2 algorithms are proposed, one for selection of candidates for SLIT and another for management of adverse reactions. A checklist to facilitate follow-up is also provided.

2. Material and methods

2.1. Search criteria

In order to perform the search for the most suitable and representative articles for each of the topics to be addressed,

a group of experts with extensive clinical experience was assembled with the objective not only of reviewing the evidence to date, but also of reaching a consensus, based on their experience, in those areas where evidence was lacking.

Working groups were formed. Each selected the key words for one of the following SLIT-related areas in order to optimize the bibliographic search:

- Patient identification and selection: indications, patient selection, pediatric patients, adult patients, rhinitis (severe, moderate, intermittent, persistent), asthma (severe, moderate, intermittent, persistent), atopic dermatitis, prevention, allergic diseases, allergic march, food allergy, sensitization profile, immune system diseases, diabetes, AIDS; cancer, pregnancy, β-blockers, angiotensin-converting enzyme inhibitors, allergens, allergen mixes, contraindications, antagonists, inhibitors, oral allergy syndrome, pollen-food allergy syndrome, plant-food allergy syndrome, profilins, pathogenesis-related proteins, cross-reactive carbohydrate determinants, panallergens, polysensitized patients, complex pollen areas, cross-reactive allergens, lipid transfer protein, profilin, polcalcin, low dose, high dose, allergen recombinant, efficacy, grass oral immunotherapy, mite oral immunotherapy, precoseasonal, multiallergen, single allergen, multiple allergen, allergen standardized.
- Treatment efficacy: clinical parameters, long-lasting effects, therapeutic effects, treatment efficacy, clinical efficacy, efficacy evaluation and assessment, skin prick test, symptom scores, grading of symptoms, symptoms scale, quality of life, medication scores, rescue medication, need for medication, pollen count, adherence, follow-up schedule, administration, acoustic rhinometry, nasal provocation test, nasal cytology, conjunctival provocation test, nasal eosinophils, fractional exhaled nitric oxide, in vitro efficacy, immunoglobulin superfamily, immunoglobulin E, G, and A, inflammatory cytokines, proinflammatory cytokines, cytokine expression, cytokine storm, cytokine levels, cytokine release, cytokine secretion, cytokine receptor, TH_1, TH_2, serum eosinophil cationic protein, eosinophil cationic protein, mast cells, epithelial cells, T cells, cell activation, optimal duration, optimal dosage, preseasonal, coseasonal and perennial regimens, cluster, rush and ultra-rush schemes, sublingual spit, sublingual swallow, drops, tablets.
- Adverse reactions: rhinitis (allergic, perennial, seasonal, intermittent, persistent), administration, safety (equipment, patient, management), adverse effects, practice (management, guidelines), best practice, epidemiology, drug tolerance, drug toxicity, anaphylaxis, signs and symptoms (digestive, respiratory), oral and skin manifestations, urticaria, angioedema, eosinophilic esophagitis, tolerability, administration (sublingual, oral, buccal, deglutition, injection, subcutaneous), side effects, premedications, drug withdrawal symptoms, cessation of treatment.

Using the terms selected, more than 850 articles were found on PubMed. Of these, 314 were selected because of their relevance and studied in depth to retrieve available evidence on this treatment. The analysis made it possible to rule out less relevant studies and to add other, more recent studies. The final sample comprised 266 articles.

2.2. OCEBM Classification

Evidence grading scales were first generated to answer diverse clinical questions [17], and have been used for decades. During this period, they have been widely discussed [18-21]. The first hierarchies [18-20] were created to help physicians and researchers to evaluate the quality of evidence for the therapeutic effects of drugs, whereas the most recent classifications were designed to guide the authors of systematic reviews [17] and clinical practice guidelines [22].

The levels of evidence established by the Oxford Centre for Evidence-Based Medicine (OCEBM) were first published in September 2000. A review was published in May 2011 (see Tables 1 and 2). These levels of evidence were designed to provide, in addition to the traditional clinical evaluation, a heuristic approach that enabled clinicians and researchers to resolve clinical issues rapidly, systematically, and without having to turn to other sources.

A distinctive characteristic of this classification is that the levels cover the complete range of clinical issues in the order required by physicians (top to bottom). Whereas most classifications consider the level of evidence according to the dangers and effects of therapy, the OCEBM system makes it possible to evaluate evidence according to prevalence, accuracy of diagnostic tests, prognosis, therapeutic effects, adverse effects, and usefulness of early screening [23]. Therefore, the participating experts opted to use this system of classifying levels of evidence and grades of recommendation when deciding on appropriate levels for SLIT.

3. Mechanism of action

In contrast with SCIT, SLIT is administered orally. Therefore, the presence of dendritic cells, which are antigen-presenting cells that activate T cells and have an immunomodulatory function, plays a key role in induction of tolerance to the allergen. Dendritic cells also have a clear tolerogenic effect [24].

The immunologic changes associated with SLIT are complex and not clearly established. However, they occur at 3 levels: changes in cellular immunity, changes in humoral immunity, and changes in the release of mediators by proinflammatory cells.

3.1. Changes in cellular immunity

Administration of AIT leads to changes in cellular immunity [25, 26], increased regulatory T-cell expression, decreased levels of type 2 helper T cells (TH_2) (which are characteristic of immunoglobulin [Ig] E_mediated allergic disease), and reduced production of interleukins (IL) (IL-4, IL-5, and IL-13) and TH_1 responses (reviewed in [27]). This effect has been observed mainly in SCIT, although many of these mechanisms have also been observed in recent studies on SLIT.

Table 1. OCEBM levels of evidence.

Level of evidence	Type of study
1a	Systematic review (with homogeneity) of randomized clinical trials.
1b	Randomized clinical trial with narrow confidence interval.
1c	Clinical practice ("all or none": when all patients die before treatment becomes available, and some survive on it; or when some patients die before treatment becomes available, but none now die on it).
2a	Systematic review (with homogeneity) of cohort studies.
2b	Poor-quality cohort study or randomized clinical trial (e.g., <80% follow-up).
2c	Outcomes research (cohort studies of patients with the same diagnosis in which events are associated with the therapy administered), ecological studies.
3a	Systematic review (with homogeneity) of case-control studies.
3b	Case-control studies.
4	Case series or poor-quality cohort studies that fail to clearly define comparison groups and/or fail to objectively measure exposures and outcomes (preferably blinded) and/or fail to identify or appropriately control known confounders and/or fail to ensure complete and sufficiently prolonged follow-up.
5	Expert opinion without explicit critical appraisal, or based on physiology or pathophysiological principles.

A minus sign (–) can be added to show that the level fails to provide conclusive evidence in the following cases:
- A randomized clinical trial with a wide confidence interval and no statistical significance.
- A systematic review with statistically significant heterogeneity.

Table 2. OCEMB grades of recommendation.

Grade	Meaning	Level of evidence.
A	Highly recommendable.	Level 1 studies.
B	Favorable.	Level 2-3 studies or extrapolation from level 1 studies.
C	Favorable but not conclusive. 2-3 studies.	Level 4 studies or extrapolation from level.
D	Neither recommended.	Level 5 studies or inconclusive studies from any level.

Extrapolation is used when the clinical situation has important differences with respect to the original study situation.

Scadding et al. [28] observed a statistically significant increase in positive Foxp3 cell levels in the mucosa of patients treated with SLIT compared with a placebo group. Similarly, immunofluorescence microscopy revealed greater expression of the Treg CD4+DC25+Foxp3+ phenotype in the nasal mucosa of patients who successfully completed SLIT. This expression was maintained years after discontinuation of therapy [25]. In one study on patients who received SLIT and SCIT with mite extract, both treatment arms had significantly higher values for IL-10 and transforming growth factor (TGF) β during the fourth month of treatment [29]. Bohle et al. [30] observed IL-10-producing regulatory T cells, allergen-specific tolerance, and immune deviation after SLIT. TGF-β seems to play a key role in these responses [26].

Finally, the changes induced by SLIT result from diminished recruitment of proinflammatory cells such as mastocytes, eosinophils, and basophils. However, the results of one study showed that activation of basophils by flow cytometry based on expression of surface molecule CD203c was not correlated with the clinical efficacy of SLIT [29].

3.2. Changes in immunoglobulin levels

A systematic review of SLIT showed that, in the 14 studies in which specific IgE was monitored, serum levels of specific IgE increased, although the results were markedly heterogeneous [31]. It has been suggested that the increase in IgE levels during the first year of immunotherapy may not be relevant, although blockade of peak IgE synthesis coinciding with environmental exposure to the allergen could be relevant [32].

Therefore, when SLIT is effective, the seasonal increase in pollen-specific IgE would be blocked during the pollination period [33]. Some authors have shown that mite-specific IgE levels fell during the first year of treatment [34], although the number of patients analyzed was too small to draw relevant conclusions.

Few data are available on the association between SLIT and IgG4 levels; however, increased IgG1 and IgG4 and a seasonal peak in IgA1 and IgA2, all of which were allergen-specific, have been reported after SLIT [28]. The authors also observed an almost statistically significant increase in the inhibitory capacity of serum in patients treated with SLIT in the IgE-facilitated allergen-binding assay (IgE-FAB), thus illustrating facilitated antigen presentation by IgE [28].

In summary, the immunological mechanisms of SLIT are similar to those of SCIT, although SLIT can take advantage of the tolerogenic ability of oral dendritic cells, which, in the absence of danger signals, are programmed to direct the response toward a TH_1/Treg profile. In addition, since no systemic exposure of the allergens administered is detected, most reactions are local [24].

4. Identification and selection of the patient and extract

4.1. Diagnosis and molecular diagnosis

Identification of the allergen responsible for the patient's symptoms is essential for appropriate prescription of immunotherapy **(level of evidence 1a, grade of recommendation B)** [35, 36]. A correlation must be established between symptoms, allergen exposure, and the results of diagnostic tests [36, 37].

In clinical practice, patients who are monosensitized to aeroallergens mainly only require prick tests and/or determination of specific IgE with whole extracts.

However, in areas with multiple-sensitization profiles, reaching a correct diagnosis is more problematic. When the patient is sensitized to panallergens, such as profilin and polcalcin, patients have a significantly higher number of positive skin tests that patients who are not sensitized to panallergens, and a low level of agreement is found between traditional diagnosis with skin testing and in vitro diagnosis. In most cases, these findings correspond to cross-reactivity and not to primary sensitization [38, 39].

Molecular or component-resolved diagnostics (CRD) is based on recombinant allergens (prefixed by "r") or purified allergens from natural sources (prefixed by "n") [40], which are used for the determination of specific IgE. This approach is usually applied using enzyme immunofluorescence and is available both for individual allergens and for multiple allergens, in which case microarray technology is used (ISAC, Phadia) [37, 41].

CRD can provide a more accurate diagnosis and prognosis on several levels [37] and enables better management of polysensitized patients [37, 42-45], since it distinguishes between whether polysensitization is the result of real sensitization to several pollens or of cross-reactivity to panallergens [38, 46-48] **(2a, B)**. Prick testing with these panallergens is a simple and inexpensive approach for the initial diagnosis [47, 48]. In up to 54% of cases, the composition of immunotherapy changed after the results of the molecular diagnosis, as compared with the results of skin testing alone [49]. A subsequent study revealed the cost-effectiveness and improved quality of life provided by CRD [50].

Furthermore, patient selection for immunotherapy is optimized, and those who are most likely to respond to treatment are more easily identified [35-38, 42-44]. Several studies posit a poorer response to immunotherapy in patients who are more sensitized to panallergens than to specific major allergens [51-53]. Valenta et al. [43] propose determination of Ole e 1, Par j 2, Phl p 1, Phl p 5, and Bet v 1 as markers of real sensitization in order to ensure appropriate prescription of immunotherapy. Douladiris et al. [52] drew up a molecular diagnostic algorithm for prescription of immunotherapy that takes into account sensitization in the south of Europe and the role of carbohydrate determinants.

CRD also makes it possible to evaluate the presence of IgE to the allergens that form part of an antigenic source and the various sensitization profiles, thus enabling identification of the primary sensitizer [37]. Consequently, in the case of grass pollen allergy, a difference is observed between major allergens, with sensitization to Phl p 1 being more common in children than in adults, who, in contrast, recognize Phl p 5 with higher frequency. Therefore, sensitization to Phl p 5 has been considered a marker of prolonged exposure [42, 44, 54-64].

Furthermore, sensitization to profilin and lipid transfer protein (LTP) has been clearly associated with food allergy and could be considered a marker of suspected food allergy [37, 38, 65] **(2a, B)**.

Sensitization to profilin has also been reported to be a risk factor for more severe reactions in patients allergic to olive pollen and grasses and in patients allergic to specific foods such as melon [41, 66].

Table 3 shows some examples of how CRD is applied in the diagnosis of allergy to aeroallergens.

It remains unclear whether there is a correlation between the severity of clinical symptoms and the level of IgE to a specific allergen **(2a, B)**. Moreover, results vary depending on the allergen: no correlation was observed in a study on allergy to ash [54] or in another on allergy to kiwi [55], whereas a correlation was observed in the case of allergy to LTP **(2a, B)** [56]. Since the consensus reached by the World Allergy Organization [37] CRD has been recommended for the evaluation of polysensitized patients with food allergy, both for early diagnosis and for avoidance measures and monitoring of progress.

Several studies posit the use of CRD when designing immunotherapy tailored to the patient's sensitization profile [42, 65], although implementation of this approach in the short term is hindered by cost and technical aspects [37].

Irrespective of the availability of CRD, evaluation of patients on an individual basis is essential before the allergologist can decide on the indication and composition of immunotherapy.

4.2. Indications for SLIT

No available biomarkers can predict the efficacy of immunotherapy or which patients are most likely to benefit from treatment [72]. SLIT should be considered for patients in whom specific IgE to the allergens present in the extract has been identified and who, moreover, have conjunctivitis, rhinitis, or asthma caused by exposure to the allergen in question. The decision to administer SLIT should be based on several factors: (*i*) availability of an appropriate extract with documented efficacy; (*ii*) the degree of exposure and the outcome of avoidance measures; (*iii*) the response to and side effects of the drugs used; and (*iv*) importantly, patient preferences and expected adherence. SLIT has been shown to reduce the likelihood of rhinitis progressing to asthma and the onset of new sensitizations; therefore, these aspects should

Table 3. Molecular diagnosis for various aeroallergens.

Grasses [43, 51, 52, 67]	rPhl p 1, rPhl p 5 (major allergens). rPhl p 7 (polcalcin) and rPhl p12 (profilin) (markers of cross-reactivity).
Olive pollen [37, 52, 67, 68]	nOle e 1 (major). Cross-reactivity with ash and privet. nOle e 2 (profilin), nOle e 3 (polcalcin). Sensitization to nOle e 7 (LTP) and rOle e 9 is relevant in areas of high olive pollen concentrations.
Mites [41, 67, 69]	nDer p 1/ and rDer p 2/ (major). rDer p 10 (tropomyosin), considered a marker of cross-reactivity with crustaceans and mollusks. Other: nDer p 4, rDer p 7, and rDer p 8.
Molds [37, 67, 70]	rAlt a 1. rAsp f 2, 4, and 6 (associated with allergic bronchopulmonary aspergillosis). rAsp 1 and/or 3 (associated with asthma).
Cat [41, 67, 71]	rFel d 1 (uteroglobin), nFel d 2 (serum albumin).
Dog [37, 41, 67]	rCan f 1 (lipocalin), rCan f2 (lipocalin), nCan f3 (serum albumin), nCan f 5 (prostate derivative).

be taken into account when prescribing treatment. Lastly, some studies show the efficacy of SLIT in atopic dermatitis associated with sensitization to aeroallergens [73, 74]. In a recent meta-analysis on the effect of immunotherapy on atopic dermatitis [75], which included double-blind, placebo-controlled trials, both with SCIT and with SLIT, the authors found moderate evidence in favor of specific immunotherapy in atopic dermatitis **(1a–, B)**, although, for now, this indication should be considered of potential future use. The authors did not observe statistically significant evidence for SLIT, although it is important to remember that they only analyzed 2 double-blind studies with small samples.

SLIT can be considered an initial treatment, since lack of adherence to other drug regimens should not necessarily be a prerequisite for prescription **(5, D)**.

SLIT is not subject to age limits (minimum or maximum) and is safe and efficacious in all age groups if an allergic mechanism is involved in pathogenesis, although evidence on efficacy in children aged less than 5 years is lacking. One meta-analysis showed SLIT to be efficacious in children aged 3-18 years with allergic rhinitis **(1a, A)** [76]. Another study showed that SLIT is poorly or moderately efficacious in children aged less than 4 years who are monosensitized to house dust mites and present symptoms of mild to moderate asthma [77]. SLIT is safe in children aged more than 3 years [78].

Pediatric patients can obtain greater benefit from SLIT than SCIT because of its superior safety profile, since SLIT is associated with less severe adverse reactions [16]. Therefore, SLIT can be administered at home, rather than at a health center. An additional advantage of SLIT is that it does not involve injections, which often lead children to reject the approach.

As for elderly persons, a recent placebo-controlled, double-blind study with SLIT for mite allergy in patients aged 60-75 years with mite-induced allergic rhinitis demonstrated a clinically significant improvement with good tolerance in the active treatment group compared with the placebo group [79]. Although further studies are necessary, SLIT seems to be safe and efficacious in elderly patients **(2b, B)**.

Prescription of immunotherapy to patients with immunological or autoimmune diseases should be on an individual basis, and the risk-benefit ratio should be taken into account in each case, since there are no controlled studies on the effectiveness of or risks associated with immunotherapy in these patients **(5, D)**. The possibility that patients with immunological/autoimmune diseases present a greater risk of unexpected reactions is merely hypothetical.

Few data are available for HIV-infected patients [80, 81]. Empiric immunotherapy can be administered (after obtaining informed consent) in patients with controlled infection (≥400 CD4 cells/mm^3), no history of opportunistic infections or other AIDS-associated conditions, and absence of HIV viral load. However, the patient should be monitored closely during the first 3 months of immunotherapy **(4, D)**.

4.3. Efficacy of SLIT

SLIT is considered efficacious in adult patients with rhinoconjunctivitis when it is based on extracts of mite, molds, pollen, and animal dander **(1b, A)** [82-87], and in children with rhinoconjunctivitis **(1a, A)** [76, 88]. Furthermore, in patients with rhinoconjunctivitis, SLIT can prevent progression to asthma **(2b, B)** [89].

Furthermore, its efficacy is maintained long after immunotherapy is discontinued **(1b, A)** [90]. Thus, in a double-blind, placebo-controlled study of sublingual grass pollen tablets, the authors showed that the improvement in symptoms and in the use of medication was maintained for at least 1 year after discontinuation, with immunological changes that support the effect of therapy even 2 and 3 years later [91].

SLIT for a single allergen has proven efficacious in polysensitized patients, monosensitized patients, and in cases of concomitant sensitization without cross-reactivity [92].

4.3.1 Allergic rhinitis

In patients with allergic rhinitis, SLIT has a significant effect compared with placebo on symptom relief and consumption of medication, both in children and in adults **(1a, A)**. Table 4 shows findings from several meta-analyses that support this effect [76, 83, 93-99], although some authors found discrepancies, inconsistencies, and a lack of robustness [78, 100].

However, since the year 2006, large-sample clinical trials have been performed based on SLIT with pollen. Their methodology, calculation of statistical power, study variables, and statistical analysis were suitably defined. These studies are shown in Table 5 and provide the best available evidence

Table 4. Meta-analyses of SLIT in respiratory allergy.

Authors	Year	N	Trials	Age group	Disease	Symptoms, SD (95%CI)	Medication, SD (95%CI)	Comments
Wilson et al. [93]	2005	979	16 with pollen and 6 with mites.	Adults and children.	Rhinitis.	−0.42 (−0.69 to −0.15). P = 0.002.	−0.43 (−0.63 to −0.23). P = 0.00003.	Insufficient studies to evaluate asthma.
Olaguibel et al. [94]	2005	256	4 with mites, 1 with grasses, 1 with olive, 1 with parietaria wall pellitory.	Children.	Rhinitis and asthma.	−0.44 (−1.22 to −0.35) for rhinitis. −1.42 (−2.51 to −0.34) for asthma.	1.01 (−2.06 to −0.04).	
Penagos et al. [76]	2006	484	5 with pollen and 4 with mites.	Children.	Rhinitis.	–0.56 (−1.01 to −0.10). P = 0.02.	−0.76 (−1.46 to −0.06). P = 0.03.	Immunotherapy for at least 18 months; immunotherapy more efficacious in pollen allergy.
Di Bona et al. [95]	2010	2,791	19 with pollen.	Adults and children.	Rhinitis.	–0.32 (−0.44 to −0.21). P < 0.0001.	−0.33 (−0.50 to −0.16).	More pronounced effect in adults and after more than 12 weeks of treatment.
Radulovic et al. [83]	2010	4,589	60 with pollen.	Adults and children.	Rhinitis.	–0.49 (−0.64 to −0.34). P < 0.00001.	−0.32 (−0.43 to −0.21). P < 0.00001.	
Sieber et al. [96]	2010	1,052	3 with pollen.	Adults and children.	Rhinitis.	Reduced symptom score: - Coseasonal: −2.39. - Perennial: −2.5. P < 0.0001 for both regimens.	Reduced medication score: - Coseasonal: −1.41. - Perennial: −1.73. P < 0.0001 for both regimens.	Meta-analysis of individual patient data from observational studies with retrospective recording of symptoms.
Calamita et al. [97]	2006	1,706	16 with pollen, 10 with mites, 1 with molds, and 1 with latex.	Adults and children.	Asthma.	−0.38 (−0.79 to 0.03). NS.	−0.82 (−1.25 to −0.39).	No effect on asthma symptoms, effect with combined asthma-rhinitis medication.
Penagos et al. [98]	2008	441	3 with pollen and 3 with mites.	Children.	Asthma.	−1.42 (−2.10 to −0.18). P = 0.02.	−1.63 (−2.83 to −0.44). P = 0.007.	
Akdis et al. [12], Dretzke et al. [13]	2013		SLIT vs PCB: 63.	Adults and children.	Rhinitis and asthma.	SLIT vs PCB: –0.33 (–0.42 to –0.25). P < 0.00001.	SLIT vs PCB: -0.27 (–0.37 to –0.17). P < 0.00001.	
			SCIT vs PCB: 65.					
			SCIT vs SLIT: 1.			Indirect comparison SCIT vs SLIT: SD 0.35 (0.13 to 0.59) in favor of SCIT.	Indirect comparison SCIT vs SLIT: SD 0.27 (0.03 to 0.53) in favor of SCIT.	Evaluation of the combined symptom/medication score and quality of life revealed no differences between SLIT and SCIT.

Abbreviations: SD, standard deviation; CI, confidence interval; NS, not shown.

Table 5. Studies on the efficacy of SLIT in patients with rhinitis caused by pollen allergy.

Authors	Year	Active/PCB	Age	Allergen	Duration	Symptoms, % relief	Medication, % reduction (P value)	Comments
Durham et al. [103]	2006	569/286	Adults	Grasses	6 months	16	28	Effect observed on cumulative monthly dose of 450 µg.
Dahl et al. [104]	2006	316/318	Adults	Grasses	6 months	30	38	
Dahl et al. [105]	2006	74/40	Adults	Grasses	5 months	37	41	
De Blay et al. [106]	2007	61/57	Adults	Grasses	10 months	0	22 (P = 0.02)	
Didier et al. [107]	2007	472/156 157 (100 IR) 155 (300 IR) 160 (500 IR)	Adults	Grasses	6 months	 4 27 24	 23 46 47	
Roder et al. [108]	2007	108/96	Children	Grasses	2 years	0	0	
Pfaar et al. [109]	2008	94/91	Adults	Grasses	2 years			Effect on symptoms-medication combination: AUC < 0.1 and VAS.
Wahn et al. [110]	2009	139/139	Children	Grasses	8 months	28	24	
Ott et al. [111]	2009	142/67	Adults	Grasses	5 years	47	0	
Bufe et al. [112]	2009	126/127	Children	Grasses	6 months	24	34	
Horak et al. [113]	2009	45/44	Adults	Grasses	4 months	29	–	
Durham et al. [103]	2006	170/138	Adults	Grasses	3 years	29	40	
Durham et al. [90]	2010	157/126	Adults	Grasses	4 years	26	29	
Halken et al. [88]	2010	139/139	Children	Grasses	4 months	28 (P = 0.0009)	48.7 (P = 0.0102)	Significant increase in VAS (P < 0.001).
Passali et al. [114]	2010	64/22	Adults	Grasses, Parietaria, birch, and mites	6 months		(P < 0.02)	
Skoner et al. [115]	2010	75/40	Adults	Ragweed	6 months	15 (NS) 15 (NS)	37 51	
Didier et al. [86]	2011	207/219	Adults	Grasses	3 years pre and coseasonal: - Preseasonal: 2 months. - Preseasonal: 4 months.	 36.6 (P < 0.001) 33.9 (P < 0.001)	 34.8 (P = 0.0007) 33.4 (P = 0.0011)	
Kuna et al. [116]	2011	94/91	Adults	Grasses	3 years	- 34 with respect to the second year (P < 0.0001) - 66 with respect to baseline	36 with respect to the second year (P = 0.0006) 68 with respect to baseline	Progressive increase in effect after 3 years of treatment.
Quercia et al. [117]	2011	21/11	Adults	Grasses	2 years: - Perennial. - Preseasonal.	 65 (P < 0.05) 57 (P < 0.05)	 60 (P < 0.05) 72 (P < 0.05)	Increase in VAS (P < 0.05).
Blaiss et al. [118]	2011	Total 345	Children	Grasses	4 months			Increased quality of life in rhinitis.
Nelson et al. [119]	2011	Total 439	Adults	Grasses	4 months	18 (P = 0.02)	26 (P = 0.08)	Increased quality of life in rhinitis, 17%, P = 0.02.
Stelmach et al. [120]	2012	36/18	Children	Grasses	1 year: - Perennial - Precoseasonal. 6 months.	 28 (P < 0.05) 48 (P < 0.01)	 5 (NS) 58 (P < 0.01)	
Didier et al. [91]	2013	280/155	Adults	Grasses	3 years pre and coseasonal: - Preseasonal: 2 months. - Preseasonal: 4 months. With follow-up after 1 year without immunotherapy.	 28 (P < 0.05) 21 (P < 0.05)	 28 (P < 0.05) 25 (P < 0.05)	2013

Abbreviations: AUC, area under the curve; NS, non-signficant; PCB, placebo; VAS, visual analog scale.

on the efficacy of SLIT in pediatric and adult populations. All the trials but one [101], showed an improvement (from 25% to more than 50%) in all the clinical variables analyzed in patients with pollen-induced allergic rhinitis who were treated with SLIT compared with the control group **(1b, A)** [102].

4.3.2 Allergic asthma

Although the quality of life of patients with asthma improves with SLIT [121], the effect of this approach in allergic asthma is controversial [78, 94]. SLIT has proven effective in pollen-induced allergic asthma in adults and children **(2b, B)** [122], but the optimal dose for mite-induced asthma remains unknown. In recent studies with sublingual tablets, the dosing range was evaluated [123].

In trials that include evaluation of asthma as an objective (Table 6), albeit not as a primary objective [105, 106, 112, 124-130], most report a significant impact for SLIT on asthma symptoms [112, 124, 125, 127-130] and on use of medication [112, 125, 127], and, in 2 studies, a reduction in bronchial hyperreactivity in pollen-allergic children and adults [126, 127].

Only 2 trials report negative results [105, 106]. However, in one, patients were asymptomatic at recruitment, thus preventing improvement from being assessed [105]; in the other, randomization was unsuitable, since the active treatment group included more patients with asthma, and more severe asthma, than the control group [106].

Furthermore, 2 meta-analyses were specifically designed to evaluate the effect of SLIT in asthma. In one, no improvement in asthma symptoms or use of medication was observed [94]. However, in the other, which was performed in children, a significant improvement was observed in both parameters [76]. In an excellent and exhaustive review [99], the authors conclude that the level of evidence for SLIT is high with respect to asthma symptoms, but moderate with respect to use of medication, combined asthma and rhinitis score, and quality of life.

Given the controversial nature of these results, more specifically designed clinical trials are necessary to evaluate the efficacy of SLIT in allergic asthma, particularly in children.

4.3.3 Food allergy

SCIT can induce adverse reactions that make it unsuitable for the treatment of food allergy; administration of SLIT to treat food allergy could bring about desensitization and even tolerance [131, 132]. Studies on SLIT with foods show promising results for the treatment of food allergy, although before these results can be applied in daily clinical practice, it is necessary to clearly define certain parameters, such as the optimal maintenance dose, duration of therapy, and degree of protection after discontinuation. The results of studies performed to date are difficult to compare because of the diverse nature of the extracts used, the lack of standardized protocols, and the variable duration of therapy before a preventive or protective effect is achieved.

Table 7 presents the main characteristics of studies that have shown the efficacy and tolerance of SLIT with extracts of hazelnut [133, 134], peanut [135, 136], birch pollen (in birch-apple syndrome) [137], Pru p 3 [138], kiwi [139, 140], peach [138, 141], and milk [142-144].

None of the studies provide unique criteria that determine which patients are candidates for SLIT with foods, since they include allergic patients of all ages, with reactions of differing intensity (local, mild to moderate systemic, and anaphylactic), and wide variation in the time since diagnosis. Furthermore, the extract used differs with respect to the method of production and the quantification of the major allergens, which is only defined in the studies with peach [138] and hazelnut [134].

At the end of the maintenance period of treatment with SLIT, all studies show an increase in the mean quantity of food tolerated with respect to baseline [133, 134, 138, 142-144]. In some placebo-controlled studies (with hazelnut [134] and with peanut [135]), the difference reached statistical significance, although this was not the case with peach [138] **(1b–, B)**. In the other published papers, the increase in the dose tolerated was not compared or could not be differentiated from baseline or that of the placebo group **(2b, C)**.

Immunological modifications have been observed in studies on SLIT with foods. In most, an increase in IgG4 levels was recorded after maintenance treatment. A significant increase in salivary IgA was also recorded [136]. Increased IL-10 levels over baseline were observed in the active treatment group, and these were maintained after 10 months of maintenance treatment [133, 134].

In most studies, the reactions are local. Systemic reactions have been observed, although they are uncommon and similar to, and even less severe than, those described in control groups [134, 138] (especially with respect to cutaneous pruritus [135]). In addition, the reactions seem to be more frequent when the dose escalation phase is longer [135].

Although patients continue to tolerate the food after discontinuation of treatment [134, 140, 144], it is necessary to perform further studies comparing the benefits of SLIT with oral tolerance induction to achieve long-term tolerance.

4.3.4 Other diseases

Further studies are necessary on the use of SLIT in the following 3 cases.

1. Allergy to hymenoptera venom. In one study on SLIT with bee venom [145], the extent of local reactions was reduced, and the safety profile was good. However, local reactions do not constitute an indication for immunotherapy with bee venom; therefore, the efficacy of SLIT should be evaluated in patients with systemic reactions.
2. Atopic dermatitis. SLIT with a standardized mite extract showed efficacy in children with mild-to-moderate atopic dermatitis, although the benefit was variable in the severe form [73] **(2b, B)**.
3. Latex allergy. Good efficacy was achieved with better tolerance than when the extract was administered subcutaneously [146, 147]. Furthermore, results for latex-allergic children who have undergone several surgical procedures were shown to be promising, although the sample size is too small to draw definitive conclusions **(3b, B)**.

Table 6. Studies on the efficacy of SLIT in patients with asthma due to pollen allergy.

Authors	Year	Active/PBC	Age	Allergen	Duration	Symptoms (relief)	Medication (reduction)	Comments
Vourdas et al. [124]	1998	34/32	Children	Olive	2 seasons	Reduced dyspnea score. First season: P < 0.04. Second season: P < 0.03.	No effect.	
Pajno et al. [125]	2003	15/15	Children	Parietaria	13 months	Reduced, P < 0.001.	Reduction, P = 0.043.	Improvement in VAS (P = 0.025). Reduction in nonspecific bronchial hyperreactivity.
Pajno et al. [126]	2004	79 in total	Adults	Birch	4 seasons	Reduced score P < 0.01.	Reduction P < 0.01.	Effect from the second season onward.
Marogna et al. [127]	2005							
Dahl et al. [105]	2006	74/40	Adults	Grasses	5 months	No effect.	No effect.	Effect in RC.
De Blay et al. [106]	2007	127 in total	Adults	Grasses	10 months	Nonsignificant reduction.		More patients with asthma in the active treatment group (P = 0.02).
Moreno-Ancillo et al. [128]	2007	105 in total	Adults	Grasses and olive	2 seasons for 6 months preseasonal	Reduced score, P = 0,004.		Improvement in QOL and VAS in symptoms and medication (P = 0.006).
Stelmach et al. [129]	2009	25/25	Children	Grasses	2 seasons preseasonal	41%	10%	
Bufe et al. [112]	2009	126/127	Children	Grasses	6 months	64%	34%	
Voltolini et al. [130]	2010	14/10	Adults	Birch	2 seasons precoseasonal	Reduction of 77% in days with asthma (P = 0.05).		

Abbreviations: PBC, placebo; QOL, quality of life; RC, rhinoconjunctivitis; VAS, visual analog scale.

4.4. Selection of the extract

Successful SLIT depends on the appropriate extract, which should be standardized, with efficacy demonstrated in double-blind, placebo-controlled, randomized clinical trials. Trial results are available for the following allergens: grass pollens [85, 88, 106, 107, 109-113, 118, 119, 128, 129, 148-153], birch [130, 154], olive [124, 128, 155], *Parietaria* [125, 126, 156-159], cypress [160, 161], ragweed [115, 162, 163], mites [10, 79, 164-171], cat [172], *Alternaria* [173, 174], and latex [175, 176].

As for comparison between extracts, laboratories in Europe use different units (the same laboratory sometimes uses different units for different products). Some studies have revealed major differences in extract composition [177-180]. Extracts should be standardized so that they can be compared. Manufacturing quality standards should be put in place to guarantee that batches and processing methods do not affect extract content and to ensure that the quality of the extract is not degraded between manufacture and administration. Traceability should also be taken into account.

4.4.1 Mixes

As a general rule, single-component extracts are preferred, since most relevant clinical trials have been performed with this type. Data are available on the effect of single-component SLIT in patients sensitized to several allergens. The post hoc analyses of 2 studies on single-component SLIT with tablets revealed that therapy was efficacious in both monosensitized and polysensitized patients [181, 182]. However, in these studies, the clinical relevance of sensitization to allergens other than that used in the extract remains unclear, ie, the sensitizations observed may well have been irrelevant **(5, D)**.

The other possibility involves administration of multicomponent SLIT to polysensitized patients. Amar et al [183] analyzed 54 patients who received placebo, single-component SLIT (standardized *Phleum* extract with a daily dose of 19 µg of Phl p 5), and multicomponent SLIT (the same dose of Phl p 5 and a further 9 pollen extracts). The authors found no statistically significant differences with regard to the symptom score and use of medication for any of the extracts compared with placebo. (The authors attributed this finding to the low pollen count during the season.) Nevertheless, they did record significant differences for placebo and single-component SLIT—but not multicomponent SLIT—in various immunological parameters; therefore, the authors suggested that SLIT could be considered less efficacious.

The general recommendation for polysensitized patients is to treat only with clinically relevant extracts **(3b, C)** [184].

4.4.2 Doses

The importance of using an adequate dose of allergen has been studied for both SLIT and SCIT [185]. The cumulative SLIT dose should be much higher than that used in SCIT [186].

Few appropriate dose-response trials have been performed for SLIT. The 2 most important, which have enabled a dose-response curve to be constructed, are those performed with grass tablets [103, 107, 151] **(1b, A)**. Studies have also been performed with tree pollen mixes (*Betula verrucosa, Corylus avellana,* and *Alnus glutinosa*) [187, 188] and ragweed [115].

However, in most allergens, no complete dose-response curve has been constructed, and doses other than those used in the studies could be efficacious **(5, D)**.

4.5. Associated factors

The use of SLIT in clinical practice is subject to special circumstances, such as sensitization to panallergens, the presence of oral allergy syndrome (OAS), and the need for treatment that could interfere with immunotherapy.

4.5.1 Sensitization to panallergens

Patients who are sensitized to panallergens should be evaluated carefully on an individual basis to ensure an optimal safety and efficacy profile.

The cross-reactivity that characterizes panallergen-sensitized patients varies geographically. One study showed the frequency of asthma caused by panallergens in patients with vegetable allergy was as high as 59%, compared with 47% in patients who are sensitized exclusively to aeroallergens, but who were not allergic to vegetables [46, 66].

One study showed that SLIT for profilin allergy proved satisfactory in 2 patients who presented food allergy and respiratory allergy [189]: after treatment with profilin, neither patient experienced symptoms (double-blind, placebo-controlled oral challenge), and the level of IgE to profilin and to the vegetables involved decreased **(4, D)** [189]. In 2 studies of treatment with tablets, no patients developed new sensitizations to panallergens [190, 191].

Ole e 2 or Phl p 12 (profilins) and Ole e 3 or Phl p 7 (polcalcins) are markers of polysensitization; however, given that they have not been measured in extracts currently used for immunotherapy, evaluation could prove useful in complex cases. To date, identification of these allergens does not constitute a clear contraindication for starting treatment [192].

4.5.2 Oral allergy syndrome

OAS is produced by cross-reactivity between allergens from pollens and plants. It manifests with oropharyngeal symptoms mediated by activation of mastocytes [193] after ingestion of the culprit food and is generally self-limiting. The common embryonic origin of the respiratory and digestive epithelia could account for the symptoms of this syndrome.

The term OAS was coined by Amlot in 1987 in birch-allergic patients [194]. It is probably the most common symptom of food allergy, and its prevalence ranges from 5% to 70% depending on the series [195]. According to an article by Kontastinou and Grattan, OAS was detected in up to 67% of patients polysensitized to pollen in a population in Norwich [196]. The authors referred to OAS as food contact hypersensitivity syndrome, comparing it with contact urticaria and including cross-reactivity between pollens and latex [197].

Table 7. Summary of studies on SLIT with foods.

Characteristics	Extract	Dose increase	Maintenance of treatment	Maintenance dose reached	Local reactions	Gastrointestinal reactions	Systemic reactions	Clinical efficacy	Immunological changes	Observations
- Case report [139, 140]. - Patient aged 29 with several episodes of anaphylaxis.	Kiwi.	–	- 6 weeks initially. - Subsequently indefinite.	1 mL of fresh kiwi daily.	With dose increase.	With dose increase.	With dose increase.	Tolerance to 1 mL of fresh kiwi daily.	- ↓ IgE - ↑ IgG4	- Maintained tolerance after a 4-month interruption. - No challenge with additional doses.
- Randomized, double-blind, placebo-controlled trial [133, 134]. - 29 adults. - SLIT (spat out).	Hazelnut.	4 days.	- 12 weeks initially. - Suspended for 3 months and restarted for a further 10 months with no initiation phase.	- 13.2 mg (37.6 µg Cor a 1 and 24.4 µg Cor a 8) daily.	- 7.4% of total doses, especially in the active treatment group. On increase, maintenance, and re-initiation.	- 0.3% of the total doses, only in the active treatment group. - With dose increase.	- 0.2% of total doses, both in the active treatment and in placebo. - With dose increases.	- Significant increase in the mean tolerated dose in the active treatment group: - From 2.3 to 11.6 g (week 12). - From 2.3 to 14.5 g (10 months).	- Significant increase maintained in IgG4 and IL-10 after 10 months vs baseline.	- Consumption of hazelnut unknown during the 3 months without treatment.
- Randomized, double-blind, placebo-controlled trial [135, 136]. - 18 children. - SLIT (swallowed).	Peanut.	6 months.	6 months.	2 mg daily.	- Active: 9.3% of doses. - Placebo: 1.5% of doses.	- Active: 1.2% of the doses. - Placebo: 1.8% of the doses.	- Active treatment: 2.2% of the doses. - Placebo: 7.1% of the doses (symptom= pruritus).	- Significant increase in the dose tolerated in the active treatment group compared with placebo: 1,710 mg vs 85 mg.	- Significant reduction in SPT, activation of basophils, and IL-5. - Significant increase in IgG4 and nonsignificant increase in Treg cells vs placebo. - Significant increase in IgA in saliva vs placebo.	- No challenge before SLIT. - IgA in saliva is well correlated with the result of the challenge test.
- Randomized, double-blind, placebo-controlled trial [138]. - SLIT (swallowed).	Peach.	5 days.	6 months.	10 µg of Pru p 3 Monday, Wednesday, and Friday.	- Active treatment: 39% of the doses. - Placebo: 0.4% of the doses.	- Active: 2% of the doses. - Placebo: 0.1%.	- Active treatment: 0.4% of the doses. - Placebo: 0.2% of the doses.	- Significant increase in dose (x 9) to induce LR and x 3 to induce SR. - Nonsignificant differences vs placebo.	- Significant increase in IgE, sIgE for Pru p 3, and IgG4 (vs placebo) compared to baseline. - Significant reduction in SPT vs placebo.	No differences between groups in dose tolerated.
- Case report [141]. - Patient aged 36 years with OAS and systemic reactions to vegetables.	Peach.	1 day.	12 months.	10 µg of Pru p 3 for 5 days a week.	- OAS in initial phase.	No.	No.	- Increased tolerance: from 18.7 to 150 g at 4, 8, and 12 months.	- Reduction in SPT. - No relevant changes in IgE, IgG1, or IgG4.	At 12 months, only nuts and pepper were not permited.

- 8 pediatric patients [142]. - Initial open challenge.	Milk.	–	6 months.	1 ml daily.	- OAS in a patient receiving maintenance treatment.	No.	- Abdominal pain that resolved (1 patient).	Increase in mean milk volume: 39 to 143 mL.	–	No placebo group.
- Patient aged 6 years with allergy goat and cow milk [143]. - SLIT and OTI.	Goat and cow milk.	12 days in total.	12 days in total.	120 mL.	- OAS in a dose with spontaneous resolution.		No.	Tolerance to total dose of cow milk and goat milk	Increased IgG4 with goat milk, sheep milk, and cow milk.	Changes are maintained after 2 years.
- Patients aged 6 and 21 randomly assigned to 3 groups [144]: - 1: SLIT - 2: SLIT + OTI (1 g). - 3: SLIT + OTI (2 g).	Milk.	Variable.	- 12 weeks. - 60 weeks. - Withdrawal 1 week. - Withdrawal 6 weeks.	- 1: 7 mg. - 2: 1 g. - 3: 2 g.	Initial: - 1: 26% of the dose. - 2 and 3: 29.6%. Maintenance: - 1: 27.99%. - 2: 24.07%. - 3: 21.99%.	- Initial 1: 2.97%. - Maintenance 1: 0.38%. - Initial OTI: 7.17% - Initial 2 and maintenance: 7.97%. - Initial 3 and maintenance: 3.15%.	Initial: - 1: 6.24%. - 2 and 3: 12.54%. Maintenance: - 1: 0.57%. - 2: 12.28%. - 3: 8.66%.	Tolerance to total dose: 60 weeks of maintenance: - 1: 1/10. - 2: 6/10. - 3: 8/10. 6 weeks after withdrawal: - 1: 1/1. - 2: 3/6. - 3: 5/8.	- Nonsignificant reduction in CD63 and CD203 between the groups. - Nonsignificant increase in IgG4 between the groups.	No placebo group.

Abbreviations: OTI, oral tolerance induction; LR, local reactions; SR, systemic reactions; OAS, oral allergy syndrome; SPT, skin prick test.

In the Mediterranean basin, 20% of individuals sensitized to pollen (mainly grasses and *Parietaria*) have pollen-food syndrome [197]. In the rest of Europe, almost 50% of pollen-allergic patients have OAS, although <10% progress to a systemic reaction and <1% develop anaphylactic reactions [198]. Treatment to date has involved avoidance to prevent symptoms that can considerably affect quality of life.

The presence of OAS is neither an indication nor a contraindication for starting immunotherapy, although more controlled studies are necessary before it can be recommended in this patient population [199]. In a recently published study, the efficacy of birch pollen SLIT was verified by statistically significant reductions in overall symptom scores and in the use of rescue medication (compared to placebo) in patients with and without OAS [200].

4.5.3 Concomitant treatment

In patients taking β-blockers, angiotensin-converting enzyme inhibitors (ACEIs), monoamine oxidase inhibitors (MAOIs), and/or tricyclic antidepressants (TCAs), immunotherapy should be administered on an individual basis. Patients with a personal history of ischemic heart disease should be monitored **(5, D)**. However, most studies to date have been performed in patients who were receiving SCIT; therefore, more studies should be performed with SLIT (which is also safer) to confirm these conclusions. By analogy, recommendations can be extended to SLIT; however, the risk-benefit ratio should always be assessed on an individual basis.

4.5.3.1 β-Blockers

Endogenous production of histamine and other major mediators of anaphylaxis is normally inhibited by neurohumoral β-adrenergic mechanisms via cyclic adenosine monophosphate and is stimulated by cholinergic and alfa-adrenergic mechanisms. β-Blockers alter this homeostatic balance by increasing intracellular synthesis and releasing mediators of anaphylaxis [201, 202].

β-Blockers also increase the response to mediators released in the lung, the cardiovascular system, and the skin, thus increasing the mortality rate after experimental anaphylaxis, whether by immunological mechanisms [203] or nonimmunological mechanisms [204-206].

In animal models [205, 206], the use of β-blockers in vivo revealed increased probability of anaphylactic reactions or more severe adverse reactions associated with the release of mediators of the allergic response to a specific antigen.

β-Blockers can diminish the response to treatment with adrenaline in cases of anaphylaxis, owing to a paradoxical alfa-adrenergic and vagotonic effect. However, in some studies, a greater frequency of adverse effects was not detected in patients who were taking β-blockers and receiving immunotherapy against hymenoptera venom and/or aeroallergens [207]. Thus, in one prospective cohort study (3,178 patients receiving immunotherapy with aeroallergens, hymenoptera venom, or both), the authors did not record a greater frequency of adverse reactions in patients taking β-blockers than in patients who were not [207]. Two retrospective cohort studies did not reveal significant differences in the number of adverse reactions in patients treated with β-blockers who were receiving immunotherapy with hymenoptera venom [208, 209] or aeroallergens [208].

Adverse reactions with concomitant β-blockers, whether oral or in eye drops, which, while not more frequent, can be more severe and treatment-refractory [210-212]. β-Blockers can increase the risk of anaphylaxis, with more severe reactions in patients who receive immunotherapy; therefore, immunotherapy should be initiated on an individual basis after evaluating the risk-benefit ratio **(4, C)**. Intravenous glucagon proved satisfactory for the treatment of hypotension caused by an anaphylactic reaction secondary to immunotherapy in a patient receiving β-blockers [213] **(4, C)**.

4.5.3.2 Monoamine oxidase inhibitors (isocarboxazid, selegiline, phenelzine, and tranylcypromine) and tricyclic antidepressants (amitriptyline, nortriptyline, doxepin, imipramine, and propizepine)

MAOIs and TCAs prevent the normal catabolism of adrenaline or its reuptake; therefore, at least in theory, they can increase its pharmacological effects during an anaphylactic reaction [87, 214]. In patients treated with these agents, immunotherapy should only be initiated after an appropriate assessment of the risk-benefit ratio. Although administration of these agents is considered a relative contraindication, no evidence is available to support the contraindication **(5, D)**.

4.5.3.3 ACEIs

ACEIs have been associated with an increased risk of severe adverse reaction to immunotherapy and after accidental hymenoptera sting [215-217] **(4, C)**. Treatment with ACEIs should be on an individual basis at the initiation of immunotherapy to hymenoptera venom; it can be continued providing no efficacious alternative is available and the risk-benefit ratio is taken into account. The adverse reactions caused by ACEIs seem to result from malfunction of the compensatory mechanisms that usually originates in the renin-angiotensin system. ACEIs also increase levels of bradykinin, a potent vasoactive mediator that can lead to hypovolemia, hypotension, and angioedema and has been observed in patients with severe anaphylaxis [218].

A study on the role of ACEIs in anaphylaxis showed that 2 patients who were receiving SCIT with hymenoptera venom presented anaphylactic reactions after their injection, although the reactions resolved once treatment was discontinued. The anaphylaxis symptoms reappeared once the drugs were reintroduced [216]. Elsewhere in the literature, anaphylactic reactions did not subside after suspension of concomitant ACEIs [217]. Similarly, 2 retrospective studies in patients receiving immunotherapy for allergy to aeroallergens and hymenoptera venom did not reveal a greater frequency of adverse events in patients receiving treatment with ACEIs, although there is a greater risk of more severe reactions when ACEIs are used in combination with immunotherapy [219, 220] **(4, D)**.

A large-scale multicenter study revealed that taking ACEIs during the induction phase of immunotherapy led to a statistically significant increase in the risk of more severe anaphylactic reactions [221]. Therefore, discontinuation of ACEIs should be evaluated in order to reduce the potential risk of more severe anaphylactic reactions to hymenoptera-based immunotherapy. Nevertheless, the risk-benefit ratio should be assessed on an individual basis before withdrawal [221].

5. Algorithm for selecting candidates for immunotherapy

Figure 1 shows the algorithm proposed by the QUASAR group for selecting candidates for immunotherapy **(5, D)**.

1. In order to be considered a candidate for immunotherapy, the patient should present symptoms compatible with allergic asthma, rhinitis, or conjunctivitis in the case of aeroallergens or a systemic reaction in the case of hymenoptera venom. *Patients sensitized to aeroallergens with atopic dermatitis can also be evaluated, although this cannot be considered an established indication.
2. It must be demonstrated that patients have specific IgE to aeroallergens or hymenoptera venom, either by skin testing (the cheapest and most widely used method) or determination of specific IgE.
3. A correlation must be demonstrated between symptoms and exposure to the aeroallergen the patient is sensitized to. In the case of a patient with positive specific IgE or skin test results but no compatible symptoms or association with the exposure, sensitization is considered asymptomatic, and immunotherapy would not be indicated.
4. For immunotherapy to be efficacious, the specific aeroallergen to which the patient presents symptoms should be determined, especially in the case of polysensitized patients. Therefore, it is necessary to make an accurate diagnosis in order to select the appropriate extract. If the diagnosis can be made with skin testing and determination of specific IgE (e.g., in a monosensitized patient or a patient who is allergic to cat dander), further studies are unnecessary. If not, molecular testing should be performed, particularly in the case of sensitization to panallergens, owing to the problem of cross-reactivity.
5. Molecular testing enables accurate identification of the specific allergen the patient is sensitized to. Whereas skin testing and determination of specific IgE to extracts only reveal the source of sensitization, molecular diagnosis using recombinant proteins clearly identifies the culprit allergen. If molecular testing is not available, the patient should be evaluated on an individual basis by the allergologist prescribing therapy.
6. For immunotherapy to be genuinely effective, it is advisable to have well-standardized extracts of proven quality and supported by sufficient evidence from studies. If this is not possible, the indication should be evaluated on an individual basis. The same is true for allergen mixes. However, allergen mixes are advised against if they are not strictly necessary.
7. Once it is clear that a patient is a candidate for immunotherapy, the clinician should consider a series of factors, such as the risk-benefit ratio, the degree of response to or adverse effects with previous treatments, potential concomitant conditions that could increase risk, degree of disease control and severity, and, of course, patient preference. Informed consent should also be obtained.
8. Once the patient is considered a candidate for immunotherapy, the decision should be taken whether to administer treatment subcutaneously (native or modified extract) or sublingually (in drops or tablets). Once again, patient preference should be taken into account, as should personal circumstances (e.g., possibility of or limitations in transport to receive therapy, needle phobia) and other circumstances that might arise. Furthermore, the level of evidence should be taken into account when selecting the extract.

6. Follow-up of patients taking SLIT

6.1. Determination of efficacy in vivo

Various in vivo parameters have been proposed to measure the efficacy of SLIT for the treatment of allergic rhinitis. It is somewhat complicated to generalize the efficacy of these parameters, since the biologic potency of the extracts and challenge procedures used (e.g., conjunctival, nasal) vary widely. In one meta-analysis of 14 studies, sensitivity to an allergen was measured before and after immunotherapy [222]: 13 evaluated skin tests, 4 nasal challenge, and 2 conjunctival challenge. Given the wide variability in methodology and the lack of sufficient data, no relevant conclusions could be drawn on the use of these techniques. This finding remained unchanged in subsequent analyses [83, 95]. Therefore, although in vivo parameters should be included to verify the efficacy of SLIT with pollen, particularly grass pollen **(2a, C)**, and measurement of these parameters could be useful for obtaining additional data, this approach should never replace the associated analysis of the findings of questionnaires on symptoms. The use of medication to treat symptoms is considered the main variable for demonstrating the efficacy of immunotherapy [102, 223].

Nevertheless, as stated in the Practicing Allergology (PRACTALL) consensus document on the use of immunotherapy [14], which was prepared by experts from the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology, more information is necessary in the field of standardization and validation of clinical measures of efficacy with AIT, SCIT, and SLIT. These measures should be universally accepted by physicians, researchers, the pharmaceutical industry, and regulatory authorities and should include authorization of allergen exposure chambers or determination of efficacy via real-life studies, as well as development of biomarkers that predict clinical response.

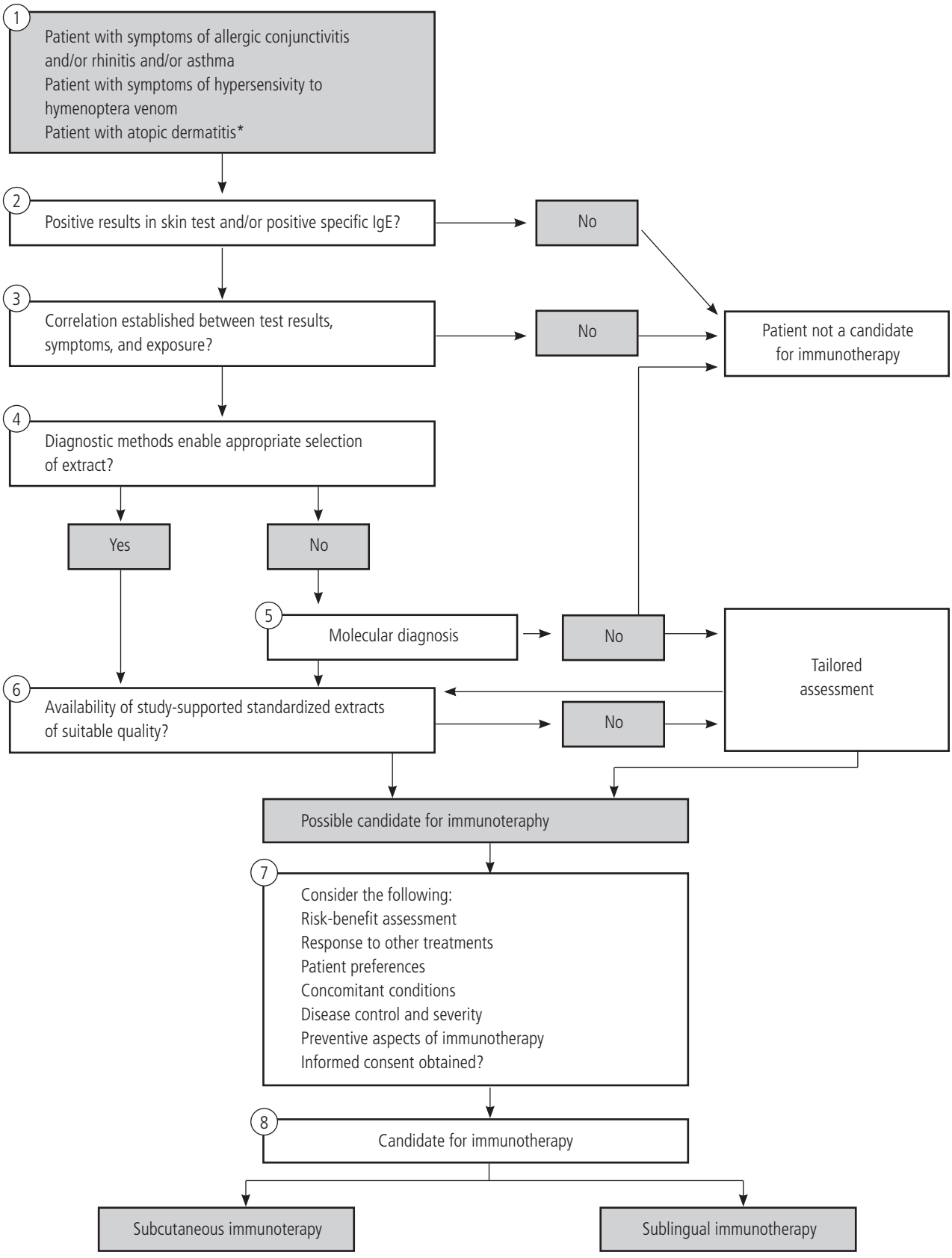


Figure 1. Algorithm proposed by the QUASAR Group for selecting candidates for immunotherapy.

6.1.1 Skin tests

No meta-analyses have analyzed the effect of SLIT on the size of the wheal obtained in skin tests. This assertion includes tests based on immediate reading, endpoint titer, and delayed response.

Some studies have shown that wheal diameter decreases in patients in the active treatment group with allergy to Pru p 3 [138], *Alternaria* [173], or pollens, although cutoffs that predict a good clinical response with SLIT have not been established.

6.1.2 Conjunctival allergen challenge

Various studies show that SLIT increases the amount of allergen necessary to induce a conjunctival response in a challenge test. In 2011, a meta-analysis of 42 double-blind placebo-controlled randomized trials evaluated conjunctival symptoms in patients with conjunctivitis and allergic rhinoconjunctivitis (ARC) receiving SLIT, independently of the culprit allergen [224]. Despite the markedly heterogeneous nature of the procedures and allergens used, tolerance to the allergen increased during the conjunctival allergen challenge. In patients with ARC and conjunctivitis, conjunctival allergen challenge is the procedure of choice if a specific allergen is to be used to evaluate the efficacy of SLIT **(4, C)**.

6.1.3 Nasal challenge test

Few studies analyze the nasal challenge test as an efficacy parameter for SLIT. Furthermore, the procedure used and the allergens tested are widely heterogeneous. In general, tolerance to allergen exposure generally improves after SLIT, irrespective of the allergen or the regimen administered. However, few studies present this parameter as the main one or are performed as double-blind randomized clinical trials [225]. While other studies are well performed, they do not have a true placebo-treated control group [114].

6.1.4 Lung function in asthma

Data confirming the effect of SLIT on lung function in asthma patients are lacking. In addition, no studies have been specifically designed for this purpose. However, when this variable was assessed, improved values were recorded for forced expiratory volume in 1 second (FEV1) in adults [226], and a double-blind, placebo-controlled, randomized controlled trial showed a decrease in the degree of nonspecific bronchial hyperreactivity in children [126].

6.1.5 Fractional exhaled nitric oxide

One randomized clinical trial [120] showed that levels of fractional exhaled nitric oxide fell during the pollen season in patients aged 6 to 18 years with grass pollen–induced allergic rhinoconjunctivitis who were receiving SLIT. The authors did not reach the same conclusion for the control group.

6.2. Biomarkers: efficacy parameters in vivo

SLIT administered for a sufficiently long period increases regulatory T-cell levels, although the association between these changes and clinical efficacy for individual patients is unknown [30]. Therefore, SLIT could reduce specific memory B-cell and T-cell levels, a possibility that is consistent with the frequently observed fall in serum IgE levels during the first year of immunotherapy; however, the clinical significance of this finding remains unknown [27].

Monitoring of levels of other immunoglobulins, particularly IgG, could prove useful. SLIT can induce an increase in IgG-blocking antibody titers [60, 143]. These immunoglobulins, especially IgG4, would act by inhibiting binding of the antigen with the complex formed by the B cell and the IgE bound to its receptor on the cell, thus blocking the allergic cascade. Nevertheless, the in vivo function of blocking antibodies has not been shown to be useful for determining whether SLIT is efficacious or whether the increase in antibody levels is simply the effect of prolonged administration of the vaccine, with no clinical correlation implied **(4−, D)**. In fact, in studies carried out with SCIT in grass pollen-allergic patients, IgG4 concentrations fell to pre-immunotherapy levels 1 year after suspension, even though the clinical benefit is maintained and IgE blockade has been shown to persist (also with SLIT) [24].

It has been proposed that the increase in IgG4 is associated only with immunotherapy based on a sufficient dose of allergen [227] and that it is dose-dependent. In a clinical trial with SLIT administered as tablets at 3 different allergen concentrations for 18 months [103], an early increase in IgG levels was recorded (after 8 weeks of treatment) in patients who received the highest dose of allergen. This increase persisted during the second year of treatment. However, in the group that received the intermediate dose, increased IgG levels were observed after 18 weeks of treatment. Other authors [228] have proposed that an association between specific IgE/total IgE or a decrease in the IgE/IgG4 ratio is more important than independent evolution of specific IgE or IgG4 values, although such an association has not been confirmed in double-blind, placebo-controlled studies [24]. The increase in serum levels of tolerogenic monocyte-derived markers such as C1Q and stabilin-1 (which was selectively detected in patients with a good response to immunotherapy) has been proposed as an efficacious marker of early response to immunotherapy. However, these markers should be validated in studies with larger samples [24].

Finally, allergen-specific secretory IgA levels have been reported to increase in association with SLIT over a period of at least 2 years with intermediate and high doses of ragweed pollen [229].

6.3. Regimens and efficacy

SLIT with pollen can be preseasonal (begins before and finishes at the beginning of the pollen season), coseasonal (begins and finishes during the pollen season), precoseasonal (begins before the pollen season and continues until the end), or perennial (throughout the year, irrespective of the pollen season).

6.3.1 Precoseasonal regimen vs preseasonal regimen

The current tendency is to prescribe precoseasonal regimens, because longer maintenance regimens can lead

to nonadherence. An analysis of 41 double-blind, placebo-controlled trials with pollen-based SLIT [230], showed that 3 studies had used a preseasonal regimen, 3 a coseasonal regimen, 8 a perennial regimen, and 27 a precoseasonal regimen.

Furthermore, in a placebo-controlled open-label study in children with ARC caused by grass pollen, the authors compared the clinical efficacy and safety profile of a preseasonal regimen with that of a precoseasonal regimen (the latter with different maintenance doses). The precoseasonal regimen was shown to be more efficacious, especially with the highest maintenance dose [231].

Compared with the preseasonal SLIT regimen with pollen (particularly grass pollen) the precoseasonal regimen starting at least 8 weeks before the pollen season and continuing until the end is the better option for ensuring efficacious SLIT from the first pollen season **(2b, B)**.

6.3.2 Precoseasonal regimen vs perennial regimen

Few publications compare precoseasonal regimens with perennial regimens or their effect on efficacy over several pollen seasons. One placebo-controlled prospective clinical trial that was specifically designed to investigate the clinical efficacy of these regimens [129] compared 2 SLIT regimens (precoseasonal and perennial) over 2 years. Both protocols were effective compared with placebo and showed similar efficacy for relief of symptoms and use of medication, as well as for secondary parameters such as monitoring of peak expiratory flow rate (PEFR), FEV1, the provocative dose (PD_{20}) in the methacholine challenge test, and determination of fractional exhaled nitric oxide. Precoseasonal treatment was more effective at relieving nasal symptoms, with no significant differences in bronchial or ocular symptoms.

Other, more recent, well-designed studies have shown that SLIT with sublingual tablets (5-grass pollen 300IR) in a precoseasonal regimen for 3 pollen seasons was efficacious at relieving symptoms and reducing the need for rescue medication from the first pollen season analyzed onward [86, 232].

6.4. Optimal duration of SLIT

With respect to the duration of treatment before the first pollen season, the results of several studies suggest that the duration of preseasonal treatment can affect clinical efficacy. Patients who receive more than 8 weeks of SLIT with grass pollen before the pollen season show a better clinical improvement than those who receive fewer than 8 weeks of therapy **(1a, B)** [76, 93-95]. Other studies of SLIT with pollen administered as a perennial regimen show benefits in rhinitis and asthma [98].

The immunological changes brought about by SLIT lead to an improvement in the patient's clinical condition and this effect lasts once treatment has been suspended [104-106]. The duration of treatment varies considerably from one study to another, from 3 months of treatment to 3, 4, or even 5 years [109-113]. It seems that the duration of the effect depends in part on the duration of SLIT itself [233, 234]. Nevertheless, virtually no studies evaluate efficacy in terms of optimal duration.

The duration of SLIT that is necessary to induce long-term improvement is at least 3 years; no significant improvements have been observed in cycles lasting more than 5 years **(1a, B)**.

The authors of an open-label, placebo-controlled prospective study [232] evaluated patients with respiratory allergy and bronchial hyperreactivity who were monosensitized to mites. SLIT was administered for 3, 4, and 5 years, and efficacy was evaluated in the long term. In the case of the patients who received SLIT for 3 years, the benefits persisted for 7 years, whereas in those treated for 4 or 5 years the improvement persisted 8 years later. New sensitizations were detected in all the patients in the control group; among patients receiving the active treatment, less than 25% experienced new sensitizations (21%, 12%, and 11%, respectively).

6.5. The problem of adherence

Adherence to SLIT could be considered poorer than adherence to SCIT, since administration depends on the patient, whereas SLIT is managed by health professionals. Nevertheless, between 10% and 34% of patients are estimated to discontinue SCIT [235]. Nonadherence in patients taking SCIT has been reported to range from 11% to 50%; in patients taking SLIT, the frequency of nonadherence ranges from 3% to 25% [236].

In 2012, a study comparing the degree of adherence to both SCIT and SLIT [237], revealed no significant differences in nonadherence rates between the 2 approaches, although a trend toward early discontinuation in patients taking SCIT was recorded. The reasons for discontinuation were considerably different between the groups: patients complained of discomfort with SCIT as the main reason for stopping therapy, whereas patients taking SLIT were concerned about efficacy.

In another recent multicenter randomized clinical trial [237], the authors evaluated adherence, tolerance, safety, and efficacy of SLIT with grasses in patients with grass-induced respiratory allergy and found an adherence rate >90% and a significant clinical improvement in >80% of the patients.

A placebo-controlled randomized trial assessing adherence to SLIT in young patients with ARC due to grass pollen revealed that doubts on efficacy and cost were the main problems affecting adherence [101]. These were also the main determinants of adherence in a questionnaire-based survey by 296 Italian allergologists in 2010 [238].

Therefore, we can state that the main reasons for nonadherence differ with the therapeutic approach (SCIT or SLIT). Whereas nonadherence with SCIT results mainly from having to attend a health center regularly, discomfort with administration, and cost [239], the main reasons for nonadherence to SLIT are recurrent local reaction in the buccal mucosa or gastrointestinal tract [240], the erroneous perception that SLIT is no longer necessary once allergic symptoms improve [241], the feeling of inefficacy experienced by some patients, and cost [242].

The last point is open to interpretation. Although SLIT contains a larger amount of allergen, the pharmacy price of the drug increases with respect to SCIT. Therefore, it is necessary

to perform pharmacoeconomic studies that have a follow-up period of at least 3 years and take into account other costs such as those arising from administration of SCIT by health professionals and direct and indirect costs, including intangible costs associated with reduced use of health care resources and medication and improvement in quality of life produced by AIT in allergic patients [14]. Furthermore, the current economic recession that has affected many countries, especially Spain, has affected adherence to immunotherapy, regardless of the route of administration. However, in a recent Spanish study analyzing adherence before and after the economic recession in patients aged under 12 years, the adherence rate continued to be higher than in the adult population. It is noteworthy that SLIT was the main approach used (81%) in children aged under 12 years, whereas SCIT was the preferred option in the remaining 19% [243].

6.6. Improving adherence

In real life, adherence depends on age, the allergen, treatment duration, cost, and patient education [244]. Children and patients receiving SLIT with perennial allergens have better adherence than adults or patients receiving SLIT with pollens [244]. Therefore, some measures could prove useful for improving adherence to SLIT. Evaluating the remaining volume of extract in the vials (at a scheduled visit) and the volume consumed (telephone interview) has provided satisfactory results: adherence was >80% in all the studies **(4, D)** [92, 245, 246].

In a survey analyzing the opinion of allergologists on factors that positively impact adherence to SLIT, the questions considered most important were those on patient perception of efficacy, good tolerance to treatment, and patient education [247], which proved to be essential **(3b, C)**. Recent studies show a clear difference in adherence between patients who received a complete training course on SLIT and those who received only the standard instructions [92, 245]. Improved training in SLIT for prescribers would also increase adherence [246].

6.7. Checklist for follow-up of patients taking SLIT

The QUASAR Group proposes the following checklist for follow-up of patients with AR caused by aeroallergens who are receiving SLIT **(5, D)**.

1. Establish exactly where the patient is with respect to total duration of treatment: minimum 3 years.
2. Verify the degree of adherence according to the regimen prescribed.
3. Meet with the patient to review administration technique, dosing, possible adverse effects, and any other variables that could affect adherence.
4. Retrospectively analyze the intensity of nasal symptoms during the previous pollen season according to the criteria set out by ARIA (duration and severity of symptoms). In pollen-allergic patients, the number of symptom-free days should be evaluated if it has been recorded.
5. Analyze the consumption of medication during the last pollen season.
6. It is recommended that patient complete a quality of life questionnaire (ESPRINT15 or similar) and a visual analog scale to assess his/her perception of symptoms during SLIT.
7. An allergen-specific conjunctival allergen challenge could be performed —especially if a reference is available at the start of SLIT— in cases where it is difficult to evaluate whether the vaccine is proving to be efficacious or whether it should be withdrawn.

7. Adverse reactions

Safety is a key advantage of SLIT. The favorable safety and tolerability profile enable administration of high doses of the allergen extract in both children and adults in order to bring about the immunological changes that lead to suitable clinical efficacy and modification of disease course in the long term. SLIT does not generally cause severe adverse reactions or reactions that lead to interruption of treatment [99].

The excellent safety profile of SLIT can be explained in part by the absence of detectable systemic exposure to intact allergens. Adverse effects more frequently take the form of local reactions and, rarely, systemic reactions. In addition, the fact that no new sensitizations are observed during SLIT supports the favorable safety profile of this type of immunotherapy [24].

Nevertheless, SLIT should not be considered risk-free and must be administered according to appropriate instructions and indications, with follow-up by a specialist [31]. Clinical practice guidelines on the management of adverse reactions to SLIT are necessary, especially with respect to local reactions, which are the most common [248].

Adverse reactions to SLIT can be local or systemic. Local reactions occur close to the administration site and can be immediate (30-60 minutes after administration) or late (>1 hour after administration).

Local reactions can affect the oral mucosa (oropharyngeal pruritus, angioedema) and gastrointestinal tract (nausea, vomiting, diarrhea, abdominal pain). Onset is usually at initiation of treatment, and the reaction subsides as treatment is continued.

Systemic reactions appear at some distance from the site of administration and may be immediate or delayed. The most common are rhinitis, asthma, angioedema, urticaria, gastrointestinal symptoms (accompanied by systemic symptoms), and anaphylaxis.

In studies on SLIT that have reported adverse effects as the reason for ending the trial, a dose increase was not associated with increased frequency of adverse effects, possibly reflecting different sites of action within the immune system. Recent studies on the safety of SLIT revealed a logarithmic distribution that was associated with a continuous increase in both the frequency and the severity of adverse effects [185].

7.1. Frequency and description

The frequency of adverse reactions caused by SLIT has been determined in 1 systematic review **(1a, A)** [31], 1 review [249], and 2 additional publications [120, 250], which comprise a total of 68 studies including more than 4,500 patients and more than 1,200,000 doses.

The studies conclude that local reactions are frequent and appear in 40-75% of cases. The reactions generally affect the oral mucosa (pruritus, angioedema) and gastrointestinal tract (pain, nausea, vomiting, diarrhea). In no cases was it necessary to reduce the dose or interrupt treatment. Furthermore, in post-marketing studies, most adverse reactions were local and mild, with a frequency of <10 per 1,000 doses [186].

Systemic reactions are uncommon (<5% of all adverse reactions) [251]. The most frequent symptoms are rhinitis, asthma, abdominal pain/vomiting, and urticaria. In clinical trials, no severe systemic reactions, anaphylaxis, or deaths have been recorded [118, 119]. Adrenaline was not used in any of the studies analyzed, although 2 recent studies report administration to 2 patients [118, 119].

Both local reactions and systemic reactions are considered mild or moderate in all the studies. The vast majority of local reactions are mild and resolve without treatment. Onset is with the initial doses, and the reaction usually disappears as treatment continues.

As for severe reactions, only 11 cases described as "anaphylaxis" have been reported in peer-reviewed indexed journals (ie, 1 adverse reaction of this type per 100 million administrations) [249].

Evaluation of adverse reactions has not revealed an association with specific allergens or their degree of sensitization [249], differences between extracts with a single or multiple allergens [252], differences between conventional and ultrarush strategies [250], or differences between a precoseasonal regimen and a continuous regimen [120], although discontinuous regimens lead more frequently to local reactions [31]. One study on SLIT in 5-grass pollen extract tablets administered preseasonally and coseasonally for 3 years showed that the incidence and severity of adverse reactions decreased gradually with each year of treatment [86].

Although frequency of reactions seems to be dose-dependent in some studies, a systematic review of SLIT revealed no association between the dose administered and the development of a systemic reaction, whereas local reactions were more common during treatment with low-dose extracts [253] and gastrointestinal reactions with high-dose extracts [251].

Overdosing was considered the cause of the reaction in 3 children with severe asthma [252].

7.2. Risk factors

Given that few cases of systemic reaction have been reported, it is difficult to determine risk factors. The analysis of the 11 published cases of anaphylaxis [249] revealed the following:

- The extracts used were latex (3 cases: 2 in health professionals during the initiation stage, 1 using a rush strategy), house dust mite (2 cases), grasses (2 cases), and mixes of very different aeroallergens (4 cases). The allergens used in the extracts were standardized in only 5 cases.
- Severe reactions were recorded in 2 patients who had previously received SCIT.
- Patients had bronchial asthma in most cases.
- In 1 case, the reaction occurred in the maintenance phase, during the peak of the pollen season.
- In 1 case, the patient experienced the reaction after a 3-week interruption of treatment and received a maintenance dose 6-fold higher than the indicated dose.
- Screening for mastocytosis (baseline tryptase) was not performed in any cases.

Safety in patients with a history of intolerance to SCIT is not clear, and this aspect has been poorly studied [251]. The literature contains 6 cases of systemic reactions (rhinitis and asthma) to SLIT, even with the initial dose, in patients in whom SCIT had previously been withdrawn because of systemic reactions (mainly respiratory) [254-256]. These were isolated cases with insufficient data to know whether the reactions with SCIT are a risk factor for treatment with SLIT, although some authors recommend not administering SLIT in patients who have previously presented severe reactions with SCIT [223] **(5, D)**.

As for age, SLIT is safe in children and can be used in those aged under 5 years [252, 255]. Clinical trials in pediatric patients did not reveal severe or systemic reactions; only 3 patients presented severe asthma after overdosing [252].

Asthma does not increase the frequency of adverse reactions, and SLIT is safe in patients with mild or moderate asthma. However, severe or poorly controlled asthma is considered a contraindication for SLIT [257].

With regard to food allergy, 90% of patients who received SLIT with Pru p 3 had local mild reactions (oral pruritus) during the initiation phase and first week of maintenance. This frequency was slightly higher than that observed with latex and aeroallergen extracts [138]. With other foods (hazelnut [134] and milk [144]), local reactions were more frequent than in the active treatment group, whereas mild systemic reactions were equally frequent in both the active treatment and placebo groups.

Despite very limited evidence, eosinophilic esophagitis induced by oral immunotherapy with food has been reported [258].

7.3. Special situations

SLIT should be suspended temporarily in the case of oropharyngeal infections, oral surgery, tooth extraction or loss, oral lesions and/or inflammations, acute gastroenteritis, exacerbations of asthma, PEF <80% of personal best value, and when administered with viral vaccines **(5, D)** [259].

7.3.1 Pregnancy

As with SCIT, the physician should assess the benefit of immunotherapy in terms of the potential risks for the pregnant woman. An evaluation of retrospective studies indicates that immunotherapy can be continued, although it is not usually initiated in a pregnant woman **(5, D)**. Interruption should be considered during the initial phase of immunotherapy **(5, D)** [64]. The only available data on SLIT in this context are from a prospective study [260] that analyzed 185 pregnancies in women receiving SLIT. In 24 cases, immunotherapy was initiated during pregnancy. The incidence of obstetric complications was lower than in the general population and than in women who only received pharmacological treatment. With SLIT, 7% of patients experienced local reactions, and none had a systemic reaction.

The authors concluded that SLIT is safe during pregnancy and that it can be initiated during this period **(4, D)**.

7.3.2 Infection

In general, SLIT should not be administered to patients with infections, especially respiratory or oral infections (oral thrush, oral ulcers, gingivitis, or periodontitis). The doses should be delayed in the same circumstances as in SCIT until the infection has resolved **(5, D)**.

7.3.3 Oral surgery or tooth extraction

In cases of oral surgery or tooth extraction, treatment should be suspended for 7 days and restarted with the same dose. In any case, treatment should not be restarted until 24-48 hours after the patient's health status returns to normal. In the case of longer interruptions, treatment should be restarted at the previous dose and under medical supervision [87] **(4, D)**.

In children, treatment should also be suspended temporarily after the loss of milk teeth and until the wound has completely healed.

7.4. Management of adverse reactions

No consensus has been reached on the treatment of adverse reactions. Classifying severity can help to decide whether SLIT should be suspended (both in the case of severe adverse reactions and if local symptoms become intolerable) or whether it is possible to continue with treatment [251].

7.4.1 Local reactions

Local adverse reactions are more common with the initial dose and are controlled by adjusting the dose to reach the maintenance dose gradually. Treatment is unnecessary in most cases, since the reaction usually improves spontaneously within 30 minutes. These reactions tend to disappear spontaneously in 7-14 days [88, 261], although they have been reported to persist after 1 month of treatment in 21% of cases [262].

Local symptoms such as oropharyngeal pruritus are easily treated with antihistamines on demand. However, antihistamines can also be scheduled as regular pretreatment [36] **(4, C)**. A favorable response is also achieved in these cases and, if SLIT is continued, symptoms usually disappear with time and with no need to continue pretreatment for long periods.

Gastrointestinal symptoms improve spontaneously 13 to 44 days after suspending SLIT [165]. When SLIT is continued, intestinal reactions are better controlled if the dose is spat out instead of swallowed [263]. In a clinical trial on SLIT with hazelnut, the frequency of reactions was lower (7.4% of doses) than reported with other types of SLIT when the dose was spat out. The patients only presented oral pruritus, and only 4 out of 12 in the active treatment group experienced abdominal discomfort (1 occasion each) [134]. In a clinical trial analyzing SLIT with peach, local reactions (oral pruritus and gastrointestinal symptoms) improved spontaneously or were treated successfully with antihistamines, antacids, and/or omeprazole [138] **(2b, C)**.

The lactose content of some tablets should be taken into account in lactose-intolerant patients.

7.4.2 Systemic reactions

Very few cases of anaphylactic reaction have been reported. Treatment of anaphylactic reaction is symptomatic with regular medication: adrenaline, corticosteroids, systemic antihistamines, and β2-agonists (respiratory symptoms) [254-256]. When this type of reaction occurs, SLIT should be withdrawn [249] **(4, D)**.

Most systemic reactions are mild and resolve with symptomatic treatment, depending on the organ or system affected.

Table 8 presents the World Allergy Organization classification of systemic reactions with SCIT [264], which can also be used to establish the degree of systemic reaction with SLIT.

7.4.3 Restarting treatment after an adverse event

An important area for which clinical practice guidelines have not yet been developed is re-initiation of therapy after an adverse event (depending on the grade or persistence) [251]. The recommended regimen is as follows **(5, D)** [265].

- In the case of local reactions and/or mild or moderate systemic reactions, the patient should take the previously tolerated dose for 2 days before returning to the habitual SLIT regimen. The need for premedication should be evaluated.
- In the case of major local reactions and/or systemic reactions, SLIT should be suspended for 48 hours. If symptoms resolve, treatment should be restarted by reducing the dose by 50% before scaling up (always under medical supervision). The need for premedication should be evaluated.

8. Algorithm for the management of adverse reactions

After evaluating the available evidence, the QUASAR Group proposes the following algorithms (Figures 2-5) for the management of adverse reactions that can occur during SLIT **(5, D)**.

A. Up to 40% of patients can present oral pruritus or a burning sensation in the mouth, angioedema of the tongue or mouth, and/or ear itching. Onset is usually immediately after application.
B. Some patients complain of gastrointestinal symptoms (e.g., nausea, vomiting, and abdominal pain), which are currently considered local reactions, unless they are accompanied by other systemic symptoms.
C. No standardized system has been developed for classifying local side effects, which are not usually severe. We consider pruritus as mild and edema of the mouth as moderate. Similarly, we propose that gastrointestinal reactions be considered as moderate.
D. Local reactions usually last <30 minutes and tend to resolve after 7-14 days with the medication. The

Table 8. World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System [264].

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptom(s)/sign(s) of 1 organ system present **Cutaneous** Generalized pruritus, urticaria, flushing or sensation of heat or Angioedema (not laryngeal, tongue, or uvular) or **Upper respiratory** Rhinitis (e.g., sneezing, rhinorrhea, nasal pruritus and/or nasal congestion) or Throat-clearing (itchy throat) or Cough perceived to come from the upper airway, not the lung, larynx, or trachea or **Conjunctival** Conjunctival erythema, pruritus, or tearing or Other Nausea, metallic taste, or headache	Symptom(s)/sign(s) of >1 organ system present or **Lower respiratory** Asthma: cough, wheezing, shortness of breath (e.g., drop of <40% in PEFR or FEV1, responding to an inhaled bronchodilator) or **Gastrointestinal** Abdominal pain, vomiting, or diarrhea or **Other** Uterine cramps	**Lower respiratory** Asthma (e.g., drop of 40% in PEFR or FEV1, not responding to an inhaled bronchodilator) or **Upper respiratory** Laryngeal, uvular, or tongue edema with or without stridor	**Lower or upper respiratory** Respiratory failure with or without loss of consciousness or **Cardiovascular** Hypotension with or without loss of consciousness	Death

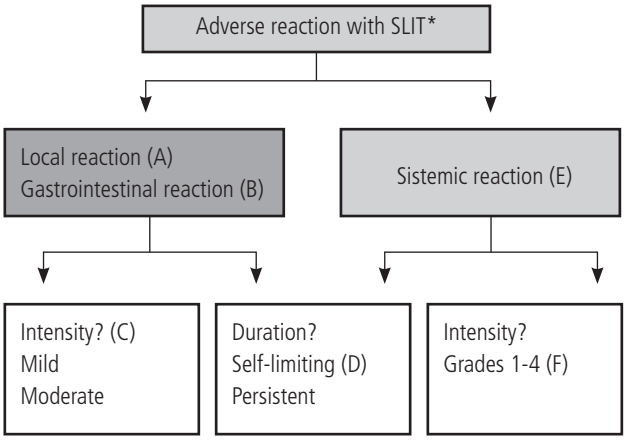


Figure 2. QUASAR group algorithm for the classification of adverse reactions to SLIT

duration of local reaction varies widely: pruritus lasts 5 days on average.

E. Systemic adverse effects (rhinitis, asthma, urticaria, angioedema, hypotension) are uncommon (<5% of patients), and onset is immediate.

F. The system for grading systemic reactions caused by SCIT is considered suitable for SLIT [264].

In relation with local adverse reactions (Figure 3), if dosing is to be continued, we propose continuing pretreatment with antihistamines preferentially for at least 15 days, since the clinical course is usually favorable and reactions tend to disappear spontaneously in 7-14 days **(5, D)**.

No references have been found on the duration of gastrointestinal reactions (number of days). We proposed 5 days as the observation period before considering treatment (Figure 4), as in the case of local reactions, since gastrointestinal reactions are considered a type of local reaction **(5, D)**. Gastrointestinal reactions have been reported to improve if the patient does not swallow the extract or receives pretreatment with proton pump inhibitors such as omeprazole, whether combined or not with antacids [138].

Grading for systemic reactions caused by SCIT is considered appropriate for SLIT (Table 8). Treatment is necessary to control the reaction (Figure 5). In the case of a severe reaction, administration should not be continued without consultation or medical supervision.

9. Recommendations for the patient

Most adverse reactions to SLIT are local and mild [266]; therefore, SLIT can be administered at home [36], although it should be initiated under medical supervision with a 1-hour observation period (sublingual grass tablets [256] and immunotherapy with latex and peach). SLIT can subsequently be administered at home [36].

The patient should be given clear instructions on how to manage adverse events, when the treatment should be interrupted, and how it should be restarted. A contact telephone number should also be provided.

The patient should be told that most adverse reactions appear during the first few days and that they are local and mild, do not require treatment, and are self-limiting [16]. Oral antihistamines should be prescribed [36].

The patient should be informed about the potential risk of systemic adverse reactions and told to interrupt treatment and contact his/her physician should a systemic reaction occur.

The patient should be informed about potential interactions with drugs such as β-blockers. He/she should also be advised on temporary interruption of SLIT in the case of respiratory or oral infections and asthma exacerbations.

The dose adjustment to be used in cases of delayed administration for any reason other than adverse events is as follows **(5, D)** [265]:

- Initiation phase
  - Do not modify the regimen if the interruption is <7 days.
  - If the interruption is 7-15 days, the dose should be reduced by 1 drop/puff for each 5 days of delay (not in the case of tablets).
  - If the interruption is >15 days, restart administration.
- Maintenance phase
  - Do not modify the regimen if the interruption is <2 weeks.
  - Between 2 and 4 weeks, reduce by 1 dosage step for each week of treatment. If in doubt, ask.
  - If the interruption is >5 weeks, restart treatment.

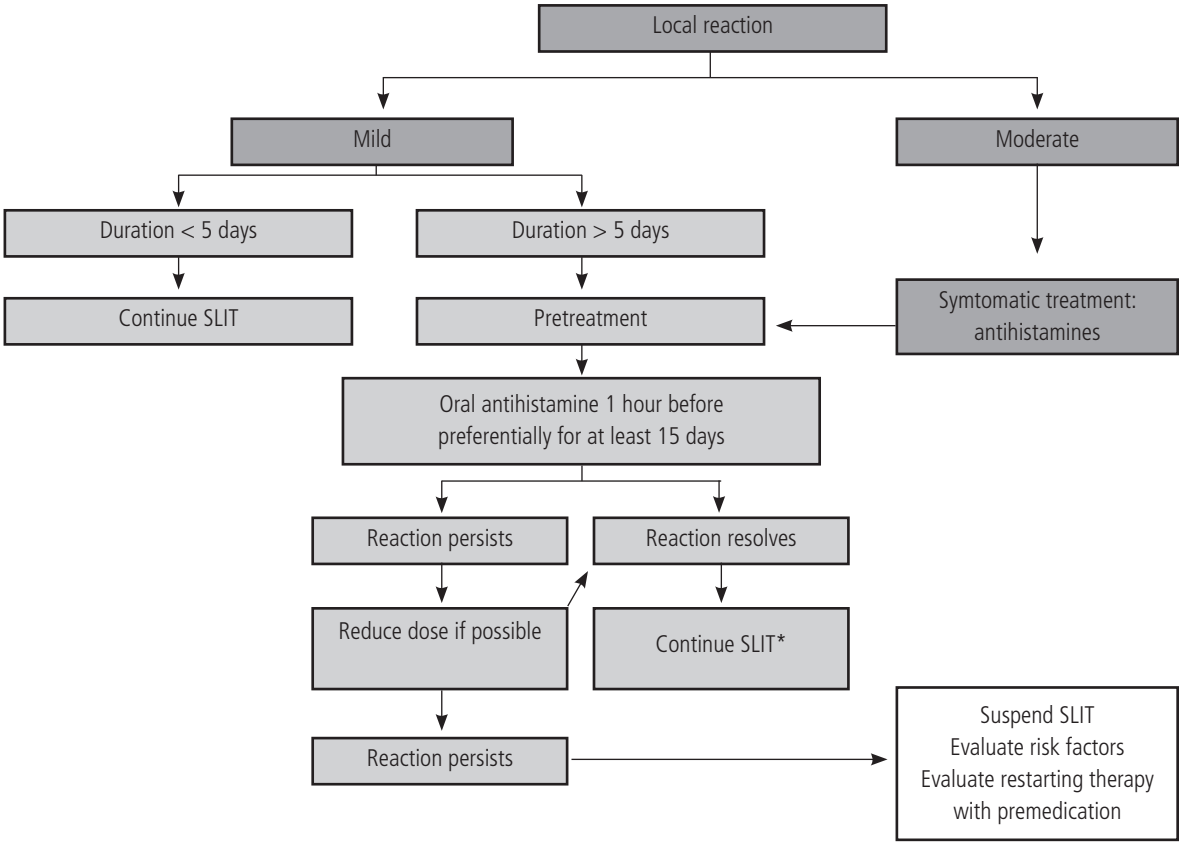
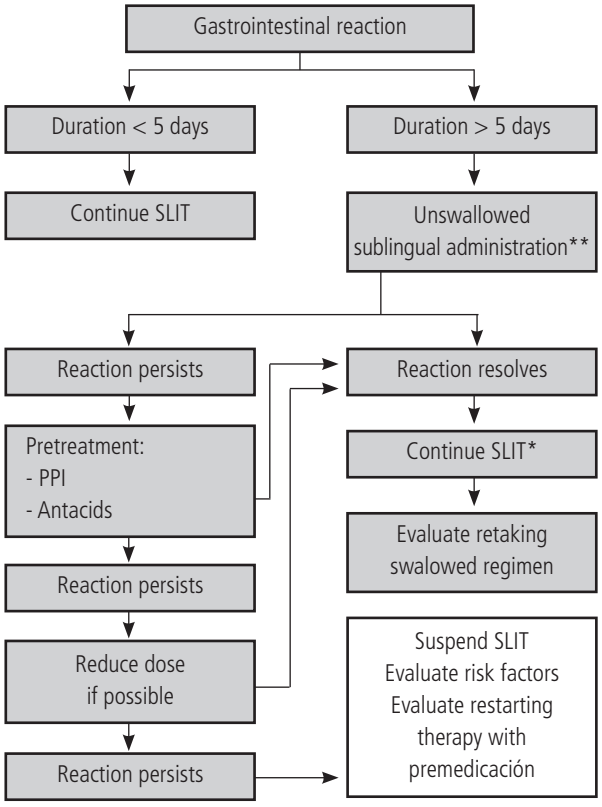


Figure 3. QUASAR Group algorithm for management of local reactions to SLIT.

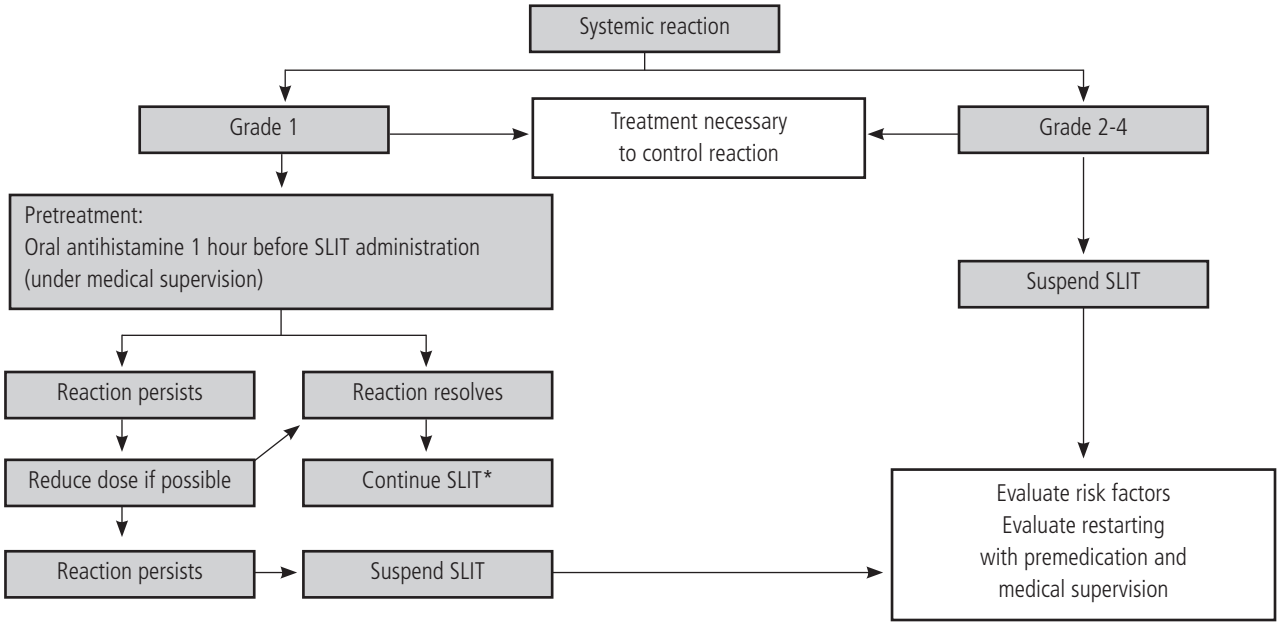


*Return to the baseline dose and scale up until maintenance dose is reached
**Spit out (drops), do not swallow (tablets)
PPI: Proton pump inhibitors

Figure 4. QUASAR Group algorithm for the management of gastrointestinal reactions to SLIT.

10. Conclusions

- SLIT is increasingly used to treat ARC with (or without) bronchial asthma in children and adults. It can be considered as initial treatment, since the lack of efficacy of other pharmacological treatments is not considered a prerequisite for use.
- Given the available scientific evidence, SLIT (for treatment of ARC) has a grade A recommendation which is guaranteed by increasingly numerous meta-analyses and systematic reviews that value its favorable efficacy and safety profile.
- In SLIT, both the patient and the extract must fulfill the criteria applied to SCIT. Other circumstances should be taken into consideration in the case of the patient (e.g., preferences, transport, and needle phobia). When selecting the extract, clinicians should evaluate current scientific evidence for each preparation.
- In pollen-allergic patients, the SLIT regimen can be perennial, preseasonal, or precoseasonal. A precoseasonal regimen is increasingly common, since it tends to improve adherence to immunotherapy. In the case of SLIT with grasses, both a liquid formulation (solution) and tablets can be used.
- Although it is recommended to include in vivo parameters and tools to measure the efficacy of SLIT, the main variable is still evaluation of symptom relief and of the need for medication.
- Local reactions appear in up to 40% of patients at initiation of SLIT. These are usually self-limiting and resolve after a few days; however, if they cause discomfort, they can be treated with antihistamines.



*Return to the baseline dose and scale up until the maintenance dose is reached

Figure 5. QUASAR Group algorithm for the management of systemic reactions to SLIT.

Gastrointestinal reactions should be treated with antacids or proton pump inhibitors. Pretreatment with antihistamines is also useful.

- Systemic reactions are very uncommon and generally not severe. In the case of a systemic reaction, SLIT should be suspended and the regimen to be followed assessed by a specialist. If SLIT is to be continued, it should be restarted under medical supervision and with premedication.
- As SLIT can be administered at home, the patient should receive written information on its management, be aware of the circumstances where it should be modified, and know when to consult a physician.

The literature review revealed unmet needs, such as standardization of patient selection, monitoring of efficacy, and management of adverse events. This review presents an algorithm for selecting candidates for immunotherapy and an algorithm for managing adverse reactions to SLIT, as well as a verification cheklist to make easier the patient follow up.

11. Conflicts of interest

In 2013:

Dr. Ignacio Dávila reports having been paid lecture fees in immunotherpy by Stallergenes and Leti; having participated in advisory boards of Stallergenes and Faes Farma; having served as consultant to Novartis; and having received research grant support from TermoFisher and Diater.

Dr. Ana M. Navarro Pulido reports having been paid lecture fees in immunotherapy by ALK, Leti and Stallergenes; having participated in advisory boards of ALK, Leti and Merck.

Dr. Javier Domínguez Ortega reports having been paid lecture fees in immunotherapy by Stallergenes and Leti; having participated in one advisory board of Merck.

Dr. Alicia Alonso Gómez reports having been paid lecture fees in immunotherapy by ALK, Stallergenes, Menarini and Uriach.

Dr. Darío Antolín-Amérigo reports having been paid lecture fees in immunotherapy by Stallergenes.

Dr. Mª. Carmen Diéguez Pastor reports having participated in one advisory board of Stallergenes.

Dr. Eloína González Mancebo reports having been paid lecture fees in immunotherapy by ALK.

Dr. Cristina Martín García reports having been paid lecture fees in immunotherapy by Stallergenes; having participated in one advisory board of Stallergenes; having served as consultant to Stallergenes; and having received research grant support from Stallergenes.

Dr. Camilo Martínez Alonso reports having been paid lecture fees in immunotherapy by Stallergenes; and having received research grant support from Stallergenes.

Dr. Beatriz Núñez Acebedo, declares to have not any conflict of interest.

Dr. Nieves Prior Gómez, declares to have not any conflict of interest.

Dr. Marta Reche Frutos reports having been paid lecture fees in immunotherapy by Stallergenes; and having participated in one advisory board of Stallergenes.

Dr. Ana Rosado Ingelmo reports having been paid lecture fees in immunotherapy by Stallergenes and ALK; and having participated in one advisory board of ALK.

Dr. Javier Ruiz-Hornillos reports having been paid lecture fees in immunotherapy by Stallergenes; and having served as consultant to Leti.

Dr. Agustín Sansosti reports having been paid lecture fees in immunotherapy by Stallergenes; having participated in one advisory board of Stallergenes; having been served as consultant to Stallergenes; and having received research grant support from Stallergenes.

Dr. Miguel Torrecillas Toro reports having been paid lecture fees in immunotherapy by Stallergenes; and having participated in advisory boards of Stallergenes and ALK.

Dr. María José Jerez reports having been paid lecture fees in immunotherapy by Stallergenes and Novartis.

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