Specific allergen immunotherapy for the treatment of allergic asthma: a review of current evidence

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Abstract

Asthma is frequently associated with atopy, characterized by the production of specific immunoglobulin E in response to environmental allergens. Currently, two types of allergen immunotherapy (AIT) are used in clinical practice: subcutaneous and sublingual immunotherapy, both accepted as key components of the therapeutic repertoire for allergic rhinitis and conjunctivitis. However, their role in asthma remains controversial. The present document is aimed at providing the clinicians with a review of the evidence on the use of AIT in asthma, focusing on the most relevant aspects of its mechanism of action, its efficacy, and existing data on safety, tolerability, and cost-effectivity, both in pediatric and adult populations. A systematic search of MEDLINE, Cochrane, and Clinical Trials databases from 2000 to April of 2016 was carried out by a panel of experts from the Spanish Allergy and Clinical Immunology Scientific Society. Relevant studies prior to the year 2000 included in ulterior systematic reviews were also considered. More than 4000 articles were identified during the search and 241 were selected to retrieve available evidence on AIT, which was graded according to the Oxford classification. All the group members reviewed the resulting text until the final version reached the consensual agreement. A summary of recommendations on the more relevant topics are proposed. The role of AIT as a valuable therapeutic strategy for prevention of exacerbation and progressive decline in lung function is highlighted. Future research should include specific tools for asthma evaluation when assessing AIT effectiveness in asthmatic patients.

Key words: Asthma treatment. Allergen immunotherapy. SLIT. SCIT. Efficacy. Safety. Children. Adults. Severe asthma. Cost-effectiveness.

Resumen

El asma se asocia frecuentemente con alergia, entendida ésta como la producción de IgE específica frente a alérgenos ambientales. Actualmente, existen dos tipos de inmunoterapia específica con alérgenos (ITE) para la práctica clínica habitual: subcutánea y sublingual, ambas indicadas en el tratamiento de la rinitis y la conjuntivitis alérgicas. Sin embargo, su papel en el asma resulta todavía controvertido.

Este documento pretende ofrecer al clínico una revisión de la evidencia del uso de ITE en asma, centrándose en aspectos más relevantes como su mecanismo de acción, eficacia, seguridad, tolerabilidad y coste-eficacia, tanto en población adulta como pediátrica. Un panel de expertos de la Sociedad Española de Alergología e Inmunología Clínica, llevó a cabo una búsqueda sistemática en las bases de datos MEDLINE, Cochrane y Clinica Trials, desde 2000 a abril de 2016. También se revisaron algunos estudios anteriores al 2000, incluidos en revisiones sistemáticas posteriores. Se identificaron más de 4000 artículos en la búsqueda y se seleccionaron 241 para documentar la evidencia disponible y graduarla según la clasificación Oxford. Todos los miembros del panel revisaron el texto resultante hasta la versión final, alcanzando un acuerdo de consenso y se propusieron recomendaciones para los aspectos más relevantes. Se señala específicamente que la ITE resulta potencialmente valorable en la prevención de las exacerbaciones y el declive progresivo de la función pulmonar, aunque se necesitan nuevos estudios que incluyan variables específicas de evaluación de asma para verificar la eficacia de la ITE en esta patología.

Palabras clave: Tratamiento del asma. Inmunoterapia con alérgenos. Inmunoterapia sublingual. Inmunoterapia subcutánea. Eficacia. Seguridad. Niños. Adultos. Asma grave. Coste-eficacia.

1. Introduction

Asthma is an obstructive pulmonary disorder with exacerbations characterized by symptoms of shortness of breath, cough, chest tightness, and/or wheezing, mainly caused by chronic airway inflammation. Asthma is a very common condition, both in adults and children. Its frequency has increased notoriously throughout the world, especially in industrialized and developing countries, with an estimated prevalence of 7-10% [1], and represents one of the leading reasons for all-cause hospitalizations [2]. The goals of asthma management are the control of the disease, with low burden of symptoms and maintenance of normal activity levels, and the prevention of exacerbations and medication side-effects [3]. Therapy for asthma has substantially evolved in the past three decades, prompted by a better understanding of the role of inflammation in the pathophysiology of the disease. Most cases of asthma are associated with atopy (defined as the production of specific immunoglobulin (Ig)E in response to common environmental allergens), and this association has led asthma to be regarded largely as an allergic disorder along with other atopic diseases. In fact, the phenotype of childhood-onset atopic asthma is solid and early sensitization is associated in some cases with severe asthma in adulthood [4]. Moreover, atopy is a prevalent feature of all the phenotypes of adult asthma, reaching a prevalence rate of 85% in high-atopy prevalence phenotypes and 66% in low-atopy prevalence ones [5].

Currently, allergen immunotherapy (AIT) in the two available forms, subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), is a widely accepted component of the therapeutic repertoire for allergic rhinitis and conjunctivitis [6-8]. However, its role in asthma remains, at least, controversial. This is mainly due to the scarce clinical trials evaluating relevant asthma endpoints as primary variables and because AIT effect may only be evident following a long treatment period [9]. In addition, other factors such as the risk of adverse reactions, the heterogeneity of allergen compounds and commercial products [10, 11], and the lack of head to head studies versus pharmacological agents might have provoked that asthma management guidelines do not provide clear recommendations about AIT use in asthma. The Spanish Guidelines for Asthma Management (GEMA) recommend AIT for patients with well-controlled, non-severe allergic asthma and proven IgE-mediated sensitization to inhaled allergens [12]. Until 2016 edition the Global Initiative for Asthma (GINA) guidelines states that AIT may be an option if allergy plays a prominent role, e.g. asthma with allergic rhinoconjunctivitis, but its potential benefits must be weighed against the risk of adverse effects, and the inconvenience and cost of the prolonged course of therapy [3].

The present report is aimed at providing the clinicians with a review of the evidence on the use of AIT in asthma, focusing especially on the most relevant aspects of its mechanism of action, its efficacy, and existing data on safety, tolerability, and cost-effectivity, both in pediatric and adult populations.

2. Material and methods

Search criteria

A panel of experts comprising 10 Spanish allergists was selected from the Spanish Allergy and Clinical Immunology Scientific Society (SEAIC) particularly from the Immunotherapy and Asthma Interest Groups. They proposed the key words for each of the following topics in order to optimize the bibliographic search:

- Mechanisms of action, molecular markers of sensitization profile, and response predictors: asthma, immunotherapy, allergy OR allergen, together with immunological mechanism, immunological response, IgE, IgG, IgG4, cytokine profile, Th1, Th2, IL-4, INF-γ, regulatory T cells, Foxp3, IL-10, molecular diagnosis, component resolved diagnosis, Phl p 1, Phl p 5, Phl p 7, Phl p 12, Ole e 1, Ole e 7, profilin, polcalcin, biomarker, predictors of failure of immunotherapy, predictors of efficacy of immunotherapy.
- Efficacy of AIT in asthma: combinations of allergen immunotherapy, asthma treatment, allergic asthma, GINA, GEMA 4.0, SCIT, SLIT and allergen tablets, efficacy of, effect of, improvement in, asthma and rhinitis treatment, prevention of asthma, evidence-

based evaluation, selected AIT products, high-dose immunotherapy, allergens (molds, *Alternaria*, house dust mites, *Dermatophagoides, Blomia, Lepidoglyphus*, pollen, grass pollen, olive pollen, salsola pollen, birch pollen, *Parietaria* pollen, *Platanus* pollen, *Cupressus* pollen, *Artemisia* pollen, tree pollen, animal dander (cat, horse, and dog dander), long time effect, long-term efficacy, simultaneous effect in asthma and rhinitis, concomitant treatment for asthma and rhinitis, immunotherapy and asthma control, optimal management, knowledge gaps of immunotherapy in asthma, AIT and asthma prevention.

– Immunotherapy in severe asthma: severe asthma/asthma exacerbation, allergen inmunotherapy/allergen-specific immunotherapy/allergy, SCIT, SLIT, allergen tablets safety, adverse events, contraindications, omalizumab.
– Immunotherapy in asthmatic children: Child* OR Pediatr* OR * Child, Preschool AND specific immunotherapy, allergen immunotherapy, SCIT, SLIT, allergen tablets, asthma, bronchial hyperreactivity, long-term effect, sustained efficacy, prevention, new sensitizations, relapse, immunotherapy/adverse effects, immunotherapy/safety, childhood asthma/cohort studies.
– Cost-effectiveness of AIT in asthma: immunotherapy AND cost of asthma treatment, comparative costs, cost-effectiveness of immunotherapy (SCIT, SLIT, and tablets), cost-utility, QALY, work productivity, health-care costs, cost-saving, economic evaluation, budget impact model.
– Clinical endpoints for asthma treatment: Allergen immunotherapy, asthma, and outcomes; Allergen immunotherapy, asthma, and knowledge gaps; Allergen immunotherapy, asthma, and regulatory agencies; Allergen immunotherapy, asthma, and regulatory guidance; Allergen immunotherapy, asthma, and exacerbation; Allergen immunotherapy, asthma, and severe exacerbation; Allergen immunotherapy, asthma, and moderate exacerbation; Allergen immunotherapy, asthma, and patient selection; Allergen immunotherapy, asthma, and biomarkers; Allergen immunotherapy, asthma, and unmet needs; Composite Asthma Severity Index, Allergen desensitization and 1 to 10.
– Clinical guidelines for asthma management: role of AIT.

A systematic search of MEDLINE, Cochrane, and Clinical Trials databases from 2000 to April of 2016 was carried out by the members of the panel with the help of experienced librarians. Relevant clinical guidelines were also searched. Additional references were identified by a hand search of reference lists from key systematic reviews, including publications previous to 2000 when considered relevant. Titles, abstracts, and the full text of retrieved articles were screened according to the relevant topics. Almost 5000 articles were identified during the search. After eliminating duplicates, articles in other languages apart from English, French and Spanish, and out-of-scope studies, 241 were selected because of their relevance and studied in depth to retrieve available evidence on AIT (Figure 1).

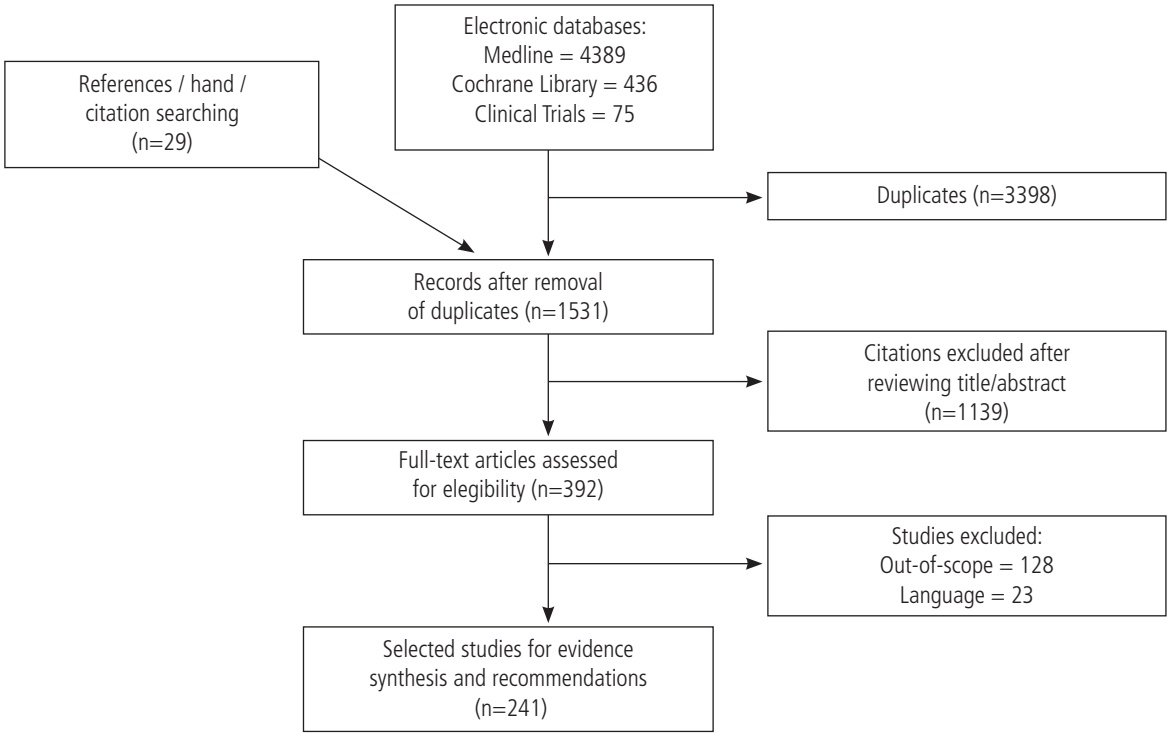

Figure. Flowchart of literature search and study selection.

Table 1. OCEBM levels of evidence and grades of recommendation (2009)

Level of evidence	Type of study	Grade of recommendation	Meaning
1a	Systematic review of randomized clinical trials (with homogeneity)	A	Highly recommendable
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 of cohort studies (with homogeneity)	B	Favorable
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 of case-control studies (with homogeneity)		
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	C	Favorable but no conclusive
5	Expert opinion without explicit critical appraisal, or based on physiology or pathophysiological principles	D	Neither recommended

OCEBM: Oxford Centre for Evidence-Based Medicine

Evidence and recommendation grading

The Oxford Centre for Evidence-Based Medicine (OCEBM) criteria was adopted as an evidence-based approach [13]. Thus, the group of experts assessed the level of existing evidence and accordingly ranked the recommendations, with level of evidence from 1 (highest) to 5 (lowest), and grade of recommendation from A (strongest) to D (weakest); see Table 1.

3. Mechanisms of action, biomarkers of sensitization and response

3.1 Main immunological changes induced by AIT

There are multiple cell types and inflammatory mediators involved in respiratory allergy pathophysiology. The airway inflammation is frequently mediated by Th2 lymphocytes, whose cytokine secretion leads to mast cell stimulation, eosinophilia, leukocytosis, and enhanced B-cell IgE production [14]. It has been shown that AIT can induce the generation of anergy and/or deletion of allergen-specific T-cells, skewing allergen-specific responses from Th2 to a more protective Th1 phenotype, which downregulates IgE-mediated immune response. Several studies have shown that AIT modifies the function of monocytes, B cells, and T cells, as well as basophils, eosinophils, and mast cells count [15-18]. At the T cell level, a key mechanism is the appearance and activity of FOXP3+ CD25+ T regulatory (reg) cells that produce Interleukin (IL)-10 and transforming growth factor beta (TGF-β) to suppress activity of allergen-specific Th2 cells with the subsequent recruitment of other inflammatory effector cells. Additionally, the production of IL-10 and TGF-β from Treg cells stimulates B cells to undergo class switching and produce the protective antibodies IgG4 and IgA2 [19-21]. Moreover, it has been shown that TGF-β mediates the immunological suppression seen early in clinically effective SLIT in addition to an increase in Treg cells with suppressor function [22]. To achieve these immunological changes, SLIT or SCIT needs to be applied at a suitable dose. In the last years, the optimal dose for some allergens has been described, although in others it remains unknown. [23].

3.2 Molecular diagnosis and sensitization profiles

A successful AIT requires the identification of patients who are suitable candidates for it. Allergic patients respond in an individualized manner to exposure to allergens from various sources, producing their own unique IgE antibody profile at the molecular level [24]. Immunotherapy vaccines, in general, consist of different allergen components with a predominance of major allergens. Molecular diagnostics can help to identify individuals who are sensitized to minor allergens or to cross-reactive allergens and who, therefore, may show a different

immune response to and clinical benefit from AIT [25]. The molecular-based allergy (MA) diagnosis is an approach to define the allergen sensitization profile of a patient using purified natural or recombinant allergen on singleplex or multiplex measurement platforms [26], and may improve the selection of specific AIT for pollen [24, 27-29] and other allergens [30, 31]. Thus, the recognition of the sensitization profile (identification of primary sensitization markers with respect to detection of specific IgE against cross-reactive allergen molecules) could better define the relevant allergens in each patient [32-34].

In a prospective study that included patients with seasonal rhinoconjunctivitis and/or asthma that received AIT with a *Phleum pratense* extract, patients' sera were analyzed for specific IgE and IgG4 reactivity to individual *P. pratense* allergens (recombinant Phl p 1, Phl p 2, Phl p 5, Phl p 6, Phl p 7, Phl p 11, Phl p12 and native Phl p 4) and natural *P. pratense* extract. The detection of specific serum IgG4 antibodies a few weeks after the start of AIT was a valuable tool to estimate the presence of relevant allergens in the immunotherapeutic allergen extract [35]. It has been shown that IgE response against grass pollen molecules can start years before symptoms onset as a weak sensitization phenomenon. It increased in serum concentration and complexity through a "molecular spreading" process during the preclinical and clinical course. Thus, testing IgE sensitization may facilitate prediction of seasonal allergic rhinitis at its early molecular sensitization stage [36]. In contrast, in patients with established allergic asthma, the variability in serum total IgE may prevent it from being used as a marker of asthma severity, although a cut point of 400 IU/mL could be suggestive of more severe disease [37].

Sensitization profile is also valuable for the presence or absence of allergic asthma and its clinical characterization [38]. In a Spanish population of mite allergic patients (both children and adults), specific IgE to eight allergens, skin prick testing (SPT) to whole mite extracts, level of mite allergen exposure, and specific IgG4 were determined [39]. The results showed that sensitization to Der p 1 was more frequent in children, whereas Lep d 2 sensitization was more frequent in adults. A higher ratio IgE/IgG4 to Der p 2 was associated with the presence of allergic asthma. Another cohort study found a correlation between low values of specific IgE to Phl p 5 and the absence of asthma in pediatric patients with grass-pollen induced allergy [40]. In asthmatic and nonasthmatic children with house dust mites (HDM) allergy, the IgE and IgG reactivity profiles to HDM allergens, as well as IgE levels to certain allergen components, differed considerably between both groups; asthmatic children showed an expanded IgE repertoire to allergen components and increased specific IgE levels [41]. This pattern was also observed in a similar study in an Italian population [35]. One publication established an association between sensitization to minor allergens of olive-tree pollen and poor tolerance to specific immunotherapy, with patients sensitized to Ole e 7 or 9 showing a 2-fold greater risk of asthmatic symptoms than patients sensitized only to Ole e 1 [42]. However, there are controversial data for grass pollen. In an Italian study that included 140 patients with rhinitis and/or asthma caused by sensitization to grass pollen, low values of sIgE to Phl p 5 were correlated with the absence of asthma [40]. In contrast, in a retrospective study among 248 patients living in the northern area of Madrid, Spain, which evaluated the profile of sensitization to recombinant-grass pollen allergens and its potential association with different clinical features, it could not be possible to identify any relationship between them. Only higher IgE levels to rPhlp1 seemed to be associated with longer disease duration [43].

3.3 Biomarkers/predictor of response

AIT is an expensive and long lasting treatment, so the availability of a marker able to predict an adequate response is of crucial relevance. Apart from SPT testing, raised serum allergen-specific IgE (sIgE) is a predictive biomarker that clearly provide important information. In a group of 75 adults with allergic rhinitis, a real-life study found that high sIgE levels could predict a favorable response to AIT. AIT effectiveness was calculated considering both clinical improvement and drug use reduction by patient self-evaluation. After 3-year SLIT, 63 patients (84%) were AIT responders. Serum-specific IgE levels were significantly higher in responder patients than in non-responder ones [44]. A retrospective study with 174 allergic patients treated with SLIT for 3 years confirmed these preliminary findings. Responder patient was identified based on a Visual Analogic Scale (VAS) (for both symptom and drug assessing) reduction of at least 30% compared with the baseline value. Response to SLIT was considered effective in 145 (83.3%) patients. A cut-off value of >9.74 kU/l) for sIgE was able to discriminate effective AIT [45]. A pediatric study investigated whether a cut-off sIgE level >10 kU/l could be associated with self-perception of effective AIT in children with allergic asthma and/or rhinitis due to HDM. Thirty-one allergic children with serum HDM-specific IgE levels >10 kU/l were evaluated. Eight allergic children with levels of sIgE to HDM <10 kU/l were considered as control. All patients were treated with SLIT for 3 years with an HDM allergen extract. All children (but one) with sIgE >10 kU/l perceived AIT efficacy, whereas only one child with sIgE <10 kU/l perceived AIT benefit. There was a strong relationship between perception of AIT efficacy by VAS and sIgE levels (r = 0.615). Also nasal VAS and Asthma Control Test significantly improved only in children with sIgE >10 kU/l [46].

It has been also suggested that the ratio of specific IgE to total IgE (sIgE/tIgE) might relate to the response to immunotherapy. In a retrospective study in adult patients that underwent AIT as part of the therapy for allergic rhinitis, a significant correlation was found between the serum sIgE/tIgE ratio and the clinical response to AIT, with high ratios (>16.2) associated with an effective response [47]. In a prospective study in children monosensitized to HDM treated with AIT during 2 years, sIgE/tIgE ratio correlated with the clinical response [48]. Another study included 185 children who had undergone 3 years of standardized-quality HDM SCIT. Four basal variables were associated with clinical response: tobacco smoke exposure, atopic family history, serum tIgE and sIgE/

tIgE ratio. The serum tIgE was superior to both the serum sIgE/tIgE ratio and sIgE levels alone in predicting clinical effectiveness [49].

The longitudinal analysis of humoral and cellular immune parameters in peripheral blood samples of patients receiving grass tablet SLIT revealed that changes in sIgE levels after therapy were linked to a specific (inhibitory) IgG4 response, and production of blocking antibodies correlated with TH2 response downregulation [18]. In fact, some evidence suggests that functional assays of inhibitory IgG4 and IgE-blocking factor may be more useful surrogates of clinical response than IgG4 levels [50]. Other proposed biomarkers are levels of IL-10 and basophil histamine release. In a prospective study, children with a diagnosis of respiratory allergy to *D. pteronyssinus* received SCIT during one year. An early IL-10 response with an increase in specific IgG4 levels and an associated beginning of the decline in Der p1 and Der p2 IgE levels were efficacy predictors of the SCIT [51]. A case-control study with AIT-treated patients and controls found that allergen–induced basophil activation was significantly higher in patients with seasonal allergic rhinitis, and was inhibited by AIT. Suppression of basophil responsiveness significantly correlated with lower allergic rhinitis symptom scores [52].

Some clinical markers have also been identified as predictors of good clinical response. In a retrospective study including children with asthma who received 2 years of AIT, ten factors were tested for correlation with clinical response to AIT. A significant correlation was found with onset age of wheezing and airway hyper-responsiveness [53].

According to the evidence described above, the following recommendations or statements are formulated:

- Determination of the sensitization profile is crucial for define the relevant allergens in each patient (LE 2c, grade B) [24, 27, 28, 30-34].
- Serum allergen-specific IgE is a predictive biomarker for adequate response to AIT (LE 3, grade C) [44-49].
- Functional assays of inhibitory IgG4 and IgE-blocking factor may be useful surrogates of clinical response (LE 1b, grade B) [18, 50].

4. Indications and contraindications of AIT in asthma

Currently, the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines give a conditional recommendation for SCIT and SLIT in patients with allergic asthma [54, 55], whereas the 2016 Global Initiative for Asthma [3] report states that AIT may be an option if allergy plays a prominent role, e.g. asthma with allergic rhinoconjunctivitis, but its potential benefits must be weighed against the risk of adverse effects, and the inconvenience and cost of the prolonged course of therapy [3]. During the risk evaluation physicians should consider the different pattern of sensitization, as it has been shown a significant association between the number of allergens that sensitized the patients, sensitization to Phl p 1+ Phl p 5 and/or Phl p 12, and the total number of adverse reactions in grass pollen allergic subjects [56]. There also has been observed an increased risk of systemic reactions during immunotherapy with olive extract in patients sensitized to Ole e 7 and Ole e 9 [57]. These findings suggest that there is a need to choose immunotherapy extracts with a controlled and uniform content in terms of Ole e 1, Ole e 7, and Ole e 9, at least in highly exposed populations to olive-tree pollen. Indications for AIT in allergic asthma include suboptimal control with medications and/or allergen avoidance, adverse effect of medications; patient's desire to avoid long-term pharmacotherapy; and presence of comorbid allergic conditions [58].

Fatal reactions related to AIT are rare: one event in 2.5 million SCIT injections has been reported in the USA and none in Europe in the last 30 years. The prevalence of very severe systemic reactions is one in 1 million injections [59]. However, there are several contraindications for AIT including comorbidities, such as autoimmune diseases and malignancies, concomitant drug treatments, particularly β-blockers and angiotensin-converting enzyme inhibitors (ACEI), pregnancy for induction therapy, and, currently, severe asthma [60, 61]. There are also some concerns about the age limits for AIT use, although elderly people have shown good tolerance and clinical improvements with SLIT for mite allergy [62, 63]. These concerns also affect to very young children but this topic will be discussed in a section below (see AIT efficacy in pediatric populations).

Patients with asthma that is severe or uncontrolled by pharmacotherapy have higher risk of more frequent and more severe systemic reactions to aeroallergens, particularly when SCIT is used [64-66], whereas for SLIT severe asthma could not be identified as an individual risk factor for systemic reactions [67, 68]. The current definition of severe asthma refers to “asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) [69]. There is no study in the published literature that included safety of SCIT in this kind of patients. In contrast, there is some evidence that SLIT might be safe in uncontrolled moderate asthma [70]. Current evidence supports that, before administering SCIT, the level of asthma control for each patient should be properly assessed, measuring peak flow and postponing the injection if lung function has decreased >20% of personal best value [71]. All patients undergoing AIT should be observed typically for at least 30 minutes after injection to ensure proper management of adverse effects [72]. The use of premedication during the induction and maintenance phases such as omalizumab as a preventive measure could broaden the indication of AIT [73, 74]. Although, there is no evidence that the risk of anaphylaxis is higher in patients receiving beta-adrenergic blocking agents (β-blockers) during AIT administration [75, 76], β-blockers reduce the response to beta-agonist agents like adrenaline and potentially aggravate anaphylaxis, contributing to more severe and treatment-refractory SCIT reactions [64, 77]. In patients

on AIT, β-blockers should be substituted, if possible, with an alternative drug. Limited data exist about concomitant ACEI administration in patients receiving AIT. Bernstein et al. [66] described one fatality in an elderly male receiving aeroallergen SCIT while on an ACEI between 1990 and 2001, but actually concerns regarding concomitant ACEI administration have been restricted to patients on venom immunotherapy [64, 78].

In pregnant women, the benefit-risk balance of AIT should be assessed in every case. Evidence suggests that AIT may be continued but not initiated, and discontinuation should be considered during the induction phase [64]. In a prospective study that analyzed 185 pregnancies in women receiving SLIT, 24 participants began AIT during pregnancy. The incidence of obstetric complications was lower than in women who only received pharmacotherapy. Seven percent of patients experienced local reactions, and none had a systemic reaction [79]. A recent review of 453 pregnancies receiving AIT concluded that continuation and initiation of AIT during pregnancy appeared safe [80].

According to the evidence described above, the following recommendations or statements are formulated:

- Immunotherapy is indicated in allergic and well controlled asthmatic patients older than 5 years (LE 1b, grade A) [54, 55, 58, 72].
- Continuation of AIT during pregnancy is feasible (LE 3a, grade C) [79, 80].

5. Efficacy of AIT in asthma

AIT has extensively been evaluated in allergic rhinitis and rhinoconjunctivitis, since these have been the primary indications, but a proportion of or all the patients enrolled also suffered from concomitant asthma, so asthma-related outcomes could be analyzed. Overall, it has been observed an improvement in clinical symptoms and a reduction in the need of symptomatic medication with no consistent effect on lung function [81]. The assessment of AIT in asthma with an adequate sample has only been reported in some few recent trials, specifically designed to address this aim [70]. No consensus exists on the optimal end-points. There is a lack of studies using standardized and validated tools to evaluate key outcomes in asthma, such as exacerbations, number of patients necessary to treat to avoid one requiring increased medication or the avoidance of an asthma exacerbation, or the number of days with well-controlled asthma, leading to controversial recommendations in current asthma management guidelines.

5.1 Adult populations

Subcutaneous immunotherapy

The last Cochrane review of SCIT in asthma [81] included 88 trials (70 randomized and placebo controlled). Although a significant heterogeneity was identified in a number of comparisons, AIT was associated with a significant reduction in asthma symptoms, rescue medication, and bronchial responsiveness. This treatment also significantly reduced allergen-induced bronchoconstriction; however, only 20 studies included pulmonary function measurements. A few years later, Erekosima et al. [82] carried out a systematic review of randomized controlled trials on the effectiveness and safety of SCIT for allergic rhinoconjunctivitis and asthma. They concluded that there was high-grade evidence that SCIT reduces asthma symptoms and asthma medication in comparison to placebo or usual care.

When limited to specific allergens, SCIT has also been evaluated in several investigations (Table 2). In regard to HDM, the classic studies performed in HDM-induced asthma in Navarra (Spain) [83-86] , demonstrated intense clinical and immunological changes in the group treated with SCIT (either with cluster or conventional schedule) that were sustained during a 5-year course of treatment. SCIT for HDM during one year consistently produced a reduction of symptoms and medication use compared with placebo treatment [87-90]. Longer SCIT duration was also associated to a clear immunomodulatory effect [91] and with significant reductions in rhinitis and asthma scores [92] in adults with HDM-allergic asthma. However, in patients with persistent mild-moderate allergic asthma due to sensitisation to *D. pteronyssinus*, a 4-months SCIT was capable of inducing in vivo and in vitro changes, but these changes were not reflected in improved clinical outcomes [93]. These results are reassuring about the mid- and long-term efficacy of SCIT on HDM-related allergic asthma, and the need of long-term treatment to achieve clinical benefit. Additionally, a recent meta-analysis of 19 studies evaluated the efficacy of SCIT in mite-sensitized subjects (adults and children) with asthma. SCIT significantly reduced the asthma symptom scores (standardized mean difference of −0.94, 95% CI −1.58 to −0.29, P =0.004) and the asthma medication scores (standardized mean difference of −1.06, 95% CI −1.70 to −0.42, P =0.001) compared with the control group. There was no significant difference in lung function [94].

SCIT studies in relation with other allergens are less abundant. Pollens are an important source of allergens and are associated with a high prevalence of allergy and a substantial burden. For olive pollen, preseason SCIT has shown to produce significant improvement both in nasal and bronchial symptoms, and a decrease in the consumption of rescue medication [95]. For birch pollen, SCIT induced immunological changes in T cell populations and Ig subtypes [96, 97] and a reduction of symptom score for rhinoconjunctivitis and asthma and total medication score [98]. Several randomized trials have evaluated the efficacy of SCIT for grass pollen allergy in patients with chest symptoms. The results consistently showed a reduction of asthma symptoms and bronchial hyper-responsiveness [99, 100], with long-term effects after termination of the treatment [101, 102]. Importantly, SCIT during one year was also associated with an improvement of patients' quality of life [103]. In *Parietaria*-sensitive

Table 2. Studies on the clinical efficacy of SCIT in adult patients with allergic asthma

Authors	Type of study (Number of participants)	Allergen / comparator	Duration	Symptoms	Medication use	Comments
Abramson et al. [81]	Cochrane review (88 trials; 3,792 patients)	All / placebo	Variable	SMD -0.59 (95% CI -0.83 to -0.35)	SMD -0.53 (95% CI -0.80 to -0.27)	Moderate to high heterogeneity between studies
Erekosima et al. [82]	Systematic review (66 studies; 3,577 patients)	All / placebo, pharmacotherapy	Variable	9 of 10 studies demonstrated greater improvement in the SCIT group than the comparator	5 of 8 studies showed greater reduction in medication use in the SCIT group	All studies (11 of 11) demonstrated significant decreases in bronchial reactivity favoring the SCIT group over the comparison group
Olaguibel et al. [83]	Open-dose titration trial (43)	High-dose vs conventional HDM	18 months	Non- significant reduction in both groups	Significant reduction in the use of bronchodilators and anti-inflammatory treatment in both groups	The clinical severity score was significantly reduced from the baseline in both groups
Olaguibel et al. [84]	Long term open study (25)	HDM maintenance immunotherapy	5 years	Symptom score was significantly reduced from the baseline period and from the first 2 years of treatment	Significant reduction in the use of bronchodilators and anti-inflammatory treatment	The clinical severity score was significantly reduced from the baseline and from the first 2 years of treatment
Tabar et al. [85]	Randomized trial (63, 33 with asthma)	Cluster / conventional HDM / untreated group	18 months	Significant reduction in both active groups	Significant reductions in both active groups	Significant improvement in the clinical severity score
Varney et al. [87]	Randomized trial (36)	HDM / placebo	12 months	Non-significant effect	Non-significant effect	Only 22 patients were asthmatic
Ameal et al. [88]	Randomized trial (63)	HDM / placebo	12 months	78% decrease	68% decrease	Improvements also in the bronchial provocation test and quality of life
Wang et al. [89]	Randomized trial (132)	HDM / placebo	52 weeks	55% decrease (p=0.019)	37% decrease (p=0.308)	The study also included children

Garcia-Robaina et al. [90]	Randomized trial (64)	HDM / placebo	54 weeks	54% improvement ($p<0.001$)	58% improvement ($p<0.001$)	Improvements also in the bronchial provocation test and quality of life
Tabar et al. [92]	Randomized trial (239, 175 with asthma)	Long term HDM / pharmacotherapy	5 years	80% decrease; 70% of patients were symptom-free after 3 years	NE	Improvements also in quality of life The study also included children
Vidal et al. [93]	Randomized trial (45)	HDM / placebo	4 months	NE	No decrease in concomitant budesonide dose	
Lu et al. [94]	Meta-analysis (19 RCTs; 796 patients)	HDM / control group	Variable	SDM -0.94 (95% CI -1.58 to -0.29)	SDM -1.06 (95% CI -1.70 to -0.42)	No differences in lung function were found The studies also included children
Gonzalez et al. [95]	Randomized trial (46)	Olive pollen / control group	1 year	Significant decrease in asthma symptoms	Significant decrease in the consumption of β2-agonists and antihistamines	Improvement in the severity of asthma in the active group, but not in the control group
Bodtger et al. [98]	Randomized trial (35, 14 with asthma)	Birch pollen / placebo	1 year	Significant reduction	Significant reduction in total medication score	Low number of asthmatic subjects
Dolz et al. [99]	Randomized trial (30)	Grass pollen / placebo	3 years	Significant improvement in bronchial symptoms	Significant reduction in medical treatment	
Walker et al. [100]	Randomized trial (44, 36 with chest symptoms)	Grass pollen / placebo	2 years	90% reduction in seasonal chest symptoms ($p<0.05$)	80% reduction in medication scores ($p=0.007$)	Improvements also in bronchial hyper-responsiveness and quality of life

Table 2. Studies on the clinical efficacy of SCIT in adult patients with allergic asthma *(continuation)*

Authors	Type of study (Number of participants)	Allergen / comparator	Duration	Symptoms	Medication use	Comments
Durham et al. [121]	Randomized discontinuation trial (47)	Grass pollen / placebo	3 years	Chest symptoms remained similar between the maintenance and discontinuation groups, and lower than in the control group	The need of oral prednisolone was markedly lower in the maintenance and discontinuation groups (3 of 16 patients in each group) than in the control group (9 of 15 patients)	
Dominicus [102]	Randomized discontinuation trial (26)	Grass pollen / control group	2 + 3 years	Significant reduction of the symptom score ($p<0.001$)	Non-significant reduction of the medication score	Improvements also in quality of life
Petersen et al. [103]	Cohort study (248)	HDM, grass pollen	15 months	Severity of the disease was diminished ($p<0.001$)	NE	Improvements also in quality of life
Ferrer et al. [104]	Randomized trial (42)	*Parietaria* / placebo	20 months	64.4% reduction ($p=0.001$)	34.1% reduction ($p=0.033$)	Significant increase in healthy days (no symptoms and no medication)
Scichilone et al. [105]	Cohort study (29)	*Parietaria* / untreated control	9 months	Stable Asthma Control Test in treated patients but not in untreated patients	NE	
Tabar et al. [106]	Randomized trial (28)	*Alternaria* / placebo	12 months	Significant decrease in asthma severity in the active treatment group ($p<0.05$). Improvements in peak expiratory flow	NE	

Varney et al. [108]	Randomized trial (28)	Cat dander / placebo	??	Marked reduction in symptoms during the cat exposure ($p<0.001$)	NE
Fernandez-Tavora et al. [110]	Prospective study (24)	Horse dander / placebo	Median 7.3 months	Reduction of asthma symptoms in 90% of patients	NE

HDM: house dust mite; NE: non evaluated; RTC: randomized controlled trial; SCIT: Subcutaneous immunotherapy; SMD: standardized mean differences.

allergic patients, the AIT produced clinical improvement and contributed to the maintenance of asthma control during the pollen season [104, 105].

As for *Alternaria* allergy, very common in warm weather, one study showed that the severity of asthma decreased in patients that received SCIT compared to placebo, and physicians judged the disease course as significantly better in the active treatment group [106]. Regarding animal dander, it has been shown that SCIT produces immunological [107] and clinical responses [108, 109] in cat allergic patients and horse allergic patients [110].

Sublingual immunotherapy

From 1990s, when SLIT was introduced, two different presentations have been developed, either as a liquid delivered in drops or as a tablet (SLIT-tablet). Since then, a number of studies clearly showed that it is effective in allergic rhinitis, although its efficacy in allergic asthma is still debated. In fact, the recent Cochrane review in this topic [111] could not achieve a definitive conclusion. However, in studies that included evaluation of asthma as secondary endpoint it has been shown a significant impact for SLIT on asthma symptoms and on use of medication [112]. A previous review of available evidence on SLIT, particularly with pollens, obtained similar results regarding to the efficacy of SLIT in asthma [113]. Table 3 shows the schematic summary of studies performed with SLIT in patients with allergic asthma.

Specifically, SLIT-tablets with standardized allergen extract from *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* for HDM-induced asthma have been assessed in randomized clinical trials [68, 114-118]. Favorable effects were observed in terms of IC doses [119], asthma control, and quality of life. Recently, the first clinical trial designed to evaluate the effect of HDM SLIT tablet on risk of asthma exacerbations among participants with mite allergy–related asthma showed an improvement of time to first moderate or severe asthma exacerbation during ICS reduction, with an estimated absolute reduction at 6 months of 9-10% [70]. Accordingly, in a phase III assessing the efficacy and safety of HDM SLIT-drops, compared with placebo, the primary efficacy endpoint was well-controlled asthma for at least 16 of the last 20 weeks of treatment [117]. Well-controlled asthma was achieved by 85% of active and 83% of placebo patients ($p=0.244$). A post-hoc analysis by asthma severity revealed that patients with moderate persistent asthma at baseline (but not with mild asthma) were well-controlled with HDM SLIT-drops (81% and 66% for the active treatment and placebo groups, respectively; $p=0.021$).

Patients with grass-related asthma and rhinoconjunctivitis receiving grass allergen tablets have consistently experienced good asthma control, considerable symptom prevention, and reduced medication use [67]. Furthermore, long term SLIT was equally effective as inhaled budesonide in treating bronchial symptoms and provided an additional benefit in treating rhinitis symptoms and bronchial hyper-responsiveness [120]. A randomized trial that evaluated the sustained (2 years) efficacy

Table 3. Studies on the clinical efficacy of SLIT in adult patients with allergic asthma

Authors	Type of study (Number of participants)	Allergen / comparator	Duration	Symptoms	Medication use	Comments
Normansell et al. [111]	Cochrane review (52 studies; 5077 participants)	All / placebo	Variable	Inconclusive results	Inconclusive results	Lack of data on specific asthma outcomes
Lin et al. [112]	Systematic review (63 studies; 5131 participants)	All / placebo, pharmacotherapy	Variable	Strong evidence for asthma symptoms improvement	Moderate evidence for medication use reduction	The studies also included children
Moschbec et al. [116]	Randomized trial (604)	HDM / placebo	12 months	No changes in lung function	Significant reduction in inhaled corticosteroids	Improvements also in quality of life
Wang et al. [89]	Randomized trial (484)	HDM / placebo	12 months	Greater achievement of well-controlled and totally controlled asthma in patients with moderate, persistent asthma	Significant reduction in inhaled corticosteroids	
Virchow et al. [70]	Randomized trial (834)	HDM / placebo	18 moths	Reduction of risk of a moderate or severe exacerbation	NE	
Dahl et al. [67]	Randomized trial (114)	Grass pollen / placebo	6 months aprox.	No differences found	No differences found	
Marogna et al. [120]	Randomized trial (51)	Grass pollen / Inhaled budesonide	5 years	Greater improvements in bronchial symptom scores and hyper-responsiveness	Lower use of bronchodilators	
Durham et al. [121]	Randomized trial (238)	Grass pollen / placebo	5 years	39%-44% reduction of the weighted asthma combined score	39%-44% reduction of the weighted asthma combined score	

Milani et al. [122]	Prospective study (65)	Tree pollen / none	2 years	89% reduction of the mean clinical score	NE	Different allergens included
Voltolini et al. [123]	Randomized trial (24)	Birch pollen /placebo	2 years	Less number of days with asthma	Step down of treatment for asthma according to GINA criteria	
Marogna et al. [124]	Randomized trial (33)	Birch pollen / montelukast	5 years	Higher score for bronchial symptoms	Reduction of bronchodilators use	
Marogna et al. [125]	Randomized trial (84)	Birch pollen + ICS / ICS	3 years	Seasonal asthma control	NE	
Irani et al. [126]	Prospective study (118)	High dose pollen / none	3 years	Significant reduction in a global asthma score	Significant reduction in an asthma medication consumption score	

HDM: house dust mite; NE: non evaluated.

Table 4. Studies on the clinical efficacy of SCIT in pediatric patients with allergic asthma

Authors	Type of study (Number of participants)	Allergen / comparator	Duration	Symptoms	Medication use	Comments
Pifferi et al. [134]	Randomized trial (29)	HDM / untreated group	3 years	Decreased number of asthma exacerbations	Significant reduction in salbutamol and oral steroids	Improvement also in bronchial responsiveness
Zielen et al. [135]	Randomized trial (65)	HDM + FP / FP	2 years	Improvement in morning peak expiratory flow ($p<0.05$)	FP dose reduction ($p<0.05$)	
Tsai et al. [136]	Randomized trial (40)	HDM / untreated group	6 months	Greater reduction in symptom score ($p<0.01$)	Greater reduction in medication score ($p<0.01$)	
Hui et al. [137]	Randomized trial (90)	HDM / untreated group	3 years	Asthma symptom scores were significantly lower during the 3 years	Greater dose reduction and discontinuation rate of ICS	Improvement also in peak expiratory flow
Baris et al. [138]	Randomized trial (50)	HDM + vitamin D / HDM / pharmacotherapy	12 months	Lower total asthma symptom score in HDM groups ($p<0.01$)	Lower medication score and ICS dosage in HDM groups ($p=0.001$)	
Chen et al. [139]	Cohort study (58)	HDM / ICS	12 months	Reduction in number of emergency visiting for asthma attack	NE	Improvements also lung in function
Gozde Kanmaz et al. [140]	Cohort study (102)	HDM / pharmacotherapy	??	Lower number of acute asthma attacks in the previous year ($p<0.001$)	Higher ICS discontinuation rate	The study included polysensitized children
Stelman et al. [141]	Cohort study (90)	Long term HDM / control group	3-5 years	Higher rates of asthma remission	Significant reduction in minimal daily ICS controlling dose	No differences in lung function were found
Arroabarren et al. [142]	Randomized study (81)	3 years HDM / 5 years HDM	5 years	100% reduction in asthma global score in both groups	100% reduction in medication score in both groups	

Roberts et al. [143]	Randomized trial (39)	Grass pollen / placebo	2 pollen seasons	Reduction in the asthma symptom-medication score (p=0.04)	Trend toward a reduction in the total corticosteroid score	No differences in lung function were found
Kuna et al. [144]	Randomized trial (50)	*Alternaria* / placebo	3 years	63.5% reduction in symptom-medication score	Significant reduction in medical treatment	Improvements also in quality of life
Zapatero et al. [145]	Prospective study (99)	*Alternaria*	12 months	No effects on asthma symptoms but better asthma control	Less use of bronchodilators, ICS and anti-leukotrienes	Improvements also in quality of life
Kilic et al. [146]	Cohort study (16)	*Alternaria* / untreated group	12 months	Significant reduction in bronchial responsiveness	NE	
SCIT and/vs SLIT						
Keles et al. [177]	Randomized trial (51)	HDM SCIT+SLIT / SCIT / SLIT / pharmacotherapy	18 months	Reduced number of asthma attacks with SCIT containing regimens (p<0.05)	Reduced dose of ICS with SCIT containing regimens (p<0.05)	
Antunez et al. [178]	Cohort study (23)	HDM SCIT / SLIT	2 years	NE	NE	Clinical improvement according to VAS in both groups
Eifan et al. [179]	Randomized trial (48)	HDM SCIT / SLIT / pharmacotherapy	12 months	Significant reduction in total asthma symptom score with SCIT and SLIT	Significant reduction in total medication score with SLIT	
Karakoc-Aydiner et al. [180]	Randomized trial (48)	HDM SCIT / SLIT / pharmacotherapy	3 years	Significant reduction in total asthma symptom score with SCIT and SLIT	Significant reduction in total medication score with SCIT and SLIT	
Yukselen et al. [181]	Randomized trial (39)	HDM SCIT / SLIT / placebo	12 months	Significant reduction in asthma symptom score with SCIT	Significant reduction in asthma medication score with SCIT	

FP: Fluticasone propionate; HDM: house dust mite; ICS: inhaled corticosteroids; NE: non evaluated; SLIT: Sublingual immunotherapy; SCIT: Subcutaneous inmmunotherapy.

of SLIT after completion of a 3-year period of treatment found that the weighted asthma combined score was reduced by 39% in the active group relative to placebo over the entire grass pollen and by 44% over the peak seasons when combining all 5 years of the study [121].

Other studies have investigated the effect of SLIT with tree pollen allergens. In asthmatic patients, who were more commonly polysensitized, the mean clinical score significantly decreased after two consecutive pollen seasons [122]. Three different randomized studies including birch pollen allergic patients with asthma demonstrated that SLIT was able to step down (GINA criteria) seasonal pollen-induced asthma severity [123], its addition to background treatment provided a greater clinical benefit than montelukast [124], and together with low-dose ICS was effective in maintaining long-term seasonal asthma control [125]. High-dose pollen SLIT was associated with a significant improvement in patients with severe allergic rhinitis, and the effect was also identified in the subgroup of patients suffering from concomitant asthma in terms of reduction of global asthma symptoms and asthma medication score [126].

Few studies have compared the effectiveness of the same allergen extract administered through subcutaneous or sublingual route. A systematic review of head-to-head comparison studies showed low-graded evidence of greater effectiveness of SCIT than SLIT for asthma symptoms and a composite of rhinitis symptoms and medication use [127].

Related to this topic, and according to the evidence described above, the following recommendations or statements are formulated:

- SCIT reduces asthma symptoms and asthma medication in comparison to placebo or usual care (LE 1a, grade A) [82].
- SCIT mite-sensitized subjects requires long-term treatment to achieve its clinical benefits (LE 1b, grade A) [83-86] [92, 94].
- SLIT reduces asthma symptoms and asthma medication in comparison to placebo or usual care (LE 3a, grade C) [112].

5.2 Pediatric populations

Allergic asthma is a common chronic disease of childhood, and it generates a substantial burden in the affected children and their families [128]. Despite the pharmacological treatment, an important proportion of patients remain with uncontrolled asthmatic symptoms, and any approach allowing for reduction of ICS therapy, the mainstay of asthma management, is of crucial relevance. The systematic review on AIT for pediatric asthma conducted by Kim et al. [129] supported the efficacy of both SCIT and SLIT for treatment of asthma, although evidence for reductions in medication usage was low to moderate (Table 4). One important benefit of AIT specific to children may be the potential to modify the response to allergens at an early stage and thus prevent disease progression. In fact, AIT is currently the only treatment with the potential to modify and prevent progression of disease from allergic rhinitis to asthma [130].

SCIT in children with asthma. One important concern of the use of SCIT in asthmatic children is the risk of adverse reactions; however, systemic reactions are reported by less than 5% of the subjects and anaphylactic reactions are rare [131-133]. Most of studies have evaluated SCIT in HDM allergic patients (). In a randomized trial that included monosensitized, asthmatic children, SCIT significantly improved asthmatic symptoms and reduced drug intake, associated with a significant decrease in non-specific bronchial hyper-responsiveness [134]. Similar results were observed in other randomized studies, with reduction in fluticasone propionate doses [135], mean medication scores [136], and a higher percentage of patients who discontinued ICS therapy [137, 138]. In a prospective study comparing the efficacy of treatment with SCIT or ICS for one year in children with asthma, it was reported that the number of emergency room visits for asthma attacks was significantly lower in the SCIT group than in the ICS group; in addition, pulmonary function was significantly improved in the SCIT group [139]. Symptomatic improvement due to SCIT has been shown to be associated with better quality of life [140]. Stelmach et al. [141] explored possible differences in the long-term effectiveness between 3 and 5 years of HDM SCIT in asthmatic children. Both treatment durations produced excellent results in terms of asthma remission (50% at 3 years and 54% at 5 years); these rates of asthma remission were significantly higher when compared with those detected in the control group (3.3%). A specific analysis that evaluated the clinical efficacy of 3 vs. 5 year of SCIT in children with HDM respiratory allergy demonstrated that 3 years of SCIT induces significant improvement in children with dust mite respiratory allergy, but a 5-year course added clinical improvement in rhinitis [142].

SCIT based on other allergens has also been associated with positive effects (Table 4). In a randomized trial of SCIT for grass pollen in children with seasonal allergic asthma, the use of SCIT resulted in a reduction in asthma symptom-medication score compared with placebo, and there were also significant reductions in cutaneous, conjunctival, and bronchial symptoms [143]. In patients with bronchial asthma monosensitized to *Alternaria*, SCIT reduced symptoms of asthma and rhinoconjunctivitis, improved quality of life, and decreased concomitant drug use in children and adolescents, with a low frequency of serious side effects [144, 145]. A clear change in airway responsiveness and serum sIgE level was also reported [146].

SLIT in children with asthma. Specially in childhood, SLIT offers practical advantages over subcutaneous therapy because injections can be avoided, the treatment is generally well tolerated [147], and the risk of severe allergic reactions seems to be negligible [148-151], even when multiple allergens [152, 153] or ultra-rush and/or high-dose regimens [154, 155] are used. In addition, SLIT can be administered at home rather than at a health center, thus facilitating, theoretically at least, compliance.

Efficacy of SLIT in respiratory allergy was early confirmed in a meta-analysis of randomized double-blind placebo-controlled clinical trials involving children with either rhinitis or asthma of proved allergic etiology (Table 5). This analysis concluded that sublingual delivery of allergen vaccination constituted a safe and effective alternative to the subcutaneous route to reduce allergy respiratory symptoms and drug intake [156]. Subsequent randomized studies (Table 5) supported SLIT efficacy for grass pollen-induced asthma [157], irrespective of SLIT given continuously along the year or (pre)-co-seasonally [158, 159]. A high-dose SLIT ultra-rush protocol in asthmatic children monosensitized to grass pollen was associated with less severe allergic symptoms in the first 2 grass pollen seasons and continuously improved bronchial hyperreactivity [160]. A combined grass/olive extract vs. placebo administered to children 6 months before the pollen season did not result in different asthma outcomes between the groups, probably due to the low allergen season in which the study was conducted [161]. For *Parietaria* and tree pollen-induced asthma, SLIT has shown to be effective in reduction of pulmonary symptoms [162, 163], to the same extend as inhaled fluticasone propionate [164].

Several studies have also demonstrated SLIT efficacy in children with mite-induced allergic asthma, as summarized in a recent meta-analysis [165]. In HDM-sensitive children with mild to moderate asthma, it has been demonstrated that SLIT for 6 months was associated with a decrease in asthma symptoms and medication use, as well as with an improvement in lung function [166, 167]; however, in children with asthma optimally controlled by pharmacologic treatment and HDM avoidance, SLIT-tablets did not provide additional benefit, despite a significant reduction in allergic response to HDM [168]. Retrospective studies in this pediatric population indicate that HDM-based SLIT significantly reduces the number of acute asthma attacks [169], the duration and dose of ICS [170], and symptomatic medication use [171]. In contrast, Ferrés et al. [172] did not find any improvement in asthma severity. When SLIT efficacy and safety was compared in monosensitized and polysensitized children, the significant improvement in global clinical parameters was similar in both groups [173]. In this sense, in a case-control study that evaluated the effect of SLIT in children with allergic asthma and rhinitis, there was a significant improvement of asthma symptom and medications scores, without differences among monosensitized/polysensitized patients and between different age ranges [174]. The long-term effects of SLIT were evaluated in a prospective study in children with allergic asthma/rhinitis due to mites, divided into two matched groups: one underwent a 4- to 5-year course of SLIT and the other received only drug therapy. In the SLIT group there was a significant difference vs. baseline for the presence of asthma and the use of asthma medications. The mean peak expiratory flow was significantly higher in the active group than in the control group after 10 years [175]. Furthermore, asthmatic patients allergic to either HDM or to both HDM and grass pollen were treated with AIT during childhood, and were re-evaluated in early adulthood after a mean cessation of AIT of 9.3 ± 2.76 years. At re-evaluation, the risk of frequent asthmatic symptoms was three times higher in the control group than in the AIT-treated group; the use of anti-asthmatic medication was more pronounced in the control group, although the difference was not statistically significant [176].

SCIT and SLIT pediatric studies. The combination of the 2 modes of AIT might offer better clinical outcomes by integrating their individual advantages to potentiate mechanisms of tolerance. To our knowledge, only one study comparing SCIT plus SLIT vs. SCIT and SLIT in HDM-sensitized children with respiratory allergy has been conducted. With all three immunotherapy regimens, ICS dosage and the number of asthma attacks were reduced during treatment, with earlier and more sustained decreases in the SCIT and SCIT plus SLIT groups. Likewise, those two groups proved efficacious in terms of decreasing symptom and medication scores for asthma starting from month 4 and rhinitis at month 12, with SCIT plus SLIT even more effective than SCIT for rhinitis (Table 4). The sublingual route proved safer than the subcutaneous because no patients receiving SLIT experienced significant adverse reactions, whereas two patients receiving SCIT had to discontinue treatment because of side effects [177]. Antunez et al. [178] compared SLIT vs. SCIT over a 2-year period in children with respiratory disease monosensitized to *Dermatophagoides pteronyssinus*. Although there was a different immunologic response in peripheral blood during treatment, the clinical improvement was similar for both therapies. These results were further confirmed in randomized trials that compared SCIT, SLIT and pharmacotherapy in asthmatic/rhinitis children who were sensitized to HDM (Table 4); both SLIT and SCIT demonstrated a significant reduction of total rhinitis and asthma symptom score, total medication score, VAS and skin reactivity to HDM when compared with pharmacotherapy [179, 180]. Efficacy results of mite-specific SLIT and SCIT vs. placebo showed a significant reduction in symptom and medication scores for rhinitis and asthma with SCIT. By contrast, although SLIT reduced rhinitis and asthma symptoms and medication usage for rhinitis, this reduction was not significant when compared with the placebo [181]. Somehow, all these evidences point to a higher efficacy of SCIT than SLIT, with a better safety profile of SLIT than SCIT. In fact, a retrospective analysis of real-world data about the rate of route switching and its causes revealed that the rate of SCIT/SLIT changes was, overall, low and mainly due to poor efficacy for SLIT and because of side effects for SCIT [182].

Starting age for AIT. Early treatment with immunotherapy in children who suffer from allergic respiratory diseases has an important significance due to its preventive nature (see above), as well as the beneficial effect that has been shown on children with allergic asthma. Immunotherapy guidelines do not specify a particular lower age limit for starting AIT [72]; in fact, studies that have evaluated the safety of SCIT in children less than 5 years old have found a similar incidence and severity of AEs as in other age populations [143, 183, 184]. In relation to the

Table 5. Studies on the clinical efficacy of SCIT in pediatric patients with allergic asthma

Authors	Type of study (Number of participants)	Allergen / comparator	Duration	Symptoms	Medication use	Comments
Olaguibel et al. [156]	Meta-analysis (7 studies; 256 participants)	All / placebo	Variable	SMD -1.42 (95% CI -2.51 to -0.34)	SMD -1.01 (95% CI -2.06 to -0.01)	
Bufe et al. [157]	Randomized trial (253, 105 with asthma)	Grass pollen / placebo	1 pollen season	64% reduction in median asthma symptom score	No statistically significant difference for the asthma medication score	
Pajno et al. [158]	Randomized trial (80)	Continuous / Coseasonal grass pollen	4 years	Up to 80% reduction in chest symptoms at the end of the study	More than 60% reduction in medication score at the end of the study	No significant differences between the regimens at the end of the study
Stelmach et al. [159]	Randomized trial (60, 20 with asthma)	Continuous / Coseasonal grass pollen / placebo	2 years	SLIT significantly reduced asthma symptoms within the groups; no difference in asthma score compared to placebo	Significant decreases in the combined symptoms/ medication score within the groups and in comparison with the placebo	No differences in lung function were found
Moreno-Ancillo et al [161]	Randomized trial (105)	Grass and olive pollen / placebo	6 months	Intra-group changes in pulmonary symptoms (p=0.016)	No differences found	
Pajno et al. [162]	Randomized trial (30)	*Parietaria* / placebo	3 pollen seasons	Reduction in seasonal increase in bronchial hyper-responsiveness (p=0.001 vs placebo)	NE	No differences in lung function were found
Valovirta et al. [163]	Randomized trial (88, 36 with asthma)	Tree pollen / Placebo	17 months	Reduction of lung symptoms (p=0.02)	Reduction in the medication score during the birch pollen season (p=0.04)	

Pajno et al. [164]	Randomized trial (38)	*Parietaria* + FP/ placebo + FP	13 months	No differences	No differences found	
Liao et al. [165]	Meta-analysis (11 studies; 454 participants)	HDM / control group	Variable	SDM −1.202; 95% CI −2.071 to −0.333	SDM −0.52, 95% CI −1.753 to 0.713	High heterogeneity between studies
Lue et al [166]	Randomized trial (20)	HDM / placebo	6 months	Reduction in nighttime symptoms score ($p<0.05$)	No differences found	
Niu et al. [167]	Randomized trial (97)	HDM / placebo	6 months	Significant reductions in daily, nighttime, and daytime asthmatic scores	Not significant reduction in oral corticosteroids and antihistamines	
Pham-Thi et al. [168]	Randomized trial (11)	HDM / Placebo	18 months	No differences found	No differences found	
Nuhoglu et al. [169]	Retrospective study (39)	HDM	3 years	Significant reduction in the number of asthma attacks; 95% of remission rate	NE	
Ozdemir et al. [170]	Prospective study (90)	HDM / pharmacotherapy	3 years	NE	Reduction of duration and dosage of ICS	
Trebuchon et al. [171]	Retrospective study (736, 471 with asthma)	HDM	3,1 years (median)	64.3% of patients showed asthma symptoms improvement	29% reduction of ICS use	
Ferres et al. [172]	Retrospective study (78, 54 with asthma)	HDM	4 years	Lack of improvement of asthma severity	No differences found	
Li et al. [173]	Prospective study (112)	HDM	52 weeks	Significant improvement in total asthma symptom score	Significant improvement in total medication score	No differences were found between mono- and polysensitized patients

Table 5. Studies on the clinical efficacy of SCIT in pediatric patients with allergic asthma *(continuation)*

Authors	Type of study (Number of participants)	Allergen / comparator	Duration	Symptoms	Medication use	Comments
De Castro et al. [174]	Case-control study (140, 98 with asthma)	Grass pollen or HDM / pharmacotherapy	3 years	Significant improvement in asthma symptom score	Significant reduction in medication score	Significant improvement in lung function
Di Rienzo et al. [175]	Prospective study (60)	HDM / pharmacotherapy	4-5 years after SLIT	Reduction in the presence of asthma compared to baseline	Reduction of the number of patients taking anti-asthma medications	Significant improvement in lung function 10 years after SLIT initiation
Cools et al. [176]	Cohort study (90)	Grass pollen or HDM / pharmacotherapy	9 years after SLIT withdrawal	Less frequent asthma symptoms ($p<0.001$)	Less use of asthma medication, although not significant	

FP: fluticasone propionate; HDM: house dust mite; ICS: inhaled corticosteroids; NE: non evaluated; SMD: standardized mean differences.

injections avoidance, it has been shown that children younger than 4 receiving weekly SCIT lost their fear of injections during the treatment course; increased intervals between visits could be associated with a higher risk of experiencing fear of injections [185]. SLIT seems also to be safe and effective in this population [186-188]. A prospective pilot study investigating the safety, immunomodulatory, and sensitization-preventive effect of SLIT in monosensitized/oligosensitized, clinically asymptomatic children of 2-5 year of age showed that SLIT was safe and induced regulatory mechanisms involving allergen-specific IgG and IL-10 [189]. However, more studies need to be carried out on the efficacy and safety on children under 5.

Related to this topic, and according to the evidence described above, the following recommendations or statements are formulated:

- In children, SCIT reduces asthma symptoms and asthma medication in comparison to placebo or usual care (LE 2b, grade B) [129, 134] [143].
- In children, SLIT reduces asthma symptoms and asthma medication in comparison to placebo or usual care (LE 2b, grade B) [156, 157, 165].
- SCIT is associated with a higher efficacy than SLIT, with a better safety profile of SLIT than SCIT (LE 2b, grade B) [177], [179-182].

5.3 AIT in severe asthma

As stated before, AIT is contraindicated in patients with medical conditions that increase the risk of treatment-related severe systemic reactions, such as those with severe or poorly controlled asthma. AIT is contraindicated in severe asthma patients according to current guidelines. However, these patients could benefit the most from the reduction of allergic asthma symptoms associated with AIT, as shown the prospective study with children from 3 to 11 years affected with severe asthma [190]. At the third yearly control, the study children had a significantly greater reduction in terms of days and nights without asthma and drug usage compared with drug-treated children; spirometric parameters were also improved. Importantly, the number of SPTs and/or sIgE to inhaled allergens also decreased (desensitization) and the adverse events were only mild or transient. Another pediatric study showed that SCIT with HDM extracts was beneficial for children with moderate to severe asthma, without any child suffering systemic reactions [136]. Blumberga et al. [191] carried out a randomized trial of SCIT vs. placebo in moderate and severe HDM allergic asthmatic adults. An ICS sparing effect was evident after 2 years of treatment but no after 3 years; there was no difference in asthma assessments between the two groups. No serious reactions related to AIT injections were seen [191].

It has been suggested that the pre-administration or concomitant treatment of AIT and omalizumab (an anti-IgE humanized antibody), recommended for the treatment of severe allergic asthma, could be useful in reducing the adverse reactions of AIT and to allow its use in some few patients

with severe or uncontrolled asthma [192, 193]. Several non-randomized and non-controlled studies support this strategy, including a series of case study that concluded that pre-treatment with omalizumab in patients with persistent severe allergic asthma seemed to improve the safety and the efficacy of SCIT [73, 74, 194].

Related to this topic, and according to the evidence described above, the following proposal is formulated:

– Although the use of AIT is a contraindication in severe asthma according to current evidence, the use of omalizumab could improve asthma control and the tolerability of AIT in severe asthmatic patients (LE 3b, grade B) [73, 74, 192-194].

5.4 Preventive effects of AIT

Allergic rhinitis is a major risk factor for the development of subsequent asthma [195, 196]. Allergen specific immunotherapy is the only available treatment that can interfere with the pathophysiological mechanisms of the allergic disease and has the potential for changes in the long-term prognosis of respiratory allergy, representing a preventive strategy against asthma development [197]. This is supported by several no placebo-controlled studies investigating the long-term effects of AIT, mainly SCIT, on new onset of asthma [197-199]. In a cohort study, adult AR patients with and without allergic asthma to HDM were investigated for 5 years after initiation of a 3-year course of SCIT (SCIT group) or no SCIT (control group); in those patients without asthma at baseline, the odds ratio for no asthma was 3.57 (95% confidence interval, 1.05-12.91; P <0.05) in favor of SCIT [200]. Using routine health care data, a retrospective study found that the risk of incident asthma was significantly lower in patients with allergic rhinitis exposed to AIT (SCIT, SLIT drops, or SLIT tablets) compared with that in patients not exposed to AIT (*risk ratio* 0.60; 95% CI, 0.42-0.84; P = 0.003) [201]. However, the lack of additional evidence regarding the role of SLIT as a preventive strategy do not allow to draw definitive conclusions on its capacity to prevent secondary asthma in adults.

In 1997, a first study suggested a potential prevention of new sensitivities in HDM-monosensitized children undergoing AIT [202]; these results were subsequently confirmed by Pajno et al. [203]. In a randomized trial with 111 infants less than 1 year of age at high risk of atopy, a HDM extract (active) and appropriate placebo solution were administered orally twice daily for 12 months. There was a significant reduction in sensitization to any new allergen in the active compared with placebo treatment groups [204]. Opposite results have also been reported: Harmanci et al. [205] indicated that HDM-based SCIT administered for 4 years did not prevent the onset of new sensitizations in asthmatic children monosensitized to HDM.

As for asthma prevention, the PAT study results showed that pollen immunotherapy can reduce the risk for development of asthma in children with seasonal rhinoconjunctivitis; these protective effects were observed not only during the treatment period [206], but also 2 years [207] and 7 years [208] after AIT was finished. A randomized study on a 3-year course of coseasonal SLIT also showed the potential for prevention of seasonal allergic asthma in grass pollen allergic children suffering only from rhinitis [209]. In everyday clinical practice, SLIT during 3 years reduced the onset of new sensitizations and mild persistent asthma and decreased bronchial hyperreactivity in children with respiratory allergy [210]. Similar results were obtained in the EFESO study, a case-control study that evaluated the effectiveness of SLIT in patients with allergic rhinitis and found an association of SLIT with a lower incidence of asthma and new sensitizations [211]. The GAP study [212], a randomized, double blinded, placebo-controlled trial, is currently evaluating the preventive effect of the standardized quality *Phleum* SLIT tablet on the development of asthma in children with allergic rhinoconjunctivitis, but preliminary results are not published at this moment. Direct comparisons of SCIT vs. SLIT assessing long-term outcomes such as prevention of asthma and potential for disease modification are lacking.

Related to this topic, and according to the evidence described above, the following conclusion is formulated:

– AIT, mainly SCIT, represents a preventive strategy against asthma development (LE 2a, grade B) [197-199, 206, 209, 211].

– AIT could prevent the onset of new allergen sensitizations in children, but high-quality studies are needed to confirm or change this estimate (LE 3a, grade B) [197-199, 206, 209, 211].

6. Cost-effectiveness of AIT in asthma

The costs of allergic respiratory diseases are substantial; the cost-effectiveness findings of immunotherapy in asthma depends on the duration of the clinical benefit after treatment suspension and the balance between the direct costs of immunotherapy during its maintenance phase and the drug cost savings afforded by the introduction of immunotherapy. A number of studies suggest that immunotherapy is cost-effective versus drug treatment in application to allergic rhinoconjunctivitis and allergic rhinitis associated to asthma – particularly when taking into account the indirect costs and improvement in patient quality of life [213]. As AIT has shown to alter the natural course of disease, outcomes such as the reduction of the need of long-term symptomatic treatment, the degree of exacerbation prevention, and the break-even point of cumulative costs between immunotherapy and pharmacotherapy should be included in pharmacoeconomic studies regarding AIT in asthma. A multitude of other variables are relevant in this evaluation, including age at presentation, duration of symptoms during the year, disease severity and grade of control, and the number of sensitized allergens for which an individual requires treatment. Several pharmacoeconomic studies have been published on the cost-effectiveness of immunotherapy, most of them reviewed in [214] and [215], but their results are difficult to compare

due to their heterogeneity. AIT gives value for the money with cost-effectiveness within 6 years of treatment [216].

A French study performed using a decision-tree model from the societal perspective, compared SCIT, SLIT, and symptomatic drug treatment (SDT) in adults and adolescents with HDM and pollen allergy [217]. Adults were assumed to have received AIT for 4 years and adolescents for 3 years. In adults, the incremental cost per asthma case avoided with SCIT versus SDT was €393 for HDM and €1327 for pollen allergy over a 6-year period. In adolescents, the incremental cost per asthma case avoided with SCIT vs. SDT was €583 for HDM and €597 for pollen allergy over a 7-year period. The incremental cost-effectiveness ratio per additional improved patient ranged from €349 (in adolescents with HDM allergy) to €722 (in adults with pollen allergy). Authors concluded that AIT (whether delivered subcutaneously or sublingually) was a cost-effective treatment option in allergic rhinitis in combination with asthma due to pollen and HDM, and that SLIT is an attractive option in pollen-induced allergic rhinitis, particularly in children. Pokladnikova et al. [218] evaluated the cost-effectiveness of SLIT compared with SCIT and SDT over 3 years from third-party payer and societal perspectives in the Czech Republic. Total direct medical costs after 3 years of AIT were higher in the SCIT compared with the SLIT group, and from a societal perspective, SLIT was 32% less expensive than SCIT; from a patient's perspective, SCIT offered a less expensive alternative for patients who do not experience loss of income and travel costs associated with treatment.

An early economic evaluation suggested that ragweed-based SCIT as compared with pharmacotherapy showed a 30% reduction in medical costs in the immunotherapy group, but it was unlikely to be cost-effective for asthma [219]. In 2005, an economic analysis of Danish patients with seasonal (grass pollen) or perennial (HDM) allergy found that SCIT was associated with initial resource investments and subsequent resource savings in the long term compared with standard care. When all consequences were measured in monetary terms, and assuming that sick days are associated with a loss of productivity, the analysis suggested that SCIT increased societal welfare; this conclusion was also valid even if there was no loss of productivity [220]. In 2008, an economic analysis based on a Markov model compared the cost-effectiveness of SCIT plus SDT vs. SDT for the treatment of allergic rhinitis and allergic asthma from the perspectives of the German healthcare system and society [221]. Additional SCIT was associated with improved medical outcomes and cost savings compared with symptomatic treatment alone according to a societal perspective, achieving the break-even point of cumulative costs between treatment alternatives in the 10th year; however, the degree of cost-effectiveness was strongly affected by costs related to SCIT and the target population receiving such treatment. The superior cost-effectiveness of HDM-based SCIT over pharmacological treatment in patients with allergic rhinitis and asthma was also confirmed in a Chinese study [222]. A piggy-back study involving 65 children and adolescents with allergic asthma sensitized to HDM allergens who received SCIT for 3 years based on a hypoallergenic high-dose preparation concluded that due to the reduction in drug use, a decline in the costs was evident from the first year and the additional costs associated with SCIT were offset by savings in drugs for symptomatic treatment 4 years after the end of SCIT [223]. In patients with grass-pollen and/or HDM induced allergic rhino-conjunctivitis and/or asthma, SCIT was associated with reduced disease severity, decreased days with allergy symptoms, increased quality of life, and decreased number of sick days; a conservative estimate of the quality-adjusted life years (QALYs) gained by SCIT was equivalent to 0.03 QALYs gained per SCIT treated patient per year [103].

As for SLIT, a review performed of the available studies on economic evaluation of SLIT in children and adults suggested that SLIT was associated with economic advantages and/or monetary savings, supporting an effect on sparing costs for respiratory allergy [224]. An Italian study showed that this therapy improved the symptoms of 399 of 1,000 patients and prevented asthma in 229 of 1,000 patients compared with drugs alone. From both the healthcare system and societal perspectives, SLIT plus SDT was more effective and less costly than SDT alone, with 21% lower direct costs and 33% lower total costs over 6 years (3 years of SLIT or SDT and 3 years of follow-up) [225]. Two different studies that assessed the cost-effectiveness of a *Phleum*-tablet-based AIT indicated for the treatment of grass pollen-induced respiratory allergy disease in allergic rhinoconjunctivitis co-existing with asthma, concluded that it was superior to standard care for all efficacy endpoints, including QALYs gained, and resulted in significantly less use of rescue medication and fewer hours missed from work. The difference was even greater when future costs of asthma were included [226, 227]. Ariano et al. [228] conducted a cost–consequence analysis alongside a prospective study of patients with allergic asthma due to HDM. Fifty patients received a 3-year course of SLIT plus SDT and 20 SDT alone. The study spanned 5 years to include 2-year outcomes following SLIT discontinuation. Compared with patients receiving SDT alone, mean, annual per-patient costs (SLIT plus allergy-related medications) incurred by the patients receiving SLIT plus SDT were higher in year 1, equivalent in years 2 and 3, and significantly lower in years 4 and 5, with a net saving of 23%. The year 5 savings, in terms of annual per-patient incremental costs that were achieved by patients receiving SLIT plus SDT, increased with disease severity and reached 34% for severe asthmatic patients [228].

Overall, health-economic analyses provided strong evidence for the cost-effectiveness of AIT over SDT, especially if persistent beneficial clinical effects after discontinuation of AIT are considered. However, most of the studies included patients with allergic rhinitis co-existing with asthma, but not asthma separately and it should be considered that the studies employed only single allergen AIT [215]. Moreover, there is considerable variability in the way the economic outcomes are measured. Currently, there is no sufficient evidence to affirm that SCIT is more cost-effective than SLIT in comparison to

SDT alone. Further research is needed, using standardized pharmacoeconomic methodology and long-term studies, in order to assess the cost-effectiveness of AIT in asthma.

7. Clinical research criteria of AIT in asthma

Despite the huge amount of evidence gathered in this report, there is still a great need of further high-quality research to maximize the potential of AIT in asthma. It has been shown that, as in other areas of medicine, the quality of reporting of most immunotherapy trials is low. For example, it has been stated that only 4.2% of AIT randomized controlled trials met all of the criteria of the CONSORT Statement [229]. Studies of AIT in asthma should include only patients with allergic asthma and should be performed following standardized protocols, with a focus on the long-term and preventive effects of the treatment [212], rather than considering only the immediate efficacy on allergic symptoms. Specific asthma features, such as lung function, bronchial reactivity, asthma control, and exacerbation rates, should be included among the study outcomes [230].

Few studies have specifically evaluated AIT in asthmatic patients, and only 2 had a formal sample size calculation [70, 116]. Most of the clinical trials evaluated clinically relevant parameters, such as symptom and medication scores (with an emphasis on the corticosteroid sparing effect) and lung function. According to the European Medicines Agency (EMA), clinical trials on AIT in asthmatic patients start as add-on therapy, which has to be considered in the evaluation of the primary end-point (e.g., evaluation in the context of a stepwise reduction in controller medication). Lung function, composite scores, number of exacerbations, or reduced need for controller medication could be considered as primary end-points. The steroid-sparing effect of AIT is of upmost importance to avoid the potential side effects of ICS in asthmatic patients, especially in children. The efficacy of products for AIT should be evaluated in special trials in the pediatric population and not in combined trials including children and adults. Finally, patient-related outcome measures, such as quality-of-life and pharmacoeconomic end points that may allow a benefit/risk assessment, should also be assessed [103]. There have been some attempts to develop objective measures of asthma disease activity, such as the Asthma Disease Activity Score (ADAS-6, ADAS-4) or the Composite Asthma Severity Index [231, 232]. The use of these tools in clinical trials may allow for separate treatment effects, predict future asthma attacks, and reduce sample size.

Recently, the US Food and Drug Administration (FDA) has published a brief guidance on prevention of respiratory allergic diseases with AIT. The FDA experts consider that studies of allergenic products for the prevention of asthma in children should be prospective, randomized, blinded, and controlled, with a primary endpoint based on case definitions that are clearly defined and consistently applied throughout the study. Studies are expected to be adequately powered to detect a clinically meaningful reduction of asthma in the treated group relative to the control group using pre-specified criteria for "success." In Europe, a demonstration of long term efficacy is required for the pediatric investigation plan that must accompany applications for marketing authorization submitted to the EMA [233].

An up-to-date search in clinical trials registries reveals that several robust clinical trials are exploring AIT efficacy and safety in allergic asthma, so uptake of the new data into guidance for physicians will result in more effective management in clinical practice.

Related to this topic, and according to the evidence described above, the following recommendation is formulated:

– Specific asthma features, such as lung function, bronchial reactivity, asthma control, and exacerbation rates, should be included among the study outcomes (LE 5, grade D) [230].

8. AIT in asthma: clinical guidelines

AIT began as the only allergy treatment modality for the medical community almost 100 years ago, before pharmacologic therapy was available, and it has remained a key component of allergy management since then. Scientific advances in the last years have aided to explain the mechanisms of action and to identify the relevant antigens and the optimal regimens of AIT. The objective of asthma management guidelines is to improve the implementation of current knowledge into daily clinical practice by establishing a consensus of scientific practices for the management of asthma. Initial guidelines were based on consensus of expert opinion but advances in asthma research has led to the development of evidence-based guidelines and a major paradigm shift to control-based asthma management [234].

One of the most important guidelines is issued by the Global Initiative for Asthma [3]; until 2016, the Global Strategy for Asthma Management and Prevention stated that AIT may be an option if allergy plays a prominent role, e.g. asthma with allergic rhinoconjunctivitis [3]. For SCIT, in people with asthma and allergic sensitization, the treatment is associated with a reduction in symptom scores and medication requirements, and improved allergen-specific and nonspecific airway hyper-responsiveness; for SLIT, modest benefits have been seen in adults and children, including a modest reduction of ICS with high dose SLIT. This reflects a shift from the previous statement that asseverated that the efficacy of AIT in asthmatic patients was limited [235].

The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines maintain a conditional recommendation for SCIT and SLIT in patients with allergic asthma [54, 55] however there has not been an update of this report since 2012. The last version of the Spanish Guideline on the Management of Asthma (GEMA) stands by the efficacy of both SCIT and SLIT contemplated in 2009 [12], and added some evidence

supporting the cost-effectiveness of AIT over pharmacological treatment alone [12]. It recommends considering AIT use in the first steps of the treatment algorithm and states that AIT is able to offer additional advantages over pharmacotherapy, such as the maintenance of clinical benefits for several years after treatment discontinuation, a halt in the progression from pollen-related allergic rhinoconjunctivitis to asthma, or the occurrence of new sensitizations in monosensitized patients. Latin America and Spain recommendations for the prevention and treatment of asthmatic exacerbations (ALERTA2 guidelines) [236] only make mention of immunotherapy potential to reduce number of exacerbations in pollen-monosensitized patients with rhinitis and mild or moderate asthma. The recommendations for medical therapy of asthma from the Expert Panel Report 3 (EPR-3) of the National Asthma Education and Prevention Program (NAEPP) [237] mention immunotherapy to be considered for patients who have persistent asthma if evidence is clear of a relationship between symptoms and exposure to an allergen to which the patient is sensitive (Evidence B).

The British guidelines on the management of asthma indicate a possible role of AIT in primary prophylaxis, a beneficial effect of SCIT and limited evidence for SLIT efficacy [238]. Again, these recommendations will likely be updated as several new studies have emerged. The Canadian Thoracic Society guideline on diagnosis and management of asthma in preschoolers, children, and adults was updated in 2012 [119]. No mention on immunotherapy was found. For severe asthma, neither the International ERS/ATS guidelines [69] nor Spanish guidelines for severe uncontrolled asthma [239] consider AIT.

Among pediatric guidelines, only the International consensus on (ICON) pediatric asthma states that AIT should be considered for children whose symptoms are clearly linked to a relevant allergen [240]. The Spanish [241] and the Canadian [242] ones do not mention this type of therapy.

9. Summary of recommendations and conclusions

Finally, despite significant advances in our understanding of allergic asthma, as well as great efforts in producing high-quality studies and evidence on AIT to support allergy management, several patients do not achieve an optimal

Topic	Recommendation / conclusion	LE / Grade
Diagnosis	Determination of the sensitization profile is crucial for define the relevant allergens in each patient	2c, B
Biomarkers of response	Serum allergen-specific IgE is a predictive biomarker for adequate response to AIT	3, C
Biomarkers of response	Functional assays of inhibitory IgG4 and IgE-blocking factor may be useful surrogates of clinical response	1b, B
Indications / contraindications	Immunotherapy is indicated in allergic and well controlled asthmatic patients older than 5 years	1b, A
Indications / contraindications	Continuation of AIT during pregnancy is feasible	3a, C
Efficacy of AIT	SCIT reduces asthma symptoms and asthma medication in comparison to placebo or usual care	1a, A
Efficacy of AIT	SCIT mite-sensitized subjects requires long-term treatment to achieve its clinical benefits	1b, A
Efficacy of AIT	SLIT reduces asthma symptoms and asthma medication in comparison to placebo or usual care	3a, C
Pediatric AIT	In children, SCIT reduces asthma symptoms and asthma medication in comparison to placebo or usual care	2b, B
Pediatric AIT	In children, SLIT reduces asthma symptoms and asthma medication in comparison to placebo or usual care	2b, B
Pediatric AIT	SCIT is associated with a higher efficacy than SLIT, with a better safety profile of SLIT than SCIT	2b, B
AIT in severe asthma	The use of omalizumab could improve asthma control and the tolerability of AIT in severe asthmatic patients	3b, B
Preventive effect of AIT	AIT, mainly SCIT, represents a preventive strategy against asthma development	2a, B
Asthma end- points	Specific asthma features, such as lung function, bronchial reactivity, asthma control, and exacerbation rates, should be included among the study outcomes	5, D

AIT: Allergen immunotherapy; SCIT: Subcutaneous immunotherapy; SLIT: Sublingual immunotherapy.

asthma control, possibly due to suboptimal treatment. It is crucial to implement studies that emphasize the relevance of AIT as a valuable therapeutic strategy in terms of prevention of exacerbation and progressive decline in lung function, and the sparing effect on ICS use. Future research should include specific tools for asthma evaluation, including objective measures of asthma disease activity, control and quality of life related to the disease, when assessing AIT effectiveness in asthmatic patients. Also of benefit would be having biomarkers and phenotypes to predict the likelihood of response. Further research is needed to clarify current concerns regarding safety and effectiveness of AIT in allergic asthma.

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Conflicts of Interest

JDO has participated in advisory boards and acted as a consultant for ALK-Abelló, Allergy Therapeutics, LETI, and Stallergenes; he has received speaker's honoraria from TEVA, MundiPharma, and GSK. JD has received speaker's honoraria from ALK-Abelló and Leti. CB has received lecture fees from ALK-Abelló and Merck. LP has received honoraria from ALK, GSK, Novartis, Boehringer Ingelheim; Advisory boards for ALK-Abelló, Astra-Zeneca, Novartis, GSK, Mundipharma, Stallergenes. EA has received speaker's honoraria from ALK-Abelló. MC has participated in clinical studies sponsorized by ALK, Stallergenes, and Novartis. AHS has received consultant fees from Leti, Merck, and ALK-Abelló. JIS declares no conflict of interest. JMVC has received speaker fees from GSK, Astra-Zeneca, Chiesi, Novartis, Boehringer-Ingelheim, Mundipharma, Pfizer, ALK-Abelló, Leti, Stallergenes, Merck, Bial, Probelte pharma, and Allergy Therapeutics. AIT has received speaker and consultant fees from ALK-Abelló, Stallergenes, GSK, Novartis, Mundipharma, and Sandoz.

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